Novel signaling and treatment regimes in Anaplastic Lymphoma Kinase driven neuroblastoma models

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To my family and friends

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ABSTRACT

In this thesis we aimed to unravel the importance of Alkal2 in neuroblastoma with the aid of preclinical murine models. We tested the hypothesis that Alkal2 can potentiate murine MYCN-driven neuroblastoma in absence of activating point mutations in the anaplastic lymphoma kinase (ALK). Furthermore, we explored the effect of DNA damage response upon ALK inhibition and how ALK signaling induces its effects on DNA damage response. Here, we investigated and compared combination treatment of ALK/ATR inhibition with ATR monotherapy both in neuroblastoma cell lines and murine neuroblastoma models.

We found that Alkal2 is important in tumor formation in murine MYCN driven neuroblastoma and that murine Alkal2 driven neuroblastoma is sensitive to ALK inhibition, suggesting that a subpopulation of neuroblastoma patients, such as patients with 2p gain, might benefit from ALK inhibition therapy although they lack activating point mutations in ALK. Furthermore, we underscore the potency of elimusertib/lorlatinib (ALKi/ATRi) treatment over ATR monotherapy in mouse NB models. This potency is explained in part by the impact of ALK signaling on components of the DNA damage response, together with a previously unappreciated effect of ATR inhibition in inducing differentiation. Together, our findings suggest a potentially potent treatment regime for ALK-positive high-risk neuroblastoma patients.

Keywords: Neuroblastoma, ALKAL2, Anaplastic lymphoma kinase, ATR

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SAMMANFATTNING PÅ SVENSKA

Barncancerformen neuroblastom är den vanligaste barncancern att diagnostiseras under det första levnadsåret. Neuroblastom är en mångfacetterad sjukdom med flera bakomliggande faktorer, däribland genetiska defekter, som påverkar risken och utfallet hos patienten. Tyvärr är prognosen för hög-risk neuroblastom dålig. Aktiverande genetiska mutationer i receptor tyrosin kinaset Anaplastisk Lymfomkinas (ALK) har visat sig vara en predispositionsgen för hög-risk neuroblastom. Vanligtvis aktiveras ALK av ligander (ALKALs), likt en nyckel till ett lås. Den initiala frågeställningen var om ett överuttryck av liganden kan öka graden av neuroblastom hos möss som uttrycker en omuterad ALK receptor. Vidare undersökte vi om hämmare av signalvägar som styr reparationsmekanismen för DNA-skada kan vara en alternativ behandlingsmetod, enskilt eller tillsammans med ALK hämmare, i ALK-positiva neuroblastomceller och Alk-positiva neuroblastom musmodeller.

Resultaten visar att överuttryckt ALKAL ligand kan öka initiering av neuroblastom hos möss utan att ALK receptorn är muterad. Det visade sig att denna neuroblastomform också kan blockeras med ALK hämmare, vilket öppnar upp en behandling för en undergrupp av patienter som överuttrycker ALKAL liganden. Vi fann även att hämning av DNA-reparation signalvägar tillsammans med en ALK hämmare är en bättre behandling av neuroblastom hos möss jämfört med att bara blockera DNA-reparation signalvägar. Denna behandlingsmodell skulle potentiellt gagna patienter med ALK-positiv hög-risk neuroblastom.

Nyckelord: Neuroblastom, ALKAL2, Anaplastic lymphoma kinase, ATR

LIST OF PAPERS

This thesis builds on the following studies. Articles are reproduced with permission from Springer Nature or under Creative Commons BY-NC-ND 4.0 https://creativecommons.org/licenses/by-nc-nd/4.0/

I. **Marcus Borenäs**†, Ganesh Umapathy†, Wei Yun Lai, Dan E Lind, Barbara Witek, Jikui Guan, Patricia Mendoza Garcia, Tafheem Masudi, Arne Claeys, Tzu Po Chuang, Abeer El Wakil, Badrul Arefin, Susanne Fransson, Jan Koster, Mathias Johansson, Jennie Gaarder, Jimmy Van den Eynden, Bengt Hallberg and Ruth H Palmer. ALK ligand ALKAL2 potentiates MYCN driven neuroblastoma in the absence of ALK mutation. The EMBO journal. 2021 Feb 1;40(3):e105784. doi: 10.15252/embj.2020105784. Epub 2021 Jan 7. https://pubmed.ncbi.nlm.nih.gov/33411331/

II. **Marcus Borenäs**†, Ganesh Umapathy†, Dan E†. Lind, Wei-Yun Lai†, Jikui Guan†, Joel Johansson, Eva Jennische, Alexander Schmidt, Yeshwant Kurhe, Jonatan L. Gabre, Agata Aniszewska, Anneli Strömberg, Mats Bemark, Michael N. Hall, Jimmy Van den Eynden, Bengt Hallberg and Ruth H. Palmer. ALK signaling primes the DNA damage response sensitizing ALK-driven neuroblastoma to therapeutic ATR inhibition. Proc Natl Acad Sci U S A. 121(1):e2315242121. doi: 10.1073/pnas.2315242121. Epub 2023. https://pubmed.ncbi.nlm.nih.gov/38154064/

III. **Marcus Borenäs**, Dan Lind, Adam Lehnberg, Edit Zenténius, Matilda Esselius, Joel Johansson, Jikui Guan, Agata Aniszewska, Bengt Hallberg, Ruth H. Palmer. ALK/ATR combination inhibition in neuroblastoma mouse tumors driven by MYCN. Manuscript.

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- Javanmardi N, Fransson S, Djos A, Umapathy G, Östensson M, Milosevic J, **Borenäs M**, Hallberg B, Kogner P, Martinsson T, Palmer RH. Analysis of ALK, MYCN, and the ALK ligand ALKAL2 (FAM150B/AUGα) in neuroblastoma patient samples with chromosome arm 2p rearrangements. Genes Chromosomes Cancer. 2020 Jan;59(1):50-57. doi: 10.1002/gcc.22790. Epub 2019 Sep 2. PMID: 31340081.

- Guan J, **Borenäs M**, Xiong J, Lai WY, Palmer RH, Hallberg B. IGF1R Contributes to Cell Proliferation in *ALK*-Mutated Neuroblastoma with Preference for Activating the PI3K-AKT Signaling Pathway. Cancers (Basel). 2023 Aug 25;15(17):4252. doi: 10.3390/cancers15174252. PMID: 37686528; PMCID: PMC10563084.

- Lai WY, Chuang TP, **Borenäs M**, Lind DE, Hallberg B, Palmer RH. Anaplastic Lymphoma Kinase signaling stabilizes SLC3A2 expression via MARCH11 to promote neuroblastoma cell growth. Cell Death Differ. 2024 Jul;31(7):910-923. doi: 10.1038/s41418-024-01319-0. Epub 2024 Jun 10. PMID: 38858548; PMCID: PMC11239919.

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ABBREVIATIONS

911	RAD9-RAD1-HUS1
ALK	Anaplastic Lymphoma Kinase
ALKAL	ALK And LTK ligand
TFM	Place caret here and press Tab for More cells in this table
ALL	Acute Lymphoblastic Leukemia
ALT	Alternative Lengthening of Telomeres
ARID	AT-Rich Interaction Domain
ATM	Ataxia-Telangiectasia Mutated
ATP	Adenosine Triphosphate
ATR	Ataxia-telangiectasia mutated and RAD3-related
ATRIP	ATR interacting protein
ATRX	ATRX chromatin remodeler
AURKA	AURORA Kinase A
BAD	BCL2 Associated Agonist of cell Death
BARD1	BRCA1 Associated RING Domain protein 1
BER	Base Excision Repair
BET	Bromodomain and Extraterminal
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
cAMP	cyclic Adenosine Monophosphate

CAMTA	Calmodulin binding Transcription Activator
CAR	Chimeric Antigen Receptor
CD	Cluster of Differentiation
CDC	Cell Division Cycle
CDK	Cyclin Dependent Kinase
cDNA	complementary DNA
cGAS	cyclic GMP–AMP Synthase
cGMP	cyclic Guanosine Monophosphate
CHD	Chromodomain Helicase DNA binding protein
CHK	Checkpoint Kinase
CNS	Central Nervous System
COG	Children's Oncology Group
CREB	Cyclic-AMP Responsive Element Binding protein
CTLA	Cytotoxic T-Lymphocyte Associated protein
DAG	Diacylglycerol
DDK	DB4 Dependent Kinase
DDR	DNA Damage Response
DFMO	Difluoromethylornithine
DLG	Discs Large MAGUK scaffold protein
DNA	Deoxyribonucleic Acid
DNA-PK	DNA-dependent Protein Kinase

DSB	Double Stranded Brake
E-box	Enhancer-box
EGFL	EGF-Like
EGFR	Epidermal Growth Factor Receptor
ETAA1	Ewing Tumor Associated Antigen 1
FA	Fanconi Anemia
FAK	Focal Adhesion Kinase
FAN1	Fanconi Associated Nuclease 1
FANC	Fanconi Anemia Complementation group
FBXW7	F-box and WD repeat domain containing 7
FGFR	Fibroblast Growth Factor Receptor
FOX	Forkhead Box
FRS2	FGF Receptor Substrate-2
GAK	G-Associated Kinase
GD	Disialoganglioside
GEMM	Genetically Engineered Mouse Model
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
GR	Glycine Rich
GRB	Growth factor Receptor-Bound protein
GTPase	Guanosine Triphosphate hydrolase
HATs	Histone Acetyl Transferases

HER2	Human Epidermal growth factor Receptor
HR	Homologous Recombination
HR-NBL1	High Risk Neuroblastoma Study 1
ICL	Intrastrand Crosslink
IL	Interleukin
INRG	International Neuroblastoma Risk Group
INRGSS	INRG staging system
IP3	Inositol (1,4,5)-triphosphate
IRF	Interferon Regulatory Factor
JAK	Janus Kinase
Jeb	Jelly belly
JNK	JUN N-terminal Kinase
KIF	Kinesin Family member
LDLa	Low-Density Lipoprotein class A
LTK	Leukocyte Tyrosine Kinase
MAM	Meprin, A-5 protein and receptor protein tyrosine phosphatase Mu
MAPK	Mitogen-Activated Protein Kinase
MAX	MYC-Associated protein X
MCM	Minichromosome Maintenance
MEK	MAPK/ERK Kinase

MIBG	Metaiodobenzylguanidine
mTOR)	mammalian Target Of Rapamycin
MYC	c-MYC
NER	Nucleotide Excision Repair
NF-κB	Nuclear Factor κB
NHEJ	Nonhomologous End Joining
NK	Natural Killer
NPM	Nucleophosmin
NSCLC	Non-Small Cell Lung Cancer
ODC	Ornithine Decarboxylase
PALB2	Partner and Localizer of BRCA2
PARP1	Poly(ADP-ribosyl) Polymerase 1
PCNA	Proliferating Cell Nuclear Antigen
PD	Programmed cell Death
PDGF	Platelet-Derived Growth Factor
PDK1	Pyruvate Dehydrogenase Kinase 1
PD-L	Programmed cell Death Ligand
PDX	Patient Derived Xenograft
PHOX	Paired like Homeobox
PI3K	Phosphatidylinositide 3 Kinase
PIKK	Phosphatidylinositol 3-Kinase-related protein Kinase

PIN	Peptidylprolyl cis/trans Isomerase, NIMA-interacting
PIP2	Phosphatidylinositol 4,5-biphosphate
PIP3	Phosphatidylinositol 3,4,5 triphosphate (
PKA	Protein Kinase A
PKC	Protein Kinase C
PLC-γ	Phospholipase C-γ
PLK1	Polo-Like Kinase 1
PP	Protein Phosphatase
PROTAC	Proteolysis-Targeting Chimera
RB	Retinoblastoma protein
RNAi	Ribonucleic Acid interference
RPA	Replication Protein A
RRM2	Ribonucleotide Reductase regulatory subunit M2
sALCL	Systemic Anaplastic Large Cell Lymphoma
sGC	soluble Guanylyl Cyclase
SH2	Src Homology 2
SHANK	SH3 and multiple Ankyrin repeat domain
SHP2	SH2-containing tyrosine Phosphatase 2
SIOPEN	Society of Paediatric Oncology Europe Neuroblastoma Group
SLC3A2	Solute Carrier Family 3, Member 2
SOS	Son Of Sevenless

SSB	Single Strand Break
STAT	Signal Transducer and Activator of Transcription
STING	Stimulator of Interferon Genes
SUN2	Sad1 and UNC84 domain containing protein 2
TERT	Telomerase Reverse Transcriptase
TFIIH	Transcription Factor 2H
TGF	Transforming Growth Factor
TGFL	TNF-Like
TH	Tyrosine Hydroxylate
TOPBP1	Topoisomerase II Binding Protein 1
UPS	Ubiquitin–Proteasome System
USP	Ubiquitin Specific Peptidase
UV-DDB	Ultraviolet radiation DNA Damage Binding protein
VEGF	Vascular Endothelial Growth Factor
XP	Xeroderma pigmentosum
XRCC1	X-ray Repair Cross Complementing protein 1

1 INTRODUCTION

1.1 THE CELL CYCLE

1.1.1 OVERVIEW OF THE CELL CYCLE

In order for an eukaryotic cell to multiply and give rise to a multicellular organism, a properly functioning cell cycle is needed where the replication of Deoxyribonucleic Acid (DNA) and the growth of the cell is rigorously monitored to ensure correct transfer of genetic information to the two diploid progeny cells. A properly functioning cell cycle is also fundamental for the multicellular organism to regenerate cells that have been lost and to give rise to haploid gametes that will produce new offspring.

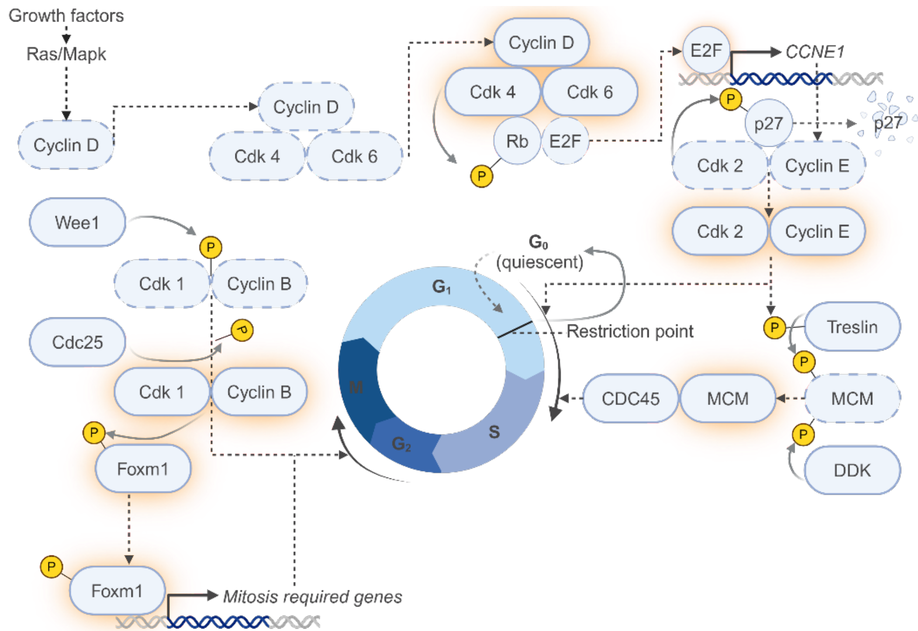

Figure 1. Schematic overview of the eukaryotic cell cycle. Created in BioRender. Borenäs, M. (2024) BioRender.com/ f99f445.

An eukaryotic cell can exist in either a mitosis (M), gap 1 (G_1), synthesis (S) or gap 2 (G_2) phase, where the last three phases together constitute the interphase. Both the G_1 and the G_2 phases are associated with cell growth while the S phase is when replication of DNA occurs. The eukaryotic cell can also

enter a quiescent (G_0) stage if there are insufficient growth factors, from which it can be recruited back if stimulated with appropriate growth factors (Figure 1). For example, fibroblasts that are activated by Platelet-Derived Growth Factor (PDGF) upon tissue damage, reenter the cell cycle in order to aid in wound healing (Cooper, 2019). Cells can also cease division and exit the cell cycle irreversibly through senescence or terminal differentiation (Buttitta & Edgar, 2007; Herranz & Gil, 2018).

Progression through a cell cycle phase and the transition from one phase to the next is intricately orchestrated by the interaction of members of the cyclin and serine/threonine Cyclin Dependent Kinase (Cdk) families and subsequent activation of Cdks through phosphorylation. For example, growth factors stimulate increased expression of cyclin D during early G_1, which in turn interacts with Cdks 4 and 6, forming a complex that will inactivate Retinoblastoma protein (Rb) through phosphorylation, allowing E2F to be released from the Rb-E2F complex. E2F subsequently acts as a transcription factor promoting expression of genes, such as *CCNE1* that encodes Cyclin E1, needed for progression of the cell cycle. The Cdk 4,6/Cyclin D complex permits transit through the restriction point in G_1, allowing for progression of the cell cycle from G_1 to S phase through the activation of Cdk2/Cyclin E which in turn will initiate DNA replication through activation of Minichromosome Maintenance (MCM) helicase proteins (Cooper, 2019). During the G_2 to M phase transition Cdk1/Cyclin B phosphorylates FOXM1 which allows transcription of genes needed to enter mitosis (Lim & Kaldis, 2013). The Cdk1/Cyclin B complex is inhibited by Wee1 through phosphorylation, but once dephosphorylated by the Cdc25 phosphatase, Cdk1/Cyclin B will drive the cell from G_2 to M phase (Cooper, 2019; Johnson & Walker, 1999) (Figure 1). This finely tuned interplay underlies the rigorous control of the cell cycle.

1.1.2 DNA REPAIR

In 1957 Francis Crick introduced the central dogma where genetic information flows in one direction through transcription and translation to produce a functioning protein (Cobb, 2017). To ensure correct transfer of information and to maintain genomic integrity several DNA repair mechanisms must be in place. Such repair mechanisms include the mismatch repair, Base Excision Repair (BER), Nucleotide Excision Repair (NER), Intrastrand Crosslink (ICL) repair, Single Strand Break (SSB) repair and for Double Stranded Brake (DSB)

Nonhomologous End Joining (NHEJ) or Homologous Recombination (HR) (Ciccia & Elledge, 2010; Cooper, 2019).

Figure 2. Schematic overview of ATRs proposed role in DNA repair. Created in BioRender. Borenäs, M. (2024) BioRender.com/ h91s316. Adapted from Pietrasik et al., 2020 and Hashimoto et al., 2016 under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

DNA polymerases δ and ε contain proofreading capabilities where newly synthesized DNA is verified, if there is a base that is mismatched the DNA polymerase will excise the base and replace it with the correct one (Cooper, 2019). Similar to the DNA polymerase proofreading capabilities, MutL Homologues (MLH/PMS) and MutS Homologues (MSH) scan the synthesized DNA for incorporated mismatches resulting in either 3´ or 5´directed excision and repair, the mechanisms of which are not fully mapped (Fishel, 2021; Fishel & Lee, 2016). Base excision repair, typically utilized when spontaneous depurination has occurred or in the present of an aberrant base, is achieved through the recognition and cleavage of the base by DNA glycosylase followed by removal of deoxyribosylphophate (Weinberg, 2014). Repair is commenced through DNA polymerase β which either inserts a correct base directly, followed by ligation of the DNA strand (Short patch BER), or excision and replacement of several nucleotides by DNA polymerase δ or ε followed by ligation of the DNA (Long patch BER) (Cooper, 2019; Krokan & Bjoras, 2013; Weinberg, 2014). Some DNA lesions, e.g. thymidine dimers, require excision of several nucleotides which is managed by nucleotide excision repair (NER) (Cooper, 2019). Xeroderma pigmentosum (XP) C identifies aberrant base pairing followed by binding of Replication Protein A (RPA) (protecting DNA from endonucleases), XPA and Transcription Factor 2H (TFIIH) (Cooper, 2019; Marteijn et al., 2014; Pietrasik et al., 2020). However, XPC can also be recruited by Ultraviolet radiation DNA Damage Binding protein (UV-DDB) which recognizes cyclobutane–pyrimidine dimers (Marteijn et al., 2014). UV-DBB also induces chromatin decondensation by ubiquitylation of histones or through its interaction with Poly(ADP-ribosyl) Polymerase 1 (PARP1) (Marteijn et al., 2014). XPD and XPB, subunits of TFIIH, harbor helicase properties, unwinding the DNA followed by recruitment of the endonucleases XPG and XPF/ERCC1 which cleave the DNA on the 3´and 5´ edges of the DNA lesion respectively (Cooper, 2019; Marteijn et al., 2014; Pietrasik et al., 2020). After incision of XPG and XPF/ERCC1, Proliferating Cell Nuclear Antigen (PCNA) recruits DNA polymerase δ or ε completing the repair (Marteijn et al., 2014; Pietrasik et al., 2020). However, exposed single stranded DNA, e.g. through stalled replication forks or NER, coated with RPA may activate Ataxia-telangiectasia mutated and RAD3-related (ATR) through ATR interacting protein (ATRIP), resulting in DNA Damage Response (DDR) signaling and phosphorylation of the histone family member H2A.X (Lindsey-Boltz, 2017; Marteijn et al., 2014; Saldivar et al., 2017) (Figure 2). Interstrand Crosslinks (ICL) are formed in nature through for example lipid peroxidation but ICL are also formed by chemotherapeutic agents (Deans & West, 2011). The mechanisms for resolving ICLs differ depending on which cell cycle phase

the cell is in. During replication, in the S phase, ICLs induce replication stalling and are recognized by Fanconi Anemia Complementation group M (FANCM) which bind branched DNA and recruit the Fanconi Anemia (FA) complex (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG and FANCL) (Deans & West, 2011). Furthermore, the stalled replication fork will expose single stranded DNA which RPA will coat, thus attracting ATR which in turn phosphorylates and activates the FA complex (Branzei & Foiani, 2010; Saldivar et al., 2017; Sirbu & Cortez, 2013). The FA complex monoubiquitylates for example FANCD2 which enhances its activity. Fanconi Associated Nuclease 1 (FAN1) interacts with FANCD2, which is now bound to the DNA, and can induce, together with other nucleases, "unhooking" resulting in one oligonucleotide with a double stranded break end and one oligonucleotide containing an ICL (Deans & West, 2011; Hashimoto et al., 2016). The subsequential oligonucleotide containing an ICL is repaired by a translesion DNA synthesis polymerase while the oligonucleotide containing a double stranded break is repaired by homologues recombination (HR) (Deans & West, 2011; Hashimoto et al., 2016). The recombinase RAD51 senses homology between DNA oligonucleotides and induces strand swap (Deans & West, 2011). Breast Cancer gene 1 (BRCA1) interacts with BRCA1 Associated RING Domain protein 1 (BARD1) to ensure correct localization of RAD51 while Breast Cancer gene 2 (BRCA2) interacts directly with RAD51 and together with Partner and Localizer of BRCA2 (PALB2) promote RAD51 relocation to recombination sites (Deans & West, 2011; Dray et al., 2010). Furthermore, Ataxia-Telangiectasia Mutated (ATM) and ATR and their associated proteins interact with BRCA1/2 and their associated proteins by phosphorylating them which is important in assemble of effector complexes required for RAD51 HR (Roy et al., 2011; Sirbu & Cortez, 2013) (Figure 2). As an alternative to HR, double stranded breaks can be repair by the more error prone Nonhomologous End Joining (NHEJ) (Cooper, 2019).

1.1.3 DNA DAMAGE CHECKPOINTS AND DNA DAMAGE RESPONSE

To maintain genomic integrity throughout the duplication process, the cell has DNA damage checkpoints integrated in the G_1, S and G_2 phase of the cell cycle. The DNA damage checkpoints sense incompletely replicated DNA or DNA damage and allow for DNA repair or completion of DNA replication. Double-stranded DNA breaks are detected by ATM, while single-stranded DNA breaks or incomplete DNA replication are detected by ATR. Activation of ATM or ATR through DNA damage leads to phosphorylation of Checkpoint Kinase

(Chk) 2 and Chk1 respectively, which independently phosphorylate the Cell Division Cycle (Cdc) 25 dual-specificity phosphatase rendering it inactive. Cdc25 is necessary for progression in the G_1, S and G_2 phase through its phosphatase activity on Cdk1 and Cdk2 activating them (Cooper, 2019). Interestingly, Chk1 has been suggested to regulate WEE1 in frogs, allowing ATR to further influence Cdc25 activity (Lee et al., 2001). In addition, ATM together with Chk2 stabilizes the TP53 transcription factor through phosphorylation, allowing TP53 to accumulate and initiate transcription of p21 or apoptosis. In turn, p21 will inhibit the Cdk2/Cyclin E complex, inducing cell cycle arrest in G_1 (Cooper, 2019; Engeland, 2022; Saldivar et al., 2017). It has been suggested that ATR acts as gatekeeper of the S to G_2 phase transition by sensing ongoing replication and blocking the Cdk1-Forkhead Box (FOX) M1 phosphorylation switch, which in turn is activated once ATR is diminished allowing for transcription of genes needed for the G_2 to M phase transition (Saldivar et al., 2018)(Figure 3).

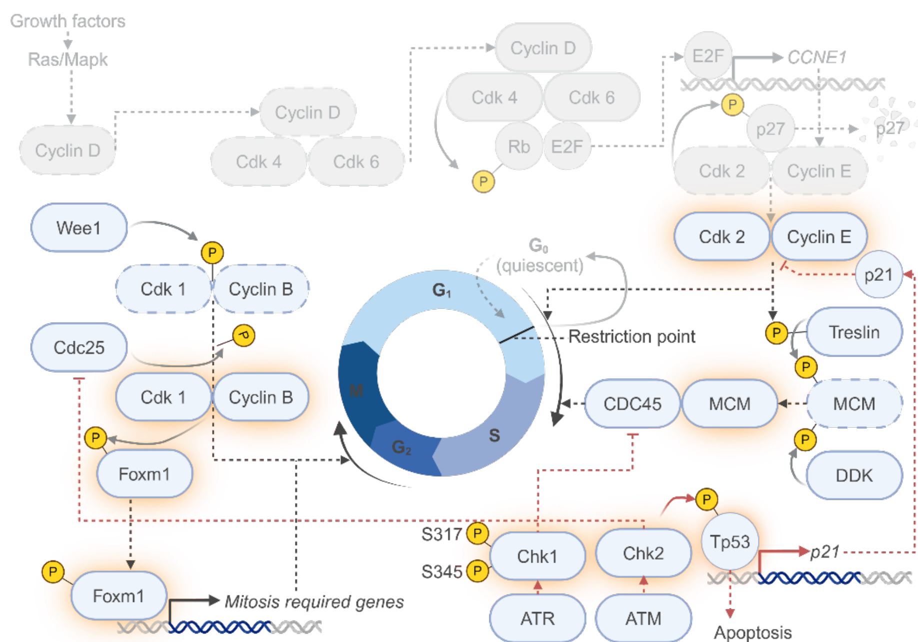

Figure 3. Inhibitory effects of DNA damage on the eukaryotic cell cycle (red). Created in BioRender. Borenäs, M. (2024) BioRender.com/ e21j540.

ATM, ATR, CHK1 and CHK2 constitute, together with PARP and DNA-dependent Protein Kinase (DNA-PK)s, the fundamental components of the DNA Damage Response (DDR) (Ciccia & Elledge, 2010). As well as arresting

the cell cycle upon DNA damage, both ATR and ATM are involved in promoting DNA repair through a variety of mechanisms. At stalled replication forks, i.e. replication stress, RPA coats the exposed single stranded DNA, which through interaction with ATRIP, recruits ATR (Gorecki et al., 2021; Saldivar et al., 2017). The DNA branching in the replication fork attracts RAD9-RAD1-HUS1 (911) which recruits the ATR activator Topoisomerase II Binding Protein 1 (TOPBP1) (Gorecki et al., 2021; Saldivar et al., 2017) (Figure 4). Another activator of ATR is Ewing Tumor Associated Antigen 1 (ETAA1) which interact with RPA directly (Gorecki et al., 2021; Saldivar et al., 2017).

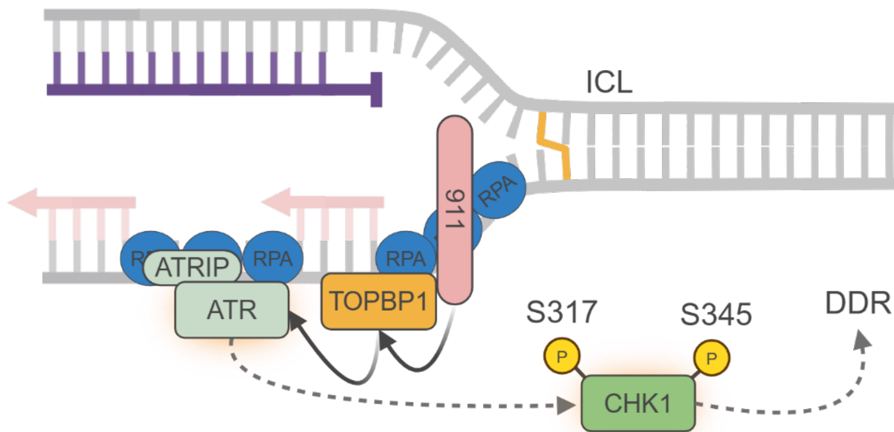

Figure 4. ATR activation mechanisms upon fork stalling. Created in BioRender. Borenäs, M. (2024) BioRender.com/ h85w430. Adapted from Gorecki et al., 2021 under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Furthermore, ATR regulates origin firing by inhibiting CDC45 interaction with helicase complex MCM2-7. MCM2-7 must first be phosphorylated by DB4 Dependent Kinase (DDK) and CDK phosphorylated Treslin for CDC45 to interact with MCM2-7. Once the preinitiation complex, including DNA polymerase, is loaded and MCM2-7 interacted with CDC45, replication can be started (Saldivar et al., 2017) (Figure 3). The recruitment of ATR to stalled replication forks stabilizes them, protecting them from fork collapse (Saldivar et al., 2017). However, if the availability of RPA is low, e.g. due to abundant exposed single stranded DNA, the replication fork may also collapse, resulting in double stranded DNA breaks (Saldivar et al., 2017). The mechanisms for how ATR induce replication restart is not clear, though DNA cleavage through endonucleases with subsequential HR have been suggested as one mechanism.

Interestingly, ATR phosphorylates PALB2 and RPA which are believed to attract RAD51, potentially priming the site for HR repair (Saldivar et al., 2017). PARP1 recognizes double stranded DNA breaks and interacts with ATM at the site of damage resulting in HR through the recruitment of BARD1 and subsequent RAD51 recruitment (Jin & Oh, 2019; Ray Chaudhuri & Nussenzweig, 2017; Roy et al., 2011). Furthermore, PARP1 is also involved in NHEJ, through stimulation of DNA-PK, and in single stranded break repair through detection of the lesion as well as recruitment of the scaffolding protein X-ray Repair Cross Complementing protein 1 (XRCC1) needed for e.g. DNA ligases (Ray Chaudhuri & Nussenzweig, 2017). Crosstalk between the ATM and ATR signaling pathways has been suggested (Bitomsky & Hofmann, 2009; Roos et al., 2016). However, different activation pathways of ATR are still being investigated and unraveled and to date there is no firm evidence of which post translational modifications activate ATR (Cimprich & Cortez, 2008; Saldivar et al., 2017). Still, once activated ATR favor a S/T-Q motif on its target protein where serine or threonine residue is phosphorylated when prior to a glutamine residue (Menolfi & Zha, 2020). CHK1 is posttranslational modified by ATR through phosphorylation on S317 and S345 which is required to activate CHK1 and thus inducing cell cycle arrest (Panagopoulos & Altmeyer, 2021; Saldivar et al., 2017) (Figure 3).

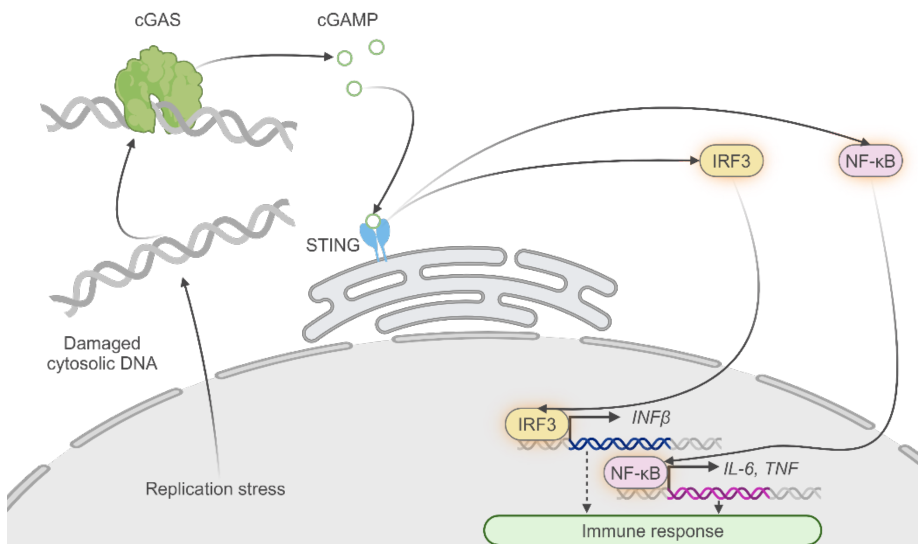

Figure 5. cGas-STING pathway and its downstream effectors. Created in BioRender. Borenäs, M. (2024) BioRender.com/ i27q453. Adapted from Zheng et al., 2020 under under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Replication stress can also result in leakage of double stranded DNA into the cytoplasm which interacts with cyclic GMP–AMP Synthase (cGAS) resulting in the production of 2′3′ cyclic GMP–AMP (cGAMP) which will activate Stimulator of Interferon Genes (STING) (Decout et al., 2021; Zheng et al., 2020) (Figure 5). Activated STING will ultimately result in activation of the transcription factors Interferon Regulatory Factor (IRF) 3 and Nuclear Factor κB (NF-κB) and the subsequent production of cytokines and recruitment of the immune system (Decout et al., 2021; Motwani et al., 2019; Zheng et al., 2020) (Figure 5).

1.2 CELL SIGNALING

1.2.1 OVERVIEW OF CELL SIGNALING

In multicellular organisms, cells need to communicate with one another in order for the organism to adapt to external or internal stimuli. There are several ways for a cell to communicate with other cells or the environment, either through cell-cell interactions, cell-matrix interactions, through signaling molecules or extracellular vesicles (Cooper, 2019; Yanez-Mo et al., 2015) (Figure 6).

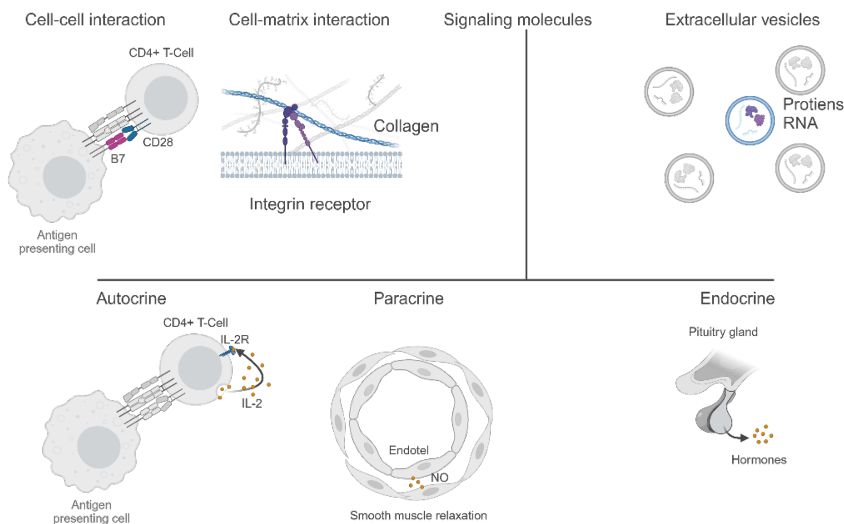

Figure 6. Schematic overview of cell communication. Created in BioRender. Borenäs, M. (2024) BioRender.com/ i54f958.

Examples of cell-cell interactions are found between antigen presenting cells and $CD4^+$ T-cells, where interaction between the surface protein Cluster of Differentiation (CD) 28 on the T-cell and B7 on the antigen presenting cell is part of the activation pathway of the $CD4^+$ T-cell and in gap junctions where small molecules and ions are allowed to move between cells (Goodenough & Paul, 2009; Lee et al., 2020; Sharpe & Freeman, 2002). Cell-matrix interactions are typically represented by integrins which attach the cell to the matrix (Cooper, 2019). Signaling molecules can be as complex as proteins or something as simple as gases. The signaling molecule can be transmitted by a cell to targets located very close or far away in the organism. Therefore, signaling through molecules can be divided into autocrine, paracrine and endocrine signaling. For example, autocrine signaling is seen in $CD4^+$ T-cells which upon antigen presentation upregulate Interleukin (IL)-2R as well as secreting IL-2 which signals through the receptor to initiate proliferation (Mak et al., 2011). Paracrine signaling is exemplified by diffusion of nitrous oxide during the relaxation of blood vessels while endocrine signaling is typically over greater distances such as hormones carried by the blood circulation to their targets (Cooper, 2019; Guyton & Hall, 2006; Lundberg & Weitzberg, 2022).

1.2.2 SIGNALING MOLECULES

Steroid hormones, which are part of the endocrine signaling system, are lipophilic and are able to diffuse through the cell membrane, reaching their receptors which, when activated, act as transcription factors (Beato & Klug, 2000; Berg et al., 2007). The mechanism by which steroid hormones act contrasts with gases, such as nitrogen oxide, which also acts on targets located inside the cell. In this case, instead of activating a receptor, nitrogen oxide chemically modifies, by nitrosylation, target enzymes such as soluble Guanylyl Cyclase (sGC) rendering them active to produce cyclic Guanosine Monophosphate cGMP that triggers an intracellular response (Lundberg & Weitzberg, 2022).

Many signaling molecules are unable to pass the cell membrane and require cell surface receptors to transduce an intracellular response through signaling pathways. In addition to the above-mentioned steroid hormones and gases, neurotransmitters, peptide hormones, neuropeptides, cytokines and growth factors all work as signaling molecules. Many of the neurotransmitters, exemplified by acetylcholine, act on ligand-dependent ion channels while other neurotransmitters, such as dopamine, act through G-protein coupled

receptors (Cooper, 2019; Purves, 2018). Peptide hormones, in contrast to steroid hormones, are a complex family that are composed of amino acids. Insulin is one example of a peptide hormone (Wilcox, 2005). Growth factors, and cytokines which affect blood cells, are polypeptides that regulate differentiation among their target cells (Cooper, 2019).

1.2.3 CELL SURFACE RECEPTORS

There are different types of cell surface receptors where the majority can broadly be classified into six different groups; ligand-gated ion channels, G-protein coupled receptors, receptor tyrosine kinases, cytokine receptor superfamily, integrin receptors and receptor serine/threonine kinases (Cooper, 2019) (Figure 7).

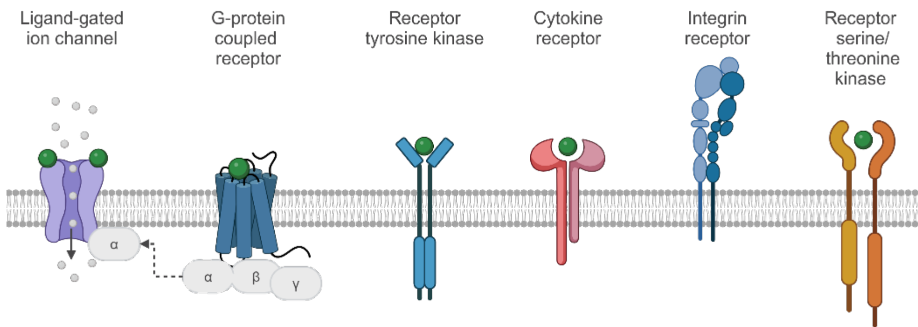

Figure 7. Schematic overview of different cell surface receptors. Created in BioRender. Borenäs, M. (2024) BioRender.com/ s11d314.

Ligand-gated ion channels are channels that are opened when ligands, such as neurotransmitters, attach to the channel, opening it and allowing for ion flux (Hucho & Weise, 2001). Ion channels can also be regulated by G proteins through activation of G-protein coupled receptors (Cooper, 2019). G-protein coupled receptors span the cell membrane with seven α helices and undergo conformational changes upon ligand binding that activate small G proteins, triggering an intracellular signaling cascade that recruits transcription factors to the nucleus to induce a cellular response (Neves et al., 2002; Oldham & Hamm, 2008). The human receptor tyrosine kinase superfamily comprises 58 different receptors, that can be subdivided into 20 subfamilies, which all have in common a single helix spanning the cell membrane, as well as an tyrosine kinase that is found in the intracellular region (Lemmon & Schlessinger, 2010). The active part of the tyrosine kinase domain of the receptor phosphorylates target proteins on tyrosine residues (Cadena & Gill, 1992). Similarly, ligand

binding of cytokine receptors leads to phosphorylation of tyrosine residues, though the tyrosine kinase is not an intrinsic part of the receptor as seen with the receptor tyrosine kinases. Instead, the tyrosine phosphorylation is carried out by Janus Kinase (JAK) cytoplasmic tyrosine kinases, closely associated with the cytokine receptor, that will phosphorylate the associated cytokine receptor rendering the receptor active for further intracellular signaling (Leonard & Lin, 2000). Integrins, responsible for the adhesion of cells to the extracellular matrix, accumulate upon matrix binding inducing auto-phosphorylation of Focal Adhesion Kinase (FAK) which in turn will attract the tyrosine kinase Src for further signal transduction (Cooper, 2019; Cooper & Giancotti, 2019; Mitra & Schlaepfer, 2006). Receptor serine/threonine kinases can be divided into two types, type I and type II, where a heterodimer consisting of one type I and one type II receptor is formed upon ligand biding. Ligands binding to the type I and type II receptors belong to the Transforming Growth Factor (TGF)-β family. The type II receptor in the heterodimer complex then phosphorylates serine and threonine residues on the type I receptor for further signal propagation (Moustakas et al., 2006; Piek et al., 1999) (Figure 8). In contrast to the receptor tyrosine kinases, cytokine receptors and serine/threonine kinases, receptor like tyrosine phosphatases dephosphorylate their substrates and hence work as an counter weight to kinase receptors (Tonks, 2006).

1.2.4 INTRACELLULAR SIGNALING PATHWAYS

Activation of receptors, located in the cytoplasm, nucleus or cell surface, initiates intracellular signal cascades that mediate a cellular response to external stimuli. Decades of biological research have led to the extensive mapping of signaling pathways. Some of the most well studied are presented here with extra focus on signaling pathways associated with receptor tyrosine kinases. As previously mentioned, cytokine receptors, as well as integrins, are associated with intracellular tyrosine kinases. Ligand binding to cytokine receptors attract JAKs which will phosphorylate intracellular regions of the cytokine receptor. The phosphorylation sites function as docking sites for Signal Transducer and Activator of Transcription (STAT) that will be phosphorylated by JAK once they are associated with the receptor. After phosphorylation of tyrosine residues on STATs, STATs will dissociate from the receptor and enter the nucleus as dimers binding to promotor sites initiating transcription (Hu et al., 2021).

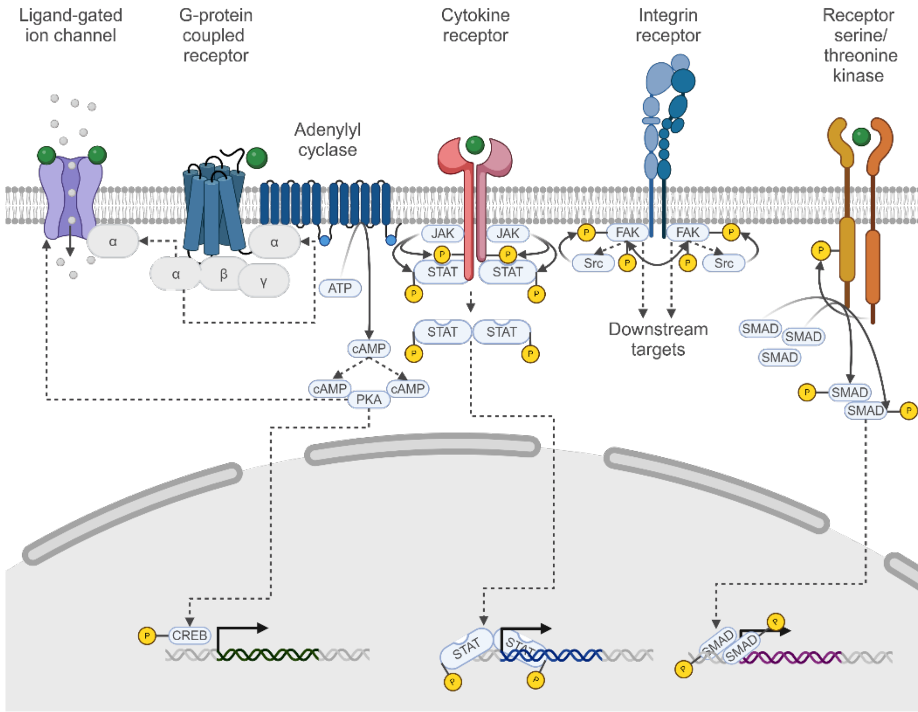

Figure 8. Schematic overview of signaling events upon ligand binding. Created in BioRender. Borenäs, M. (2024) BioRender.com/ e49d375.

Direct phosphorylation by the surface receptor on a transcription factor can also be seen in the TGF-β-SMAD pathway. Phosphorylation of serine and threonine residues on the type I receptor, by the receptor II type in the serine/threonine receptor complex, will induce signal propagation through phosphorylation of SMAD which will relocate to the nucleus where SMAD will initiate transcription of target genes (Cooper, 2019; Derynck & Zhang, 2003). G-protein coupled receptors will upon ligand binding activate the associated G-protein which consists of the α subunit and the βγ complex subunit. The α subunit and the βγ subunit can regulate ion channels directly as well as the activity of adenylyl cyclase which produces cyclic Adenosine Monophosphate (cAMP) that can activate Protein Kinase A (PKA). PKA can act on ion channels but also activate downstream enzymes or transcription factors. Cyclic-AMP Responsive Element Binding protein CREB is one example of downstream PKA activated transcription factor that will, upon activation, bind to the CRE segment inducing transcription (Cooper, 2019; Rosenbaum et al., 2009; Weis & Kobilka, 2018) (Figure 8).

For most receptor tyrosine kinases, ligand binding induces receptor dimerization leading to autophosphorylation of the receptor. The phosphorylation of the cytosolic part of the receptor results in increased kinase activity of the catalytic domain but also creating docking sites for proteins that contain Src Homology 2 (SH2) domains which will convey the signal further downstream. Growth factor Receptor-Bound protein (GRB) 2 is an adapter protein with a SH2 domain that binds to the docking sites of autophosphorylated receptor tyrosine kinases recruiting Son Of Sevenless (SOS), a guanine nucleotide exchange factor, which in turn will activate the small Guanosine Triphosphate hydrolase (GTPase) RAS. RAS is anchored to the cytosolic part of the cell membrane and upon activation activates the serine/threonine kinase RAF. RAF activation results in activation and translocation of ERK to the nucleus where it will activate transcription factors inducing cell survival, differentiation and proliferation (Cooper, 2019; Lemmon & Schlessinger, 2010; Wee & Wang, 2017; Weinberg, 2014) (Figure 9).

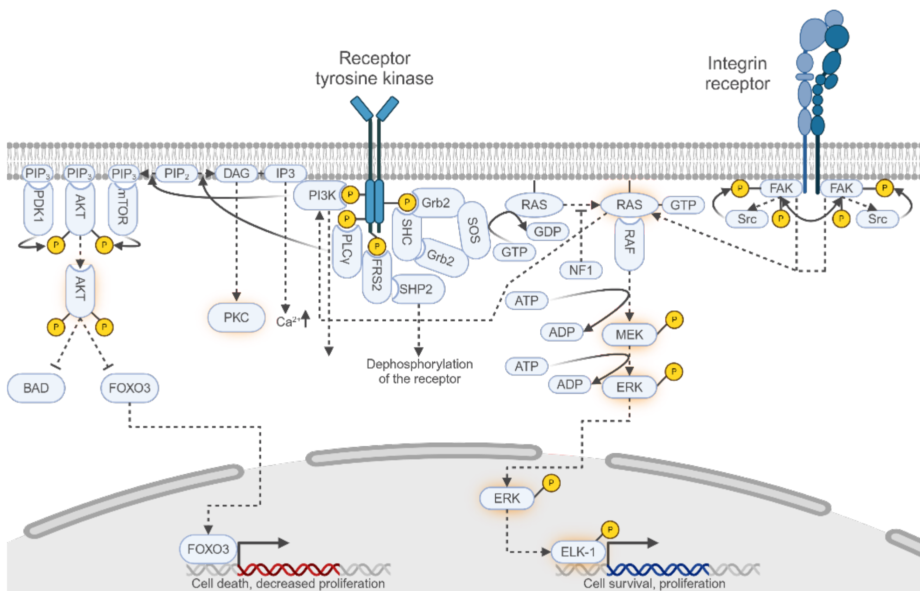

Figure 9. Overview of signaling pathways associated with receptor tyrosine kinases. Created in BioRender. Borenäs, M. (2024) BioRender.com/ u72p232. Adapted from Wee & Wang, 2017 under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

RAS can also be activated through the FAK/Src complex, linking integrins to gene regulation (Weinberg, 2014). Receptor tyrosine kinases activate the

Phosphatidylinositide 3 Kinase (PI3K) /AKT pathway through RAS activation or through interacting with the SH2 domain of PI3K which in turn will phosphorylate Phosphatidylinositol 4,5-biphosphate (PIP2), located in the cytosolic part of the cell membrane, generating Phosphatidylinositol 3,4,5 triphosphate (PIP3). PIP3 interacts with mammalian Target Of Rapamycin (mTOR)C2 and Pyruvate Dehydrogenase Kinase 1 (PDK1) as well as AKT. AKT is activated by mTORC2 and PDK1 allowing AKT to inhibit apoptosis and cell death through BCL2 Associated Agonist of cell Death (BAD) and FOXO (Cooper, 2019; Wee & Wang, 2017; Weinberg, 2014). AKT can also influence protein synthesis through the mTOR pathway, thus coupling growth factors to translation (Cooper, 2019). Moreover, SHC, also containing a SH2 domain, can bridge the interaction between the receptor tyrosine kinase and GRB2 (Weinberg, 2014). Phospholipase C-γ (PLC-γ), which also contains a SH2 domain and hence able to interact with the intracellular domain of receptor tyrosine kinases, can cleave PIP2 into Diacylglycerol (DAG) and Inositol (1,4,5)-triphosphate (IP3) ultimately leading to activation of the serine/threonine Protein Kinase C (PKC), a key intracellular effector (Weinberg, 2014). FGF Receptor Substrate-2 (FRS2) will detect and interact with phosphorylated sites on the intracellular part of the receptor tyrosine kinase leading to the phosphorylation of FRS2 by the receptor (Lemmon & Schlessinger, 2010). Activated FRS2 will recruit GRB2 and SH2-containing tyrosine Phosphatase 2 (SHP2), where SHP2 will dephosphorylate the receptor (Lemmon & Schlessinger, 2010) (Figure 9).

1.3 ONCOGENES AND TUMOR SUPRESSOR GENES

For a substantial part of the 20th century tumor formation was thought to be caused by viruses or by endogenous proviruses. However, only a few human cancer types, such as cervical carcinoma caused by human papilloma virus, have been shown to arise due to virus infections (Schiller & Lowy, 2014). Later, through the discovery of oncogenes, cancer formation was linked to genetic alterations in tumor cells. Proto-oncogenes are genes with normal cellular function that have the potential to become oncogenic upon genetic alterations such as amplification, point mutation, translocation and deletion leading to overexpressed proteins, constitutive active proteins, hybrid proteins or truncated proteins. Proto-oncogenes typically encode proteins that control differentiation and cell growth and are thus frequently involved in signaling pathways (Weinberg, 2014). From previous sections we can identify several

proto-oncogenes entities such as receptors, intracellular enzymes and transcription factors where unregulated activity can lead to uncontrolled cell growth and proliferation. One example of proto-oncogenes is Src, which was the first described tyrosine kinase, identified in Rous sarcoma virus (Hunter & Sefton, 1980). Another proto-oncogene is Epidermal Growth Factor Receptor (EGFR), which was first described as v-erbB in the avian erythroblastosis virus. Here the viral erbB oncogenic counterpart is truncated resulting in constitutive activation of downstream signaling (Downward et al., 1984). One oncogene of special interest, in the scope of this thesis, is the oncogene v-sis identified in simian sarcoma virus that causes cancer in monkeys (Doolittle et al., 1983; Theilen et al., 1971). V-sis was shown to have very similar sequence to the PDGF-B ligand and cells infected with v-sis produce high amounts of PDGF driving oncogenesis through autocrine signaling (Deuel et al., 1983; Doolittle et al., 1983; Heldin, 2012; Johnsson, Betsholtz, Heldin, et al., 1985; Johnsson, Betsholtz, von der Helm, et al., 1985; Waterfield et al., 1983).

Tumor suppressor genes serve, contrary to oncogenes, a protective function against developing malignancies. However, if the function of the suppressor gene is lost, so also is the protective function, thus allowing malignancy development. RB is a famous example of a tumor suppressor gene and also the gene described when Knudson introduced the “two-hit hypothesis” (Goodrich, 2006; Knudson, 1971). Tumor suppressor genes are on a cellular level recessive. An inherited unfunctional RB allele can, by loss of heterozygosity through for example mitotic recombination or deletion of the normal allele, become homozygote or hemizygote respectively, allowing for tumor formation (Weinberg, 2014).

1.4 TRADITIONAL AND NOVEL TREATMENT REGIMES IN MALIGNICIES

1.4.1 OVERVIEW OF TRADITIONAL TREATMENTS IN MALIGNANCIES

Traditional treatments of malignancies can broadly be divided into chemotherapy, radiation therapy and surgery. Agents used during chemotherapy can be subdivided based on their mechanism of action.

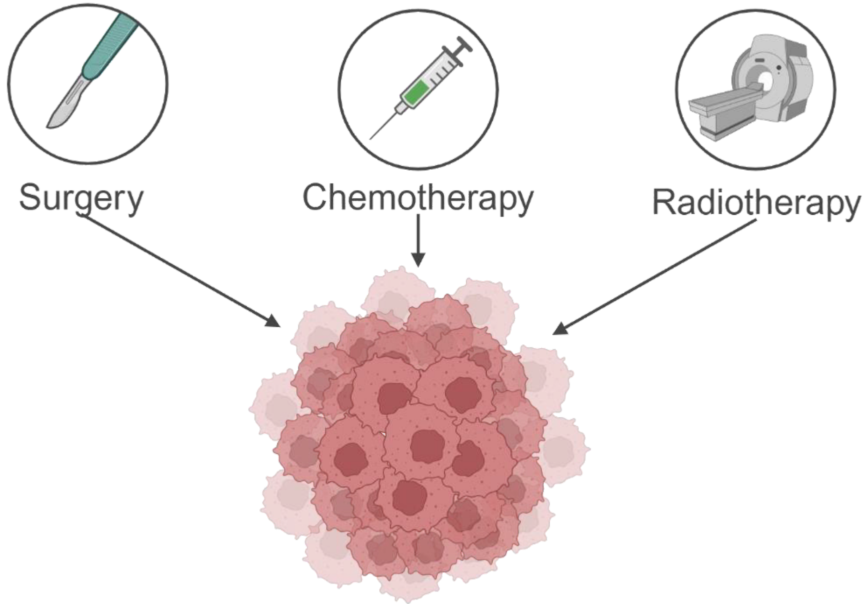

Figure 10. Traditional treatment regimes in cancer management. Created in BioRender. Borenäs, M. (2024) BioRender.com/ k34g326.

Alkylating agents operate through the transfer of alkyl groups onto DNA, introducing intrastrand or interstrand crosslinks inflicting novel mutations or blocking replication (Fu et al., 2012). Other cytotoxic agents that work in a similar fashion to alkylating agents are platinum-based agents that crosslink DNA through platination of the DNA (Dilruba & Kalayda, 2016). Antimetabolites, such as fluorouracil inhibiting thymidylate synthase, on the other hand, disrupt the synthesis of DNA and nucleotides through inhibition of the synthesis of DNA, purine, pyrimidines and folate derivatives or through incorporation of non-functional nucleotide base analogs (Anand et al., 2023). Some of the drugs used within chemotherapy are natural products, meaning they come from plants, bacteria, molds or animals (Weinberg, 2014). Antibiotics are natural products that are also used in an anti-tumor setting (Gao et al., 2020). From the world of flora, agents such as topoisomerase inhibitors and modulators of tubulin, which inhibit DNA unwinding and normal microtubular polymerization respectively (inhibiting mitotic division), have been discovered and used in an antitumor setting in the clinic (Anand et al., 2023).

As with chemotherapy, radiation therapy aims to cure the patient or to shrink the tumor as much as possible before surgery. Radiation therapy utilizes ionizing beams (photon, electron, neutron or proton beams) to induce DNA damage by introducing double or single stranded DNA breaks (Baskar et al., 2012; Borrego-Soto et al., 2015). Ionizing damage can either be delivered by an external source, such as an external beam, or could be delivered to cells through nuclide labeled compounds such as chemical elements needed for metabolism or signaling molecules and antibodies directing the radiation to tumor cells (Goldenberg & Sharkey, 2007; Gudkov et al., 2015; Kayano & Kinuya, 2018).

Chemotherapy and radiotherapy are associated with direct as well as late side effects including infertility, hematological toxicities, cardiotoxicity, neurotoxicity, hepatotoxicity, nephrotoxicity and secondary malignancies (Meirow & Nugent, 2001; van den Boogaard et al., 2022). Neutropenic fever, a life-threatening condition associated with chemotherapy, has been reported at rates as high as approximately 50% during chemotherapy and treatment related death due to infection has been reported at rates as high as 10% of treated patients (Blay et al., 1996; Bow, 1998; Crawford et al., 2004; Gomez et al., 1998). Furthermore, among children it has been reported that treatment related deaths associated with infections account for up to approximately 3 % (Boccia et al., 2022; Loeffen et al., 2019). Children are an especially vulnerable group since chemotherapy and radiotherapy are associated with secondary malignancies during later life. Indeed, an almost 14 times higher overall risk of developing secondary malignancies was reported among children treated for Acute Lymphoblastic Leukemia (ALL) (Hijiya et al., 2007).

To avoid selection of tumor cells that are inherently resistant to the compound, several compounds, with different modes of action, are usually administrated (Weinberg, 2014). Unfortunately, with time, drug resistance in cancer therapy is a common problem that accounts for up to 90% of deaths among cancer patients (Bukowski et al., 2020). Resistance to chemotherapy includes increased enzymatic inactivation of the drug, increased outflow of the drug, altered composition of the target protein, increased capacity to repair DNA, resistance to apoptosis, increased growth factor signaling in the tumor milieu or circumvention of the target protein through alternative pathways (Allocati et al., 2018; Bukowski et al., 2020; Cermak et al., 2020; Luqmani, 2005; Sever & Brugge, 2015; Wang & Lippard, 2005). These characteristic resistance traits are acquired through increasing expression of genes, epigenetic alterations,

activating or inactivating mutations, amplifications and loss of tumor suppressor genes (Bukowski et al., 2020; Luqmani, 2005).

1.4.2 OVERVIEW OF NOVEL TREATMENTS IN MALIGNANCIES

In addition to the more traditional treatment regimens of cancer, novel strategies have emerged spanning a wide range of mechanisms (Figure 11). Some of the novel cancer management regimes are presented here.

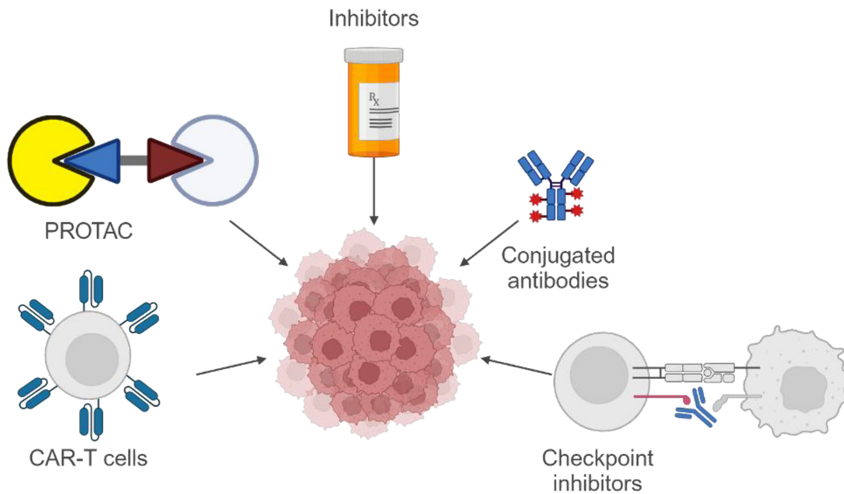

Figure 11. Examples of novel treatment regimes in cancer management. Created in BioRender. Borenäs, M. (2024) BioRender.com/ n29z936.

There are novel ways of delivering chemotherapeutic agents, through for example nanoparticles which allow for better bioavailability, with some delivery systems being more promising than others (Senapati et al., 2018). Other examples of delivery systems are through antibodies, signaling analogs or hormone analogs which, when radiolabeled, will induce DNA damage through ionizing rays (Imhof et al., 2011; Kayano & Kinuya, 2018; Larson et al., 2015). In addition to radiolabeling, antibodies can be conjugated with compounds belonging to the chemotherapeutic regime (such as topoisomerase inhibitors or microtubule inhibitors), toxins derived from plants or bacteria (for example Pseudomonas exotoxin A, moxetumomab which was discontinued in 2023) or cytokines (such as IL-2) (Paul et al., 2024; Raeber et al., 2023; Scott et al., 2012). Antibodies, both mono- and bispecific, can also be used, in an unconjugated form, to block surface receptors (such as receptor tyrosine

kinases Human Epidermal growth factor Receptor (HER) 2 or MET and EGFR) or to guide Natural Killer (NK)-cells, macrophages and T-cells to the antigen expressing cells, ideally tumor cells (Paul et al., 2024; Scott et al., 2012). Furthermore, antibodies can be used as immune checkpoint inhibitors, where antibodies against Cytotoxic T-Lymphocyte Associated protein (CTLA) 4 and Programmed cell Death (PD)-1/Programmed cell Death Ligand (PD-L)1 are clinically available (Shiravand et al., 2022). CTL4A is expressed on the surface of T-cells (CD8+ and CD4+) and competes with CD28 for the interaction of B7 on the antigen presenting cell (Mak et al., 2011; Sharma et al., 2021). CTLA4 has much higher affinity towards CD28 compared to B7 and will eventually be victorious, which will lead to decreased T-cell activation (Mak et al., 2011; Sharma et al., 2021). However, CTLA4 is expressed on the surface of activated T-cells and peaks after a few days, allowing the T-cells to perform their duty during this time (Mak et al., 2011; Sharma et al., 2021). Antibodies against CTLA4 allow the activated T-cell to maintain its activity (Hoos, 2016; Paul et al., 2024; Sharma et al., 2021; Shiravand et al., 2022). PD-1, expressed by T-cells, interacts with PD-L1 which is normally expressed on peripheral tissue to lower the activity of T-cells thus protecting the peripheral tissue from T-cell attack (Chamoto et al., 2023; Paul et al., 2024; Sharma et al., 2021). Unfortunately, a variety of cancers also exhibit PD-L1, allowing the tumor cells to evade the immune response (Chamoto et al., 2023; Paul et al., 2024; Sharma et al., 2021). Sustained tumor responses, over 3 years, have been seen in approximately 20% of metastatic melanoma when treating with monotherapy anti CTLA4 while an objective response rate of approximately 20% was seen when investigating 26 different malignancies that had received PD-1/PD-L1 targeting (Paul et al., 2024; Sharma et al., 2021; Zhao et al., 2020). However the objective response rates varies with expression of PD-L1 and cancer type (Zhao et al., 2020). Another way to utilize the inherent immune system is to optimize the patient's own (or a doners) lymphocytes through Chimeric Antigen Receptor (CAR)-T cell engineering (Zhang et al., 2017). Here, T-cells are genetically modified, with a synthetic receptor, against an antigen expressed by the tumor which will direct and active the T-cell (Sadelain et al., 2013; Sterner & Sterner, 2021). Furthermore, vaccines allow for immune system activation through administration of tumor associated antigens to the patient (M. J. Lin et al., 2022; Saxena et al., 2021). CAR-T cells are genetically modified, though there are other gene therapies that can be utilized in cancer therapy, one of which is silencing of oncogenes through Ribonucleic Acid interference (RNAi) which is being evaluated in several clinical trials (Cesur-Ergun & Demir-Dora, 2023; Sun et al., 2019).

Separate from the immune system modulators just described are the small molecule targeted therapies, which are typically inhibitors. Inhibitors mainly target oncoproteins that are involved in signaling pathways driving the tumor cell (Bedard et al., 2020; Zhong et al., 2021). There are numerous inhibitors used in the clinic including inhibitors against kinases and DNA damage repair proteins exemplified by CDK4/6, PARP, HER2, Fibroblast Growth Factor Receptor (FGFR), PI3K, JAK2, EGFR, Anaplastic Lymphoma Kinase (ALK) and MAPK/ERK Kinase (MEK) inhibitors just to mention a few (Zhong et al., 2021). Endocrine therapy can also inhibit proliferation, treatment of NET patients being one example, where the antiproliferative effect of somatostatin is exploited (Stueven et al., 2019). Another regime to stop malignant signaling is by Proteolysis-Targeting Chimera (PROTAC)s, exploiting the cells inherent Ubiquitin–Proteasome System (UPS) and hijacking the E3 ligase through a linker molecule with a ligand binding the E3 ligase in one end and a ligand binding the protein of interest in the other end, resulting in ubiquitination and subsequent degradation of the protein of interest (Bekes et al., 2022).

Similar to the more traditional tumor therapies, novel cancer therapies are also associated with resistance and side effects. Checkpoint inhibitors are associated with resistance through neo-antigens of the tumor cells and T-cell exhaustion while side effects include fatal myocarditis and immune adverse events (Blank et al., 2019; Escudier et al., 2017; Jenkins et al., 2018; Johnson et al., 2016; Johnson et al., 2022; Moslehi et al., 2018; Wang et al., 2018). Fatal events are seen in up to 1.3% of patients, while immune adverse events and chronic immune adverse events are seen in up to 60% and 40% respectively (Johnson et al., 2022; Wang et al., 2018). CAR-T cells have shown unprecedented results in treating hematological malignancies, however the treatment is limited by resistance (antigen escape), side effects, cost, manufacturing time (up to 35 days) of the T-cells and inadequate solid tumor penetration (Cappell & Kochenderfer, 2023; Mitra et al., 2023; Sterner & Sterner, 2021). Adverse effects include cytokine release syndrome, “on-target off-tumor” effects and immune effector cell-associated neurotoxicity syndrome (Mitra et al., 2023; Sterner & Sterner, 2021). Cytokine release syndrome, which may be manifested through fever, cardiac dysfunction, hypotension, organ failure or circulatory collapse, is potentially life threatening and is seen in up to 93% of CAR-T cell treated patients (Lee et al., 2019; Sterner & Sterner, 2021). Targeted therapy with small molecule inhibitors is also associated with side effects and resistance. Side effects related to small molecule inhibitors are dependent on the normal expression and function of the target protein and how target specific the inhibitor is. Side effects related

to small molecule inhibitors will be addressed in a later section, when ALK inhibitors are discussed. Focusing on small molecule kinase inhibitors, redundancy and crosstalk between signaling pathways allows resistance to be developed through circumventing the targeted protein thus maintaining malignant signaling (Sever & Brugge, 2015; Zhong et al., 2021). Resistance can also develop through mutations or amplification of the target protein, rendering the target binding domain unrecognizable by the drug or the target protein becoming abundant (Bedard et al., 2020; Bukowski et al., 2020; Zhong et al., 2021). Resistance mechanisms, in regard to ALK, will be further highlighted in later sections.

1.5 NEUROBLASTOMA

1.5.1 OVERVIEW OF NEUROBLASTOMA

Neuroblastomas constitute 4-10% of childhood cancers but simultaneously account for a disproportional amount, 10-15%, of cancer deaths among children (Lähteenmäki/SBCR, 2020; Park et al., 2013; Park et al., 2010; Ries & SEER Program (National Cancer Institute (U.S.)), 1999; Stiller & Parkin, 1992). The average age of diagnosis is approximately 2 years, with incidence rates peaking at 64 per million cases before the age of one making neuroblastoma the most common diagnosed cancer of infancy (Howlader N, 2021; London et al., 2005; Qiu & Matthay, 2022; Ries & SEER Program (National Cancer Institute (U.S.)), 1999). Neuroblastoma is believed to arise during the development of neural crest cells into either the transitional Schwann cell precursors, that will differentiate into sympathoblasts and chromaffin cells of the adrenal gland, or directly into sympathoblasts located outside the adrenal gland (Kameneva et al., 2021; Matthay et al., 2016; Qiu & Matthay, 2022; Wright, 1910). Thus, neuroblastoma is frequently found in tissues derived from the neural crest such as the adrenal glands and the sympathetic chain (Maris, 2010; Qiu & Matthay, 2022) (Figure 12). The clinical course is very heterogeneous, with some patients displaying severe metastasis that spontaneously regresses while others have refractory neuroblastoma that is resistant to multimodal therapy (D'Angio et al., 1971; Maris, 2010; Matthay et al., 2016; Qiu & Matthay, 2022).

1.5.2 RISK STRATIFICATION AND GENETIC LANDSCAPE OF NEUROBLASTOMA

Clinical features and biomarkers have been identified that are associated with neuroblastoma patient outcome resulting in several risk classification systems that are in use worldwide (Sokol & Desai, 2019). In 2009, the International Neuroblastoma Risk Group (INRG), presented a risk classification system as well as a staging system with the aim of unifying existing risk stratification systems (Cohn et al., 2009; Monclair et al., 2009; Sokol & Desai, 2019). The INRG staging system (INRGSS) bases its staging system on imaging in contrast to degree of surgical resection of the tumor previously employed, allowing risk classification before treatment (Brodeur et al., 1988; Monclair et al., 2009; Sokol & Desai, 2019). The INRG classification system considers factors such as INRG stage, age, histologic category, grade of tumor differentiation, *MYCN* status, 11q status and ploidy (Cohn et al., 2009).

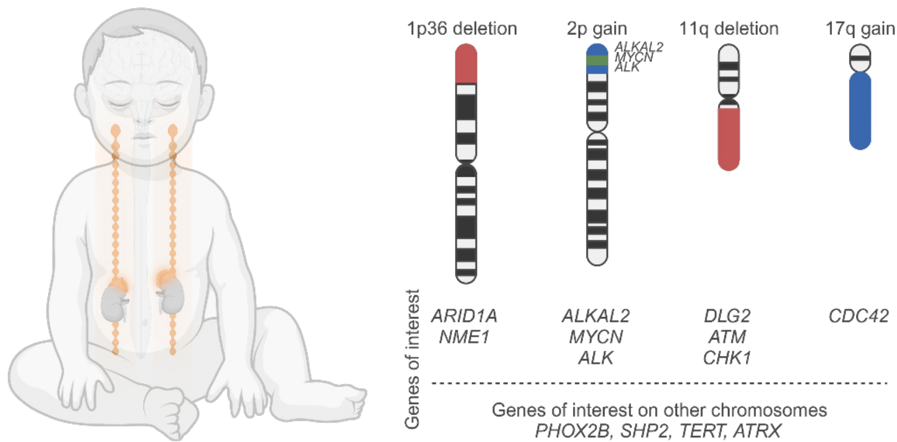

Figure 12. Typical locations of neuroblastoma formation (sympathetic trunk and adrenal glands in orange). Common chromosomal aberrations seen in neuroblastoma together with examples of genes of interest on corresponding chromosomes. Created in BioRender. Borenäs, M. (2024) BioRender.com/ k00z589. Adapted from Guan et al., 2021 under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

INRG classification defines risk groups based on the mentioned factors and 5 years Event Free Survival (EFS), generating very low-,low-, intermediate- and high-risk groups where the high-risk group has a 5 year EFS below 50% (Cohn et al., 2009). Unfortunately, the high-risk group constitute approximately 36% of the patient population, this can be compared to the Children's Oncology

Group's (COG) risk stratification where approximately 58% of the patients are classified as high-risk (Cohn et al., 2009; Park et al., 2013).

There are several other biomarkers, either disregarded at the time of, or discovered and systematized after the INRG classification system was introduced. One biomarker included in the INRG classification system is 11q deletion which is associated with high risk (Cohn et al., 2009). During the 1990s, chromosome 11 aberrations, including loss of 11p and 11q regions, total loss of chromosome 11 and translocation of 11q to 1p, were reported in neuroblastoma (Srivatsan et al., 1993). The potential importance of 11q in neuroblastoma has been shown in neuroblastoma cell lines where transfer of chromosome 11 resulted in increased differentiation (Bader et al., 1991). 11q LOH or partial loss are seen in 17-50%, frequently associated with non-MYCN amplified neuroblastoma cases, and are linked with worse outcome (Attiyeh et al., 2005; Caren, Erichsen, et al., 2008; Guan et al., 2021; Maris, Guo, White, et al., 2001; Mlakar et al., 2017; Siaw et al., 2020). Patients with 11q deletions have similar survival rates as *MYCN* amplified patients, though later onset, and in the unusual event of harboring both 11q deletion and *MYCN* amplification, prognosis is dismal (Caren et al., 2010; Siaw et al., 2020; Spitz et al., 2006).

Several genes have been suggested to be important in 11q deletion, including Discs Large MAGUK scaffold protein (*DLG) 2, ATM, CHK1, H2AFX* and SH3 and multiple Ankyrin repeat domain (*SHANK) 2* (Guan et al., 2021; Mlakar et al., 2017). *MYCN* amplification is another biomarker included in the INRG classification system which is a cornerstone of high risk neuroblastoma detected in approximately 20% (16-38%, also including gain of *MYCN* in some studies) of neuroblastoma cases and associated with poor prognosis (Brodeur et al., 1984; Cohn et al., 2009; Javanmardi et al., 2020; Matthay et al., 2016; Seeger et al., 1985). *MYCN* will be addressed in more detail in a later section.

Chromosome 1 aberrations are concentrated as 1p36.2-1p36.3 deletions, detected in 25-35% of neuroblastoma cases, and highly associated with *MYCN* amplification (Huang & Weiss, 2013; Maris, Guo, Blake, et al., 2001; White et al., 2005). During the 1990s there were mixed reports on 1p deletions' correlation with outcome, however later reports, with greater patient numbers, established that 1p36.3 deletion correlates with lower event free survival and overall survival (Attiyeh et al., 2005; Caron et al., 1996; Gehring et al., 1995; Maris, Guo, Blake, et al., 2001; Maris et al., 1995; Rubie et al., 1997; Schleiermacher et al., 1996). Several tumor suppressors genes within the 1p deletion region have been reported including AT-Rich Interaction Domain

(*ARID)1A,* Calmodulin binding Transcription Activator *(CAMTA)1,* Chromodomain Helicase DNA binding protein *(CHD)5* and Kinesin Family member (*KIF)1B* (Guan et al., 2021). The chromatin remodeling *ARID1A* displayed earlier tumor formation and tumor penetrance in zebrafish when the *ARID1A* orthologs are deleted (Shi et al., 2020). Moreover, *Arid1a* has been suggested to be a MYCN associated tumor suppressor in neural crest cells among mice and *ARID1A/ARID1B* are aberrant in approximately 11% of neuroblastoma patients and associated with worse outcome (Garcia-Lopez et al., 2020; Sausen et al., 2013). However, 1p deletions were not included in the INRG classification system due to displaying excellent overall survival within their cohort, though there was significant lower event free survival in the 1p aberration group compared to normal 1p (Cohn et al., 2009). It should also be noted that 1q gain has been suggested as possible biomarker in localized neuroblastoma (Pezzolo et al., 2009).

2p gain or amplification (where gain indicates more than 2 but less or equal to 8 copy number and amplification is 9 copies or more) is seen in approximately 30% of neuroblastoma cases (Javanmardi et al., 2020). 2p gain has previously been shown to have similar event free survival as well as overall survival when compared to *MYCN* amplified patients (Jeison et al., 2010; Szewczyk et al., 2019). Interestingly, loci encoding ALK, its ligand ALK And LTK ligand (ALKAL)2 and MYCN are all located on the p arm of chromosome 2, raising the question whether tumors with 2p gain might benefit from ALK inhibition (Guan et al., 2021; Javanmardi et al., 2020).

3p deletion is detected in approximately 20% of neuroblastoma cases and is associated with 11q aberrations and hence inversely associated with *MYCN* amplification (Breen et al., 2000; Ejeskar et al., 1998; Spitz et al., 2003; Vandesompele et al., 1998). Potential tumor suppressor genes, in the deleted region, have been investigated in neuroblastoma as well as in other cancers (Nair et al., 2007).

17q gain is frequently observed in neuroblastoma, present in approximately 50-70%, though have been reported in up to 96% of the cases, and associated with lowered survival (Guan et al., 2021; Mosse et al., 2007; Plantaz et al., 1997; Schleiermacher et al., 2012; Siaw et al., 2020). Several candidate genes in the region of 17q have been suggested where Nme1, which is a downstream transcriptional target of *Mycn*, has shown to bind the cytoskeletal modulator Cdc42 and hinder differentiation (Mosse et al., 2007; Valentijn et al., 2005). The corresponding genes for MYCN-NME1-CDC42 signaling are located in

three regions (*MYCN* amplification, 1p36 deletion and 17q gain) commonly seen in chromosome aberrations among neuroblastoma, making it highly interesting (Valentijn et al., 2005). In addition to chromosomal abnormalities several individual genes have been proposed to be important in primary neuroblastoma, including *ALK,* Paired like Homeobox *(PHOX)2B, SHP2,* chromatin remodeler *ATRX* and Telomerase Reverse Transcriptase (*TERT)* (Guan et al., 2021; Qiu & Matthay, 2022). *PHOX2B* was the first familial predisposition gene identified in neuroblastoma, accounting for an estimated 6.4% of the familial cases, however PHOX2B mutations (silencing) are detected at a lower degree in sporadic cases (Mosse et al., 2004; Raabe et al., 2008; Serra et al., 2008; Trochet et al., 2004; van Limpt et al., 2004). Interestingly, it has been suggested that the transcription factor PHOX2B contributes to neuroblastoma formation through binding the promotor region of *ALK*, thus increasing ALK expression (Bachetti et al., 2010; Zafar et al., 2021). Activating ALK mutations are detected in approximately 10% of primary neuroblastoma, however further implications of ALK mutations and signaling will be discussed in a later section (Guan et al., 2021). Telomere maintenance in neuroblastoma is seen in approximately 50% of the patients and is associated with poor outcome (Qiu & Matthay, 2022; Stainczyk & Westermann, 2022). Telomere maintenance in neuroblastoma is accomplished by either telomerase activation (through *TERT*(10-15%) putting *TERT* under super-enhancer control or *MYCN* amplification where MYCN induces TERT expression by binding to its promotor (~20%)) or through Alternative Lengthening of Telomeres (ALT)(10-15%) (where mutations of the chromatin remodeling tumor suppressor gene ATRX (~55-60%) are associated with ALT) (Peifer et al., 2015; Stainczyk & Westermann, 2022; Werr et al., 2024; Zeineldin et al., 2020).

SHP2 is a tyrosine phosphatase associated with the RAS/MAPK signaling pathway with activating mutations seen in approximately 3% of somatic cases (Bentires-Alj et al., 2004; Bunda et al., 2015; Pugh et al., 2013) (Figure 9).

In cases of relapsed neuroblastoma, mutations in TP53 pathway, *NF1* (inactivating), *RAS*, *RAF*, *ALK* and *SHP2* are more commonly seen (Guan et al., 2021; Qiu & Matthay, 2022). Mutations in the ALK/RAS/MAPK signaling pathway have been identified in 74% of relapsed neuroblastomas with between 26-43% of mutations detected in ALK alone (Eleveld et al., 2015; Schleiermacher et al., 2014). Aberrations in the TP53 signaling pathway are also frequently detected in relapsed neuroblastoma constituting 49% of cases

where silencing mutations in *TP53* account for 15% (Carr-Wilkinson et al., 2010).

In conclusion, there are several tumor suppressor genes and oncogenes, involved in RAS/MAPK signaling, telomerase maintenance, DNA damage response, TP53 pathway, identified in the heterogenic landscape of neuroblastoma with several of them presenting therapeutic potential. Interestingly, reports have indicated that TP53 and/or RAS pathway (including ALK) mutations together with elevated levels of telomere maintenance are associated with the worst outcome (Ackermann et al., 2018).

1.5.3 CONVENTIONAL TREATMENT OF NEUROBLASTOMA

Low and intermediate risk neuroblastoma can usually either be observed or treated with resection and response-based chemotherapy with an estimated five years survival equal to, or over, 95% (Qiu & Matthay, 2022). However, some studies also include radiotherapy and retinoic acid in some subgroups of intermediate risk neuroblastomas (LINES, ClinicalTrails.gov ID: NCT01728155). High risk neuroblastoma protocols differ slightly when comparing North American and European protocols, though the main outline is the same with induction, consolidation and maintenance therapy (Qiu & Matthay, 2022; Smith & Foster, 2018). Here, focus will be on high-risk neuroblastoma treatment in Europe (Figure 13). Induction therapy includes three courses (A: vincristine (tubulin inhibitor), carboplatin (platination, crosslinking DNA), etoposide (topoisomerase inhibitor). B: vincristine, cisplatin (platination, crosslinking DNA). C: vincristine, etoposide, cyclophosphamide (alkylating agent, crosslinking DNA)) given repeatedly and evaluated (Anand et al., 2023; Garaventa et al., 2021; Qiu & Matthay, 2022) (High Risk Neuroblastoma Study 1 (HR-NBL1.8) of SIOP-Europe (SIOPEN) ClinicalTrails.gov ID: NCT01704716). G-CSF is also administered during induction to prevent neutropenic fever (Ladenstein et al., 2010) (High Risk Neuroblastoma Study 1 (HR-NBL1.8) of Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) ClinicalTrails.gov ID: NCT01704716).

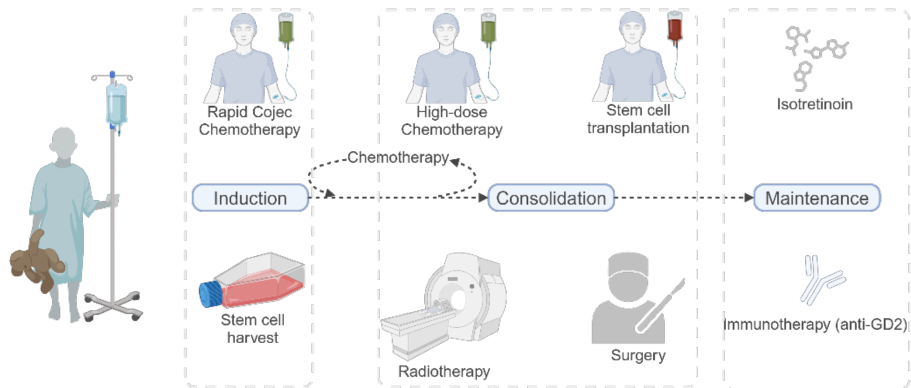

Figure 13. Conventional treatment regime for high-risk neuroblastoma in Europe. Created in BioRender. Borenäs, M. (2024) BioRender.com/ z07b620.

Autologous peripheral blood stem cell harvest is done in the end of induction therapy followed by either primary resection or an additional two courses of topotecan (topoisomerase inhibitor), vincristine and doxorubicin (topoisomerase inhibitor) depending on tumor response (Amoroso et al., 2018; Anand et al., 2023; Qiu & Matthay, 2022) (High Risk Neuroblastoma Study 1 (HR-NBL1.8) of SIOPEN ClinicalTrails.gov ID: NCT01704716). Consolidation treatment follows, with high dose busulfan (alkylating agent, crosslinking DNA) and melphalan (alkylating agent, crosslinking DNA), together with autologous stem cell transplantation and radiotherapy (Anand et al., 2023; Ladenstein et al., 2017; Qiu & Matthay, 2022) (High Risk Neuroblastoma Study 1 (HR-NBL1.8) of SIOPEN ClinicalTrails.gov ID: NCT01704716). Consolidation is followed by maintenance therapy, including immunotherapy with anti-Disialoganglioside (GD)2 antibodies and isotretinoin (Qiu & Matthay, 2022) (High Risk Neuroblastoma Study 1 (HR-NBL1.8) of SIOPEN ClinicalTrails.gov ID: NCT01704716). Immunotherapy with anti-GD2 antibodies is based on the rationale that almost all neuroblastoma tumors express GD2, though normal tissue such as neurons also expresses GD2, and has been associated with antitumor effects (Cheung et al., 1987; Mujoo et al., 1987; Nazha et al., 2020; Schulz et al., 1984; Yu et al., 2010). Isotretinoin, on the other hand, is administered due to its ability to differentiate cells (Makimoto et al., 2024).

Although the HR-NBL1.8 protocol must be evaluated in regard to short- and long-term side effects, some side effect data associated with the study has been presented. Il-2 injections together with anti-GD2 antibodies were associated

with toxicity, as compared to anti-GD2 antibodies alone, and Il2 injections were therefore discontinued in the HR-NBL1 protocol (Ladenstein et al., 2018). Furthermore, anti-GD2 antibodies are associated with neuropathic pain, in approximately 15% of patients, but been reported to be as high as 50% when combined with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) and Il-2 (Barone et al., 2021; Ladenstein et al., 2018; Nysom et al., 2023; Yu et al., 2010). Furthermore, sinusoidal obstruction syndrome, a life-threatening condition, is associated with hematopoietic stem cell transplantation and has been reported in 15-30% of high-risk neuroblastoma patients (Corbacioglu et al., 2018). From previous treatment protocols of neuroblastoma it is known that neuroblastoma survivors have a risk of long term side effects such as hearing loss, ovarian failure as well as secondary malignancies (Friedman & Henderson, 2018).

1.5.4 NOVEL TREATMENT REGIMES IN NEUROBLASTOMA

There are currently several potential therapies being evaluated in neuroblastoma including iodine 131-Metaiodobenzylguanidine (MIBG) therapy and radiotherapy directed against somatostatin receptors, anti-GD2 vaccine, CAR-T cells, immune checkpoint inhibitors or targeting therapy against ALK, AURORA kinase A/B, Bromodomain and Extraterminal (BET) as well epigenetic therapies (Qiu & Matthay, 2022). Unfortunately, single agent immune checkpoint inhibitors are not effective in neuroblastoma, likely due to low T-cell infiltration (Anderson et al., 2022; Davis et al., 2020; Qiu & Matthay, 2022). CAR-T cells engineered against GD2, on the other hand, have shown promising results in a phase I/II trial with one third of the patients displaying complete response and 63% displaying response to treatment (Del Bufalo et al., 2023).

Since *MYCN* amplification is a hallmark of high-risk neuroblastoma and detected in approximately 20%, substantial efforts have been made to block the effects of *MYCN* amplification either directly or indirectly. AURORA Kinase A (AURKA) regulates mitotic functions such as mitotic spindle formation. It has also been suggested that AURKA is involved in, telomerase activity, the DNA damage response and stabilization of MYCN (Ma & Poon, 2020). Inhibitors against AURKA have been evaluated/being evaluated in several clinical trials and have so far shown modest results in different types of cancers (Du et al., 2021; Goldberg et al., 2014; Haddad et al., 2023; Matulonis et al., 2012; O'Connor et al., 2019). In a neuroblastoma context,

AURKAs role in MYCN stabilization is very appealing, and AURKA inhibitors have shown prolonged survival in MYCN driven neuroblastoma mouse models (Brockmann et al., 2013; Otto et al., 2009; Richards et al., 2016). AURKA inhibitors have unfortunately shown very little effect among pediatric solid tumors, including neuroblastoma where only 3 out of 48 patients responded (Mosse et al., 2019). However, the new generation of AURKA inhibitors are highly specific for AURKA, with Erbumine being evaluated in neuroblastoma in a phase I clinical trial (Chu et al., 2021; Gong et al., 2019)(ClinicalTrails.gov ID: NCT04106219). Other indirect effectors of MYCN activity are the BET inhibitors which block chromatin remodeling and epigenetic reading of BET hindering transcription of *MYCN* (Mertz et al., 2011; Schnepp & Maris, 2013; Stathis & Bertoni, 2018). BET inhibition is currently being evaluated in a clinical trial which also includes neuroblastoma (ClinicalTrails.gov ID: NCT03936465).

Targeting CDK4/6 has reformed treatment regimens for hormone receptor positive breast cancer, HER2 negative and metastatic breast cancer through increasing progression free survival in these patients (Spring et al., 2019). However, hormonal resistance is inevitable and the effect on overall survival is not as clear as that for progression free survival (Finn et al., 2015; Huang et al., 2022; Turner et al., 2018). Furthermore, resistance to CDK4/6 inhibitors are associated with the cell losing its dependence of CDK4/6 through either amplification of CDK4/6, loss of RB1, activation of CDK2, increased expression of CDK7 or through signaling pathways such as RAS/Mitogen-Activated Protein Kinase (MAPK) (Huang et al., 2022; Spring et al., 2020; Stanciu et al., 2023). Losing dependency of either CDK 4 or 6 during CDK4/6 inhibition is consistent with earlier findings of CDK 4 and CDK 6 knock out mice being viable, though displaying growth retardation, increased postnatal lethality and incomplete sterility and that only CDK1 is needed in the mammalian cell cycle (Malumbres et al., 2004; Santamaria et al., 2007; Tsutsui et al., 1999). In a neuroblastoma setting, the CDK4/6 inhibitor ribociclib has been evaluated as a single agent in a phase I study which showed that 7 out of 15 achieved stable disease (Geoerger et al., 2017). However, the study was associated with disease progression as well as adverse side effects, resulting in termination of the study (Geoerger et al., 2017)(ClinicalTrails.gov ID: NCT01747876). CDK4/6 inhibition is now being investigated together with other agents and is currently in a phase I clinical trial evaluating the effect of ribociclib together with chemotherapy among neuroblastoma patients (Geoerger et al., 2017)(ClinicalTrails.gov ID: NCT05429502). Ribociclib has shown encouraging results in preclinical xenograft models when being

combined with the ALK inhibitor ceritinib (Wood et al., 2017). Unfortunately, a phase I study employing ribociclib and ceritinib in neuroblastoma was terminated with no data available to date (ClinicalTrails.gov ID: NCT02780128). The CDK4/6 inhibitor palbociclib has shown to prolong survival in a *MYCN* driven neuroblastoma models, induce differentiation among neuroblastoma cells and prohibit proliferation (Ferguson et al., 2023). Somewhat concerning, however, is a recent report showing that palbociclib directly inhibits STING, in the cGAS/STING pathway, raising the question of whether palbociclib would inhibit the inherent immune system in a neuroblastoma setting and of the potential ramifications (Gao et al., 2022).

Crizotinib, a first generation ALK inhibitor, was approved for use in ALK positive Non-Small Cell Lung Cancer (NSCLC) in 2011 after positive outcomes were reported in clinical trials (Hallberg & Palmer, 2016; Kwak et al., 2010). In 2023, after crizotinib and the second generation ALK inhibitor ceritinib had shown modest results in neuroblastoma, the first phase I trial investigating the third generation ALK inhibitor lorlatinib as a single agent or in combination with chemotherapy in neuroblastoma harboring activating ALK mutations was presented (Fischer et al., 2021; Foster et al., 2021; Goldsmith et al., 2023; Mosse et al., 2013). The phase I report presented response rates between 30-67% with almost half of responders showing complete response on MIGB follow up imaging (Goldsmith et al., 2023). The targeting of ALK in neuroblastoma treatment regimens will be further discussed in later sections.

PARP inhibitors are available in the clinic for several types of cancers such as breast, prostate, pancreas and ovarian cancer (Bhamidipati et al., 2023; Mateo et al., 2019). The DNA damage response component PARP identifies and binds to single stranded DNA breaks and induces chromatin remodeling, allowing DNA repair as well as recruiting DNA repair components to the damaged DNA (Bhamidipati et al., 2023; Mateo et al., 2019). Inhibition of PARP prevents chromatin remodeling, inhibiting the enzymatic activity of PARP and trapping PARP on damaged DNA, resulting in stalling of the replication fork and subsequent double stranded DNA breaks (Bhamidipati et al., 2023; Mateo et al., 2019). BRCA1/2 are repairers of double strand breaks through homologous recombination and normally repair stalled replication forks (Bhamidipati et al., 2023; Mateo et al., 2019). However, in tumors with BRCA1/2 deficiency, PARP inhibition results in synergistic lethality through accumulation of DNA damage (Bhamidipati et al., 2023; Mateo et al., 2019). PARP inhibition has shown, together with inhibition of ATR, encouraging

results in neuroblastoma cell lines (Southgate et al., 2020). In preclinical xenograft MYCN driven neuroblastoma models, PARP inhibitors have shown promising results together with CHK1 inhibitors, though PARP inhibition on its own did not show any difference in tumor volume compared with control (Di Giulio et al., 2021). In the clinic, a phase I study has investigated PARP inhibition among pediatric cancers, including neuroblastoma, with only one out of five neuroblastoma patients displaying a partial response (Takagi et al., 2022). However, a couple of case reports of neuroblastoma harboring mutations in BRCA1/2 associated *BARD1* and *PALB2* displayed sustained clinical response and prolonged stable disease respectively (Cohen-Gogo et al., 2024; Cupit-Link et al., 2024; Irminger-Finger & Jefford, 2006).

Other putative treatment regimes in neuroblastoma include MEK inhibitors, RAS inhibitors, EGFR inhibitors, MDM2 inhibitors, apoptosis regulator BCL2 inhibitors, AKT inhibition, FGFR inhibitors and PROTACs against for example AURKA just mentioning a few (Cimmino et al., 2022; Johnsen et al., 2018; Johnsen & Kogner, 2024; King et al., 2015; Kushner et al., 2017; Li et al., 2020; L. Lin et al., 2022; Place et al., 2018; Qiu & Matthay, 2022; Rishfi et al., 2023; Tanaka et al., 2016; Umapathy et al., 2017).

Independent of the treatment regime employed, careful consideration must be taken in choosing the right drug for the right patient.

1.6 MYCN

1.6.1 OVERVIEW OF MYCN

Together with MYC (c-MYC) and MYCL, MYCN is a member of the MYC family which regulates cell growth, proliferation, metabolism and stem cells (Dang, 2012). The different MYC paralogs are located on different chromosomes: *c-MYC* (8q24.21), *MYCL* (1p34.2) and *MYCN* (2p24.3), and exhibit differential spatial and temporal tissue expression patterns (e.g. *MYCN* is predominantly expressed in developing neural tissue)(Dang, 2012; Ruiz-Perez et al., 2017). MYCN and c-MYC are fundamental for embryonic development, since null mice lacking either gene results in lethality (Otte et al., 2020). *Mycn* expression is detected at high levels during embryogenesis but decreases to a sustained low level in for example the heart among mice (Ruiz-Perez et al., 2017; Zimmerman et al., 1986). Analysis of RNA in human single cell data shows that *MYCN* expression, is detected in male and female

reproductive systems, neuronal cells and glial cells (Uhlen et al., 2015) (Human Protein Atlas, September 2024, proteinatlas.org).

1.6.2 FUNCTION OF MYCN

Several signaling pathways converge on *MYC* expression, including signaling by receptor tyrosine kinases through the ERK/MAPK pathway (Dang, 2012). The MYC family are transcription factors that through dimerization with MYC-Associated protein X (MAX) interact with Enhancer-boxes (E-box, one of the most frequent motifs in the human genome) allowing for recruitment of Histone Acetyl Transferases (HATs), through MYCs association with TFIIH, that will render the chromatin exposed (Dang, 2012; Ruiz-Perez et al., 2017). Stabilization/degradation of MYC is achieved through phosphorylation of S62 and T58 on MYC where CDK2, ERK, Peptidylprolyl cis/trans Isomerase, NIMA-interacting (PIN)1 and serine/threonine kinase PIM-1 induce stabilizing phosphorylation events while PIN-1 and Protein Phosphatase (PP)2A induce changes in phosphorylation that result in ubiquitination by an E3 ligase with the MYC recognizing F-box subunit F-box and WD repeat domain containing 7 (FBXW7) (Chambard et al., 2007; Farrell & Sears, 2014; Llombart & Mansour, 2022)

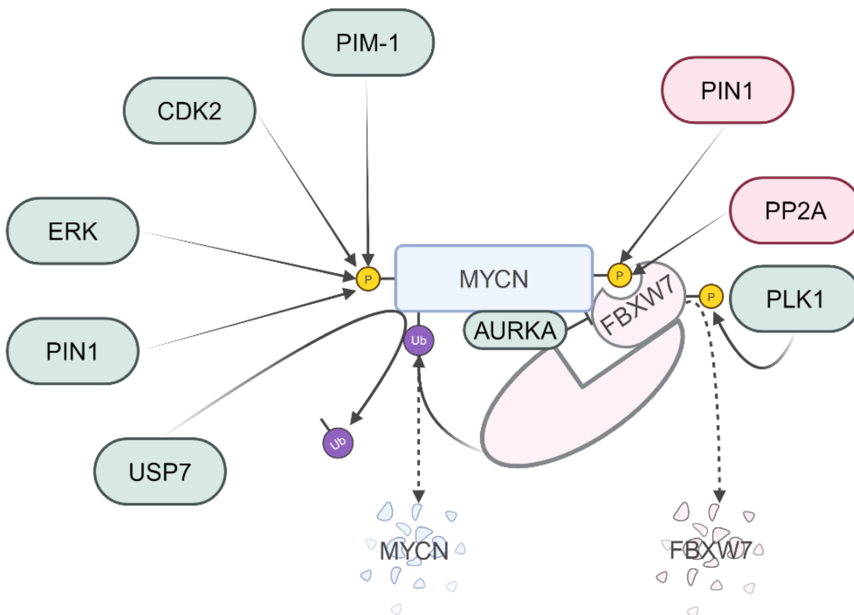

Figure 14. Stabilators of MYCN mark in green and destabilators marked in red. Created in BioRender. Borenäs, M. (2024) BioRender.com/ g86e314.

MYC is further stabilized by AURKA which binds MYC and protects it from FBXW7 (Brockmann et al., 2013; Llombart & Mansour, 2022). Polo-Like Kinase 1 (PLK1) phosphorylates FBXW7 resulting in its degradation while Ubiquitin Specific Peptidase (USP)7 deubiquitinates MYCN, thus stabilizing MYC (Llombart & Mansour, 2022) (Figure 14). Subsequently, there are several inhibitors or activators targeting MYC stabilization that are being investigated in preclinical settings and clinical trials (Llombart & Mansour, 2022). Stabilized MYC will induce expression of genes (e.g. *CCND1*) involved in cell growth, proliferation and apoptosis (Carroll et al., 2018; Chambard et al., 2007). Furthermore, overexpressed MYC is known to induce replication stress through for example elevated and untimely origin initiation (Curti & Campaner, 2021).

1.6.3 MYCN IN DISEASE

Amplification of the MYC paralogs *c-MYC, MYCL* and *MYCN* have been detected in 28% of tumors in a study of 33 human tumor types (Dhanasekaran et al., 2022; Schaub et al., 2018). As already mentioned, *MYCN* amplification is detected in approximately 20% of neuroblastoma cases and is a hallmark of high-risk neuroblastoma (Matthay et al., 2016). Other malignancies where aberrant *MYCN* expression is present include mainly childhood malignancies, although aberrant *MYCN* expression is also seen in some adult cancers such as prostate cancer (14% amplification) (Ruiz-Perez et al., 2017). Some other childhood cancers of note with *MYCN* aberrations are medulloblastoma (7-10% amplification) and Wilm's tumor (13% gain, 9% amplification and 4% mutation) (Ruiz-Perez et al., 2017). Other mechanisms of aberrant *MYC* expression include chromosomal translocation of c-*MYC* seen in for example multiple myeloma (Dang, 2012). Interestingly, *MYCN* mutations have also been detected in high-risk neuroblastoma (1.7%) that are presumed to be functional by *in silico* analyses (Pugh et al., 2013). Furthermore, in neuroblastoma, although amplification of *c-MYC* is rare, aberrant *c-MYC* expression (enhancer hijacking or enhancer amplification) or protein expression is seen in approximately 3-10% of metastatic or poorly differentiated/undifferentiated neuroblastoma (Matsuno et al., 2018; Wang et al., 2015; Zimmerman et al., 2018). Patients with positive c-MYC tumors display similar 3-year overall survival as MYCN positive tumor patients (Wang et al., 2015).

After the identification of the *MYCN* gene, in neuroblastoma, in 1983 it was assumed that MYCN was important in neuroblastoma formation (Brodeur et

al., 1984; Schwab et al., 1983). To test the direct impact of MYCN on tumorigenesis a transgenic Genetically Engineered Mouse Model (GEMM) was created by incorporation of human *MYCN* complementary DNA (cDNA) under the control of the rat Tyrosine Hydroxylate (TH) promotor (Weiss et al., 1997). The *Th-MYCN* neuroblastoma mouse model was created, which expresses MYCN in neural crest derived cells and displays a 100% neuroblastoma penetrance in a homozygote setting (Weiss et al., 1997).

1.6.4 INHIBITION OF MYCN IN MALIGNANCIES

MYCN has been traditionally regarded as undruggable, though targeting MYCN indirectly through for example AURKA or BET inhibitors have provided novel opportunities to manage *MYCN* amplified neuroblastoma (Llombart & Mansour, 2022). AURKA inhibition has also shown potency in combination with ATR inhibition where *Th-MYCN* tumor bearing mice showed sustained complete regression in 25% of treated mice (Roeschert et al., 2021). There is also an interest in inhibiting metabolic pathways needed for MYCN synthesis by inhibiting polyamine biosynthesis through blocking of Ornithine Decarboxylase (ODC), by Difluoromethylornithine (DFMO), with a phase II clinical trial currently recruiting neuroblastoma patients (Qiu & Matthay, 2022; Ruiz-Perez et al., 2017) (ClinicalTrails.gov ID: NCT02679144). One of the more interesting compounds currently being evaluated is Omomyc (OMO-103) which competes with MYC paralogs for DNA binding but also binds to the MAX component, forming Omomyc/MAX complexes, thus hindering the MYC/MAX complex from initiating transcription (Dhanasekaran et al., 2022; Duffy et al., 2021; Llombart & Mansour, 2022). Recently, a phase I study employing Omomyc, reported stable disease in 66% of the patients (8 out of 12 with advanced solid tumors), however the majority of these showed disease progression within 6 months from the first evaluation at 9 weeks (Garralda et al., 2024).

1.7 ANAPLASTIC LYMPHOMA KINASE (ALK)

1.7.1 OVERVIEW OF ALK

Anaplastic Lymphoma Kinase, a receptor tyrosine kinase and a member of the insulin receptor family, was first identified in 1994 as a fusion t(2;5)(p23;q35) together with Nucleophosmin (NPM), in cell lines from anaplastic large cell lymphoma patients, creating a hybrid protein NPM-ALK, containing the catalytic domain of the tyrosine kinase of ALK which in this setting is

constitutive active (Fujimoto et al., 1996; Morris et al., 1994; Pulford et al., 2004; Shiota et al., 1994). Full-length ALK was first characterized in 1997, constituting an extracellular, transmembrane and an intracellular domain with a tyrosine kinase region (Iwahara et al., 1997; Morris et al., 1997). Comparison of the amino sequence of *Drosophila* Alk with human ALK revealed a unique extracellular domain, containing Meprin, A-5 protein and receptor protein tyrosine phosphatase Mu (MAM), Glycine Rich (GR) and Low-Density Lipoprotein class A (LDLa) domains (Huang, 2018; Loren et al., 2001). ALKs closest relative within the insulin receptor family, Leukocyte Tyrosine Kinase (LTK), has been suggested to be a result of gene duplication in early vertebrates, where LTK has subsequently lost the MAM and the LDLa domains of the extracellular domain in later vertebrates (Dornburg et al., 2021; Iwahara et al., 1997; Loren et al., 2001; Morris et al., 1994; Morris et al., 1997). More recent structural studies of ALK have identified an EGF-Like (EGFL) region and TNF-Like (TGFL) region, where the TGFL is associated with the GR region (De Munck et al., 2021; Li et al., 2021; Reshetnyak et al., 2021) (Figure 15).

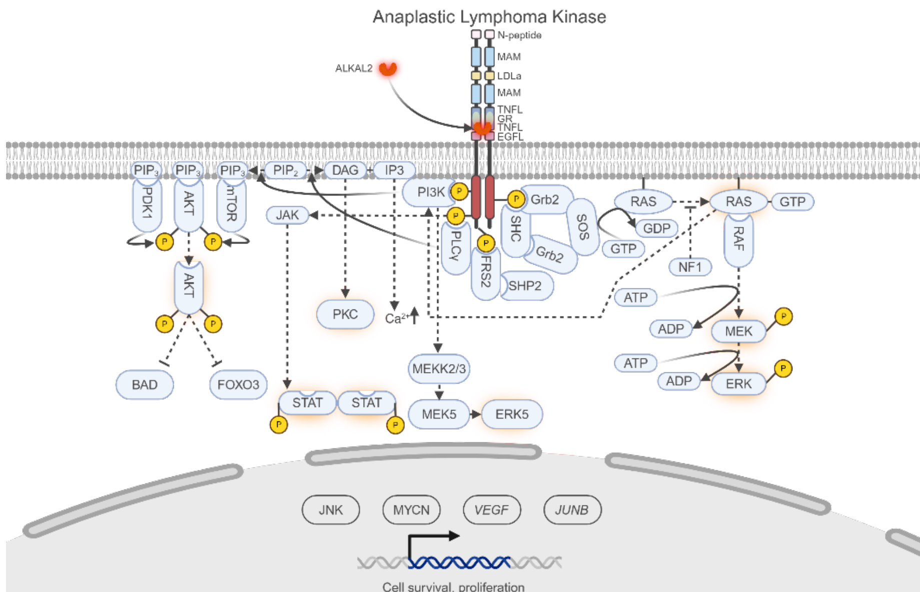

Figure 15. Overview of ALK and downstream effectors. Created in BioRender. Borenäs, M. (2024) BioRender.com/ j59t412. Adapted from Umapathy et al., 2019 under Creative Commons Attribution-Noncommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/).

1.7.2 LIGANDS OF ALK

ALK held orphan receptor status for many years, however, in 2014 two unique molecules, ALKAL1 (FAM150A, AUGβ) and ALKAL2 (FAM150B, AUGα) with 47% overall similarity and being 129 and 152 amino acids long respectively, were identified, with ALKAL1 reported to activate LTK (Zhang et al., 2014). Shortly after, ALKAL1 and ALKAL2 were characterized as ligands for ALK (Guan et al., 2015; Reshetnyak et al., 2015). ALKAL1 showed higher affinity for LTK but could still activate ALK while ALKAL2 could activate both LTK and ALK (Guan et al., 2015; Reshetnyak et al., 2015; Zhang et al., 2014). Recent studies have confirmed ALKAL1 and ALKAL2 as ligands for ALK and provided structural detail regarding receptor ligand (ALK-ALKAL) interactions (De Munck et al., 2021; Fadeev et al., 2016; Li et al., 2021; Reshetnyak et al., 2021). ALKAL2 has been reported to bind to the GR region of the extracellular domain at "site 1" of the first ALK receptor, facilitating binding at "site 2" of the second receptor resulting in dimerization and protein configuration exposing a "site 3" which allows for receptor-receptor interaction (De Munck et al., 2021). However, there are contradicting reports regarding whether one or two ligands are needed for dimerization of the ALK receptor, something that is discussed in a recently posted preprint (De Munck et al., 2021; Li et al., 2021; Reshetnyak et al., 2021)(Preprint: https://doi.org/10.1101/2024.08.08.607122). Despite the unresolved molecular mechanisms, the available data supports a model in which dimerization of the ALK receptor induces autophosphorylation and propagation of downstream intracellular signaling pathways (Hallberg & Palmer, 2016).

The ligands for Alk in *Drosophila melanogaster* and the *Caenorhabditis elegans* Alk ortholog *Scd-2* are Jelly belly (Jeb) and Hen-1 respectively (Englund et al., 2003; Ishihara et al., 2002; Lee et al., 2003; Reiner et al., 2008). Interestingly, Jeb and Hen-1 show no structural similarities with the mammalian ALKAL ligands and Jeb does not activate mouse ALK (Hallberg & Palmer, 2016; Yang et al., 2007). Furthermore, it has been suggested that Jeb was lost during evolution and that one of the Alkal ligands were introduced early in vertebrates and later duplicated simultaneously as Alk was duplicated to give rise to Ltk (Dornburg et al., 2021). In zebrafish, the LTK (ltk) and ALK (alk) orthologs are very similar, with the LTK ortholog still containing one MAM-domain and the LDLa domain (Lopes et al., 2008). While *ltk* has been detected in developing neural crest cells giving rise to iridophores *alk*

expression has been reported in the developing central nervous system (Lopes et al., 2008; Yao et al., 2013).

ALKAL2 expression is poorly characterized, however the Human Protein Atlas (September 2024), confirms the previously reported high levels of ALKAL2 expression in the adrenal gland, with lower levels detected in several tissues including pancreas, ovary, testis, adipose and brain tissue (Uhlen et al., 2015; Zhang et al., 2014)(Human Protein Atlas proteinatlas.org). Alkal2 expression in the dorsal root ganglion has also been reported in response to pain in sensory neurons, resulting in activation of Alk in the spinal cord which in turn can be blocked with ALK inhibitors (Defaye et al., 2022). Furthermore, Alkal2 has been reported as an important component in seasonal fluctuation among ewes (Lomet et al., 2018). In addition, *Alkal2* has been shown to be expressed in neurons that control body metabolism and loss of *Alkal2* is linked with elevated physical activity and thinness in mice (Ahmed et al., 2022). Further establishing ALKALs role in the neural system is the characterization of *ALKAL* orthologs (*alkal1*, *alkal2a* and *alkal2b*) expression pattern in zebrafish, which overlaps with *ltk* expression in neural crest derived cells, there among iridophores (Fadeev et al., 2018). Furthermore, lack of function mutations of all three ligands results in larval lethality and loss of iridophores, a phenotype indistinguishable from the *ltk* mutant (Fadeev et al., 2018).

1.7.3 SIGNALLING AND FUNCTION OF ALK

The precise mechanisms of ALK kinase domain activation are still not fully understood. However, the kinase domain contains an Adenosine Triphosphate (ATP) binding pocket which allows ALK to phosphorylate adaptor proteins, by transferring the terminal phosphate group from ATP to target tyrosine residues, thus conveying an extracellular signal to an intracellular signal (Hallberg & Palmer, 2016; Huang, 2018). Phosphorylation of the activation loop, including Y1278, is thought to be the initial step in ALK kinase domain activation, while phosphorylation of Y1507 and Y1604 are crucial for interaction with adaptor proteins (Bai et al., 1998; Chen et al., 2016; Chikamori et al., 2007; Galkin et al., 2007; Hallberg & Palmer, 2016; Turner et al., 2007). Adaptor proteins and associated intracellular proteins include for example Shp2, Grb2, FRS2 and SHC resulting in intracellular signal transduction through signaling pathways such as PI3K-AKT, JAK-STAT, MEKK2/3-MEK5-ERK5, PLC-γ and MAPK/ERK (Hallberg & Palmer, 2013, 2016; Umapathy et al., 2019) (Figure 15). Activation of ALK results in transcription of a variety of genes such as JUN N-terminal Kinase *(JNK), NfKB,* Vascular

Endothelial Growth Factor *(VEGF), JUNB* and *MYCN* resulting in proliferation, survival, cell growth and differentiation (Hallberg & Palmer, 2013, 2016; Umapathy et al., 2019). Of special note is the effect of ALK on regulation of *MYCN* transcription through ERK5 (Schonherr et al., 2012; Umapathy et al., 2014). Interestingly, MYCN has been shown to regulate *ALK* expression thus potentially creating a vicious circle in unregulated cells (Hasan et al., 2013). Furthermore, ALK has been proposed to affect amino acid transportation and transportation of polyamines through Solute Carrier Family 3, Member 2 (SLC3A2) (Lai et al., 2024). ALK is normally activated by its ligands, but in an oncogenic context can also be activated in ligand independent manner, either through amplification of the receptor, activating point mutations in the kinase domain or translocations (Umapathy et al., 2019). Interestingly, the downstream target of ALK, AKT, has been suggested to be a target of ATR as well as affecting DNA damage response and repair, for example by preventing HR by inhibiting BRCA1 (Liu et al., 2022).

The function of ALK in vertebrates is poorly characterized. ALK mRNA or protein expression has been reported in human testis, small intestine and brain, although not in leucocytes which is in contrast with LTK (Ben-Neriah & Bauskin, 1988; Bernards & de la Monte, 1990; Morris et al., 1994; Pulford et al., 1997). *ALK* is expressed in tissues such as brain, retina, pituitary gland and testis while ALK can be detected in the brain, adrenal gland, testis and skin with cells such as neuronal, Purkinje and melanocytes expressing medium to high levels of ALK (Uhlen et al., 2015) (Human Protein Atlas, September 2024, proteinatlas.org). Alk mRNA or protein is detected in central and/or peripheral neural tissue in developing chicks, mice, rats as well as in adult mice with expression of Alk being most intense during embryogenesis and birth and then declining to a low level state approximately 3 weeks postpartum (Bilsland et al., 2008; Degoutin et al., 2009; Hurley et al., 2006; Iwahara et al., 1997; Morris et al., 1997; Vernersson et al., 2006; Weiss et al., 2012). Furthermore, *Alk* has been detected in embryonic (E) stage E12.5 and E13.5 in sympathetic neuroblasts (Furlan et al., 2017; Huang, 2018).

The localization of ALK is mirrored in the functions of ALK thus far identified. Mice lacking Alk are viable and have been associated with increased dopaminergic signaling in the frontal cortex, increased spatial memory, decreased neurogenesis, decreased testosterone levels. thinness and increased alcohol consumption (Bilsland et al., 2008; Lasek, Lim, et al., 2011; Orthofer et al., 2020; Weiss et al., 2012; Witek et al., 2015). Other studies have also highlighted Alk's association with alcohol and cocaine consumption as well as

altered neural, metabolism and cognitive functions among mice (Dedoni et al., 2023; Dutton et al., 2017; Lasek, Gesch, et al., 2011; Mangieri et al., 2017; Schweitzer et al., 2016; Weiss, Weber, Marzulla, et al., 2017; Weiss, Weber, Torres, et al., 2017). In humans, *ALK* has also been reported in conditions such as ethanol consumption, schizophrenia and thinness (Kunugi et al., 2006; Lasek, Lim, et al., 2011; Orthofer et al., 2020; Wang et al., 2011).

The implications of normal ALK signaling can be observed in the side effects of ALK inhibition in the clinic. Patients on ALK inhibitors have been reported to display weight gain, low testosterone levels, hypercholesterolemia, hypertriglyceridemia and Central Nervous System (CNS) effects potentially reflecting on-target off-tumor effects (Camidge, 2021; de Leeuw et al., 2023; Shaw et al., 2020; Shaw et al., 2017; Weickhardt et al., 2012).

1.7.4 ALK IN MALIGNENCIES

Systemic Anaplastic Large Cell Lymphoma (sALCL) display, in 80% of the cases, rearrangement of ALK, most frequently fused to NPM, accounting for approximately 10-20% of non-Hodgkin's lymphoma among children and juveniles (Montes-Mojarro et al., 2018). In 2021, treatment of ALK positive sALCL, with the ALK inhibitor critzotinib, was approved for pediatric and young adults with relapsed or refractory tumors (Gromowsky et al., 2023; Merino et al., 2022). Since the identification of the fused hybrid protein NPM-ALK, several hybrid proteins involving ALK have been described in a variety of cancers (Hallberg & Palmer, 2016). The driving force in development of ALK inhibitors was the identification of the *EML4-ALK* gene fusion in 6.7% of NSCLC (Prokoph et al., 2018; Soda et al., 2007). Subsequently, ALK inhibitors have been approved for NSCLC with crizotinib (ALKi, ROS1i, METi) being approved in 2011 followed by ceritinib (2014, ALKi, ROS1i, IGF1Ri, IRi), alectinib (2015, ALKi, serine/threonine cyclin G-Associated Kinase (GAK)i, LTKi, RETi), brigatinib (2020, ALKi, ROS1i) and lorlatinib (2021, ALKi, ROS1i) (Cooper et al., 2022; Lin et al., 2017; Prokoph et al., 2018). *ALK* translocations are also found in malignancies such as inflammatory myofibroblastic tumour, breast cancer, colon carcinoma, diffuse large B-cell lymphomas and serous ovarian carcinoma (Hallberg & Palmer, 2016).

Point mutations in *ALK* are typically seen in neuroblastoma but can also be detected in anaplastic thyroid carcinoma (Hallberg & Palmer, 2016). Several types of point mutations in *ALK*, both somatic and germline, have been identified, accounting for approximately 10% of all primary neuroblastoma (Caren, Abel, et al., 2008; Chen et al., 2008; George et al., 2008; Guan et al.,

2021; Janoueix-Lerosey et al., 2008; Mosse et al., 2008). Furthermore, amplification or gain of *ALK* alone or together with *ALKAL2* and *MYCN* (2p gain/amplification) has been reported in up to ~30% of neuroblastoma (Caren, Abel, et al., 2008; De Brouwer et al., 2010; Janoueix-Lerosey et al., 2008; Javanmardi et al., 2020). *ALK* mutations are associated with worse outcome among high- and intermediate-risk neuroblastoma and detected at a higher rate in relapsed neuroblastoma, suggesting potential presence of *ALK* muted tumor clones at primary diagnosis or new mutations in *ALK* (Bellini et al., 2021; De Brouwer et al., 2010; Eleveld et al., 2015; Martinsson et al., 2011; Rosswog et al., 2023; Schleiermacher et al., 2014). While many different activating point mutations in *ALK*, mostly in the kinase domain, have been described, three activating point mutations are frequently reoccurring in approximately 85% of *ALK* mutated neuroblastoma; F1174(C/I/L/S/V), F1245(C/I/L/V) and R1275(L/Q) (Hallberg & Palmer, 2013, 2016). While *ALK* mutations alone are generally insufficient to drive neuroblastoma in animal models, combination with MYCN results in an large increase in tumor penetrance (Berry et al., 2012; Borenas et al., 2021; Cazes et al., 2014; Heukamp et al., 2012; Ono et al., 2019; Ueda et al., 2016; Zhu et al., 2012).

1.7.5 INHIBITION OF ALK IN MALIGNANCIES

ALK inhibitors bind to the ATP pocket of ALK through competitive inhibition with ATP (Umapathy et al., 2019). Crizotinib, the first ALK inhibitor available in the clinic, showed impressive responses in patients harboring ALK hybrid proteins such as EML4-ALK in NSCLC, though not brain penetrative, but did not perform well in neuroblastomas harboring activating point mutations such as F1174 (Kwak et al., 2010; Mosse et al., 2013; Shaw et al., 2013; Umapathy et al., 2019). However, tumor response to crizotinib in NSCLC is temporary (usually 1-2 years) with amplification of ALK, signaling circumvention, through for example EGFR, or mutations in the kinase region or gatekeeping region of ALK, such as I1171T and L1196M, among the documented resistance mechanisms (Doebele et al., 2012; Gainor et al., 2016; Hallberg & Palmer, 2016; Lin et al., 2017; Umapathy et al., 2019). Later generations of ALK inhibitors have aimed at overcoming the shortcomings of crizotinib, with the latest ALK inhibitor lorlatinib being adopted into the clinic in 2021 (Cooper et al., 2022; Umapathy et al., 2019). However, although lorlatinib has resolved challenges such as brain penetrance and potency against mutations in the kinase domain and potential steric impeding mutations, such as F1174(C/L/V) and G1202R, it is still associated with development of resistance, through complex double mutations in ALK among patients, or

circumventing signaling in NSCLC cells (Katayama et al., 2023; Lin et al., 2017; Recondo et al., 2020; Shaw et al., 2019; Umapathy et al., 2019).

In a neuroblastoma setting, although clinical trials investigating crizotinib and ceritinib did not show broad promising effects, there have been cases reporting excellent results (Fischer et al., 2021; Foster et al., 2021; Guan et al., 2018; Mosse et al., 2013). In 2023, a phase I clinical trial investigating lorlatinib alone or in combination with chemotherapy in ALK-positive relapsed or refractory neuroblastoma was presented (Goldsmith et al., 2023). Though the response rate was 30% in lorlatinib treated patients under 18 years compared with 63% for those also receiving chemotherapy, the event free survival and the overall survival between the groups were similar (Goldsmith et al., 2023). However, the response to lorlatinib as monotherapy among patients over 18 years old was 67% and displayed better event free survival and overall survival (Goldsmith et al., 2023). Currently, lorlatinib has been incorporated into a phase III clinical trial for neuroblastoma and is also expected to soon be incorporated in the European HR-NBL2 trial (Tucker et al., 2023)(ClinicalTrails.gov ID: NCT03126916, NCT04221035). Unfortunately, resistance to lorlatinib among ALK driven neuroblastoma has also been reported, including secondary mutations in the ALK tyrosine kinase domain and bypass signaling mechanisms, mainly through the RAS/MAPK signaling pathway that include mutations in RAS family members (Berko et al., 2023; Berlak et al., 2022; Ek et al., 2024). Additional, next generation ALK inhibitors have been generated, where NVL-655 shows convincing results in NSCLC xenografts, lorlatinib resistant cell lines as well as in patients with EML4-ALK with additional F1174C and/or G1202R ALK mutations enrolled in a phase I/II clinical trial (Lin et al., 2024)(ClinicalTrails.gov ID: NCT05384626).

Other treatment regimens targeting ALK driven neuroblastoma that are being investigated, in a preclinical setting, include antibodies targeting ALK and PROTACs against ALK (Gong et al., 2023; Kang et al., 2018; Sano et al., 2019; Yan et al., 2021). CAR-T cells against ALK have shown promising results in mouse xenografts and neuroblastoma GEMMs, with ALK inhibition resulting in increased Alk expression thus potentiating CAR-T treatment (Bergaggio et al., 2023). Promising combinational treatments, studied in preclinical models, incorporating ALK inhibition include combination with chemotherapy which increases survival among ALK/MYCN driven GEMMs but only displayed modest effect in neuroblastoma Patient Derived Xenograft (PDX) models when compared with lorlatinib treatment alone (Tucker et al., 2023). In the same study, the authors also explored MDM2 inhibition,

protecting tp53 from degradation, which has previously shown promising results overcoming resistance, together with lorlatinib inhibition (Miyazaki et al., 2018; Tucker et al., 2023; Wang et al., 2017). Complete response was seen in one, out of three, neuroblastoma PDX models harboring *ALK* amplification though when treatment was lifted, after approximately 80 days, the tumors resurfaced (Tucker et al., 2023). ATR

1.8 ATR

ATM was first discovered in ataxia-telangiectasia, a disorder that is linked with cancer predisposition and neural degeneration, while ATR, first described in 1996, is associated with Seckel syndrome (Bentley et al., 1996; Cimprich et al., 1996; O'Driscoll et al., 2003; Savitsky et al., 1995). Both ATM and ATR, together with DNA-PK are part of the Phosphatidylinositol 3-Kinase-related protein Kinase (PIKK)-family (Lempiainen & Halazonetis, 2009). Lack of Atr in mice is associated with embryonic lethality while Atm deficiency is associated with infertility, neurological dysfunction and decreased growth (Barlow et al., 1996; Brown & Baltimore, 2000; de Klein et al., 2000; Elson et al., 1996; Xu et al., 1996).

As previously described, ATR is a vital part of the DNA damage response (Ciccia & Elledge, 2010). Loss of ATR or CHK1 results in mitotic catastrophe which is potentiated with the loss of TP53 (Menolfi & Zha, 2020). Several cancers have displayed deficiencies in the DDR, such as TP53 deficiency, making them dependent on the remaining parts of the DDR pathway, which is in contrast to normal cells that have intact DDR and can compensate for loss of components of the DDR (Weber & Ryan, 2015). Since the discovery of VE-821 in 2011, several newer generation ATR inhibitors have been introduced such as berzosertib (VE-822, VX-970 and M6620), ceralasertib (AZD6738), gartisertib (VX-803, M4344), tuvusertib (M1774), elimusertib (BAY1895344) and camonsertib (RP-3500) with more in the pipeline (Yano & Shiotani, 2023). Several ATR and CHK1 inhibitors are being explored in clinical trials for a variety of cancers, either as monotherapy or in combination together with other compounds such as immunotherapy, chemotherapy or PARP inhibitors (Jiang et al., 2024; Yano & Shiotani, 2023). Some results on ATR inhibition from clinical trials have been presented, where one clinical trial with monotherapy of VX-970 achieved a complete response in a patient harboring DDR deficiency (Yap et al., 2020). Another trial, investigating the oral compound elimusertib in heavily pretreated patients, reported partial or stable disease in 12 out of 21 patients where the responders had ATM aberrations (Yap et al.,

2021). The study employed a 3 day on 4 days off treatment regime previously identified in preclinical models (Wengner et al., 2020; Yap et al., 2021). However, adverse effects were still seen, mainly presented as anemia which was observed in approximately 80% of the patients (Yap et al., 2021). Anemia is a well described phenomenon in ATR inhibition therapy, and is suggested to be due to elevated reactive oxygen species during erythropoiesis which is increased by ATR inhibition resulting in ferroptosis (Levy et al., 2022; Ngoi et al., 2022; Ngoi et al., 2024). CHK1 inhibitors were introduced into clinical trials earlier than ATR inhibitors, due to fear of ATR inhibition having a lethal effect on normal cells (Gorecki et al., 2021). Earlier phase I clinical trials with CHK1 inhibitors were disappointing with low response rates and associated cardiac toxicity, however later clinical trials investigating prexasertib have shown more promising results (Gorecki et al., 2021). CHK1 inhibitors, in a neuroblastoma context, are being investigated together with other compounds in preclinical models. Ribonucleotide Reductase regulatory subunit M2 (RRM2) is located on 2p25.1 and is involved in nucleotide metabolism needed for synthesis of DNA (Zuo et al., 2024). RRM2 potentiates MYCN neuroblastoma formation in zebrafish and combination of CHK1 and RRM2 inhibition have shown tumor suppression in neuroblastoma xenografts and PDX compared to monotherapy (Nunes et al., 2022).

As already mentioned, ATR inhibition has shown promising results in preclinical neuroblastoma models with 25% sustained complete response in Th-MYCN mice when combined with AURKA inhibitor and in neuroblastoma cell lines where ATR inhibition potentiated cytotoxicity by PARP inhibition (Roeschert et al., 2021; Southgate et al., 2020). Recently, ATR activity was detected downstream of ALK by first identifying modifications in presumed ATR targets sites on Sad1 and UNC84 domain containing protein 2 (SUN2) upon inhibition with ALK inhibitors in neuroblastoma cells (Szydzik et al., 2021). ALK inhibition resulted in dephosphorylation of ATR at S435, S436 and S437 in neuroblastoma cells while ATR inhibition resulted in dephosphorylation/downregulation or hyperphosphorylation/upregulation of DDR and TP53 pathways respectively on a phosphoproteomic and transcriptional level in neuroblastoma cell lines (Szydzik et al., 2021). Hypothesizing that ALK/MYCN driven neuroblastoma is prone to endogenous replication stress and thus highly dependent on intact ATR function, the authors utilized a 14 day combinational treatment regime of ALK and ATR inhibitor in ALK/MYCN driven GEMMs (Szydzik et al., 2021). Early tumor response displayed signs of immune cell infiltration and apoptosis of the tumor cells, however, after 14 days treatment the tumors were in complete remission

(Szydzik et al., 2021). Moreover, lifting the treatment after 14 days resulted in sustained complete tumor response for over 200 days (Szydzik et al., 2021).

2 AIM

This thesis summarizes our investigations into the role of the ALKAL2 ALK ligand in neuroblastoma using mouse tumor models. It also explores putative therapeutic options arising from our preclinical studies of ALK signal transduction pathways, with focus on the DDR kinase ATR as a therapeutic target.

Paper I

ALK, *MYCN* and *ALKAL2* are all located on 2p. As chromosome 2p aberrations, such as gain and amplification, are observed in approximately 30% of neuroblastomas and that patients harbouring 2p gain have poor prognosis, we hypothesized that ALKAL2 might play a role in neuroblastoma tumor development (Javanmardi et al., 2020; Jeison et al., 2010; Szewczyk et al., 2019).

Paper II

A recent paper reported effective tumor suppression in ALK/MYCN driven neuroblastoma mouse models in response to 14-day treatment regime employing combined ALK/ATR inhibition (Szydzik et al., 2021). In this work we tested the hypothesis that combination therapy is superior to monotherapy, comparing ALK/ATR inhibition with ATR inhibition alone. We also assessed responses to several different ATR inhibitors in our ALK/MYCN driven neuroblastoma mouse models. Parallel omics analyses were conducted to identify potentially important signaling events in the ALK signaling pathways that might impact on the DDR response and provide mechanistic insight into the dramatic effect of combined ALK/ATR inhibition on tumor suppression. Moreover, Szydzik et al. previously reported CD68 positive immune cell (macrophage) infiltration in ATR inhibitor treated murine neuroblastomas, we conducted additional experimental analyses to test the hypothesis that the immune system is an important component in this tumor response.

Paper III (Manuscript)

With the well-established association between MYCN and ALK we hypothesized that naïve ALK signaling may play an underappreciated role in tumor formation and treatment response in MYCN driven neuroblastoma

mouse models. In this work we tested this hypothesis both genetically and pharmacologically in mouse NB models.

3 METHODS

3.1 MOUSE HUSBANDRY

To investigate the potential impact of *Alkal2* expression in MYCN-driven neuroblastoma mouse model, a custom *Alkal2* mouse was generated by Ozgene Pty Ltd (Australia). Homologous recombination was used to incorporate codon-optimized Alkal2 cDNA at the ubiquitously expressed *Gt(ROSA)26S* locus, creating the *Rosa26_Alkal2* transgenic line. The insertion was confirmed by whole genome sequencing, as well as by sequencing of PCR products after DNA extraction with DNeasy Blood & Tissue Kit (Qiagen Cat. # 69506). *Rosa26_Alkal2* mice were viable and were backcrossed for at least five generations to *129X1/SvJ* (JAX stock #000691). Mice were genotyped with primers 5′-CGCTAAATTCTGGCCGTT-3′ and 5′-ACCAGGTTAGCCTTTAAG-3′. *Rosa26_Alkal2* mice were crossed with Th-MYCN mice and tumor penetrance was followed.

Alk-F1178S, corresponding to human ALK-F1174S, mice were custom made by PolyGene Transgenetics (Switzerland). A vector containing F1178S mutation in exon 23 of *Alk* preceded by two loxp sites surrounding a minigene of exon-23-29, PolyA and a neo-cassette between two FRT sites. The construct was electroporated into embryonic stem cells and following homologous recombination was incorporated at the *Alk* locus, creating the *Alk_F1178S* line after injection of stem cells into blastocysts. Mice were bred with Flp-mice with the resulting loss of the neo-cassette. Offspring were breed against Cre-mice generating a non-conditional line harbouring the F1178S mutation in the *Alk* locus. Offspring were backcrossed to 129X1/SvJ (JAX stock #000691) and genotyping was carried out by either first DNA extraction with DNeasy Blood & Tissue Kit (Qiagen Cat. # 69506) or HotShot buffer and subsequential PCR with primers 5′–CCCTTTCAGAAGCCAGTCCTT-3′ and 5′-GAGAAGACTGCCTCTCACTC-3′ (Truett et al., 2000). Alk-F1178S mice were crossed with Th-MYCN mice and tumor penetrance was followed.

Additional strains used in this thesis are *AlkKO* and *Th-MYCN* mice which have been previously published and backcrossed to a 129X1/SvJ (JAX stock #000691) background (Weiss et al., 1997; Witek et al., 2015). AlkKO were crossed with Th-MYCN mice and tumor penetrance was followed.

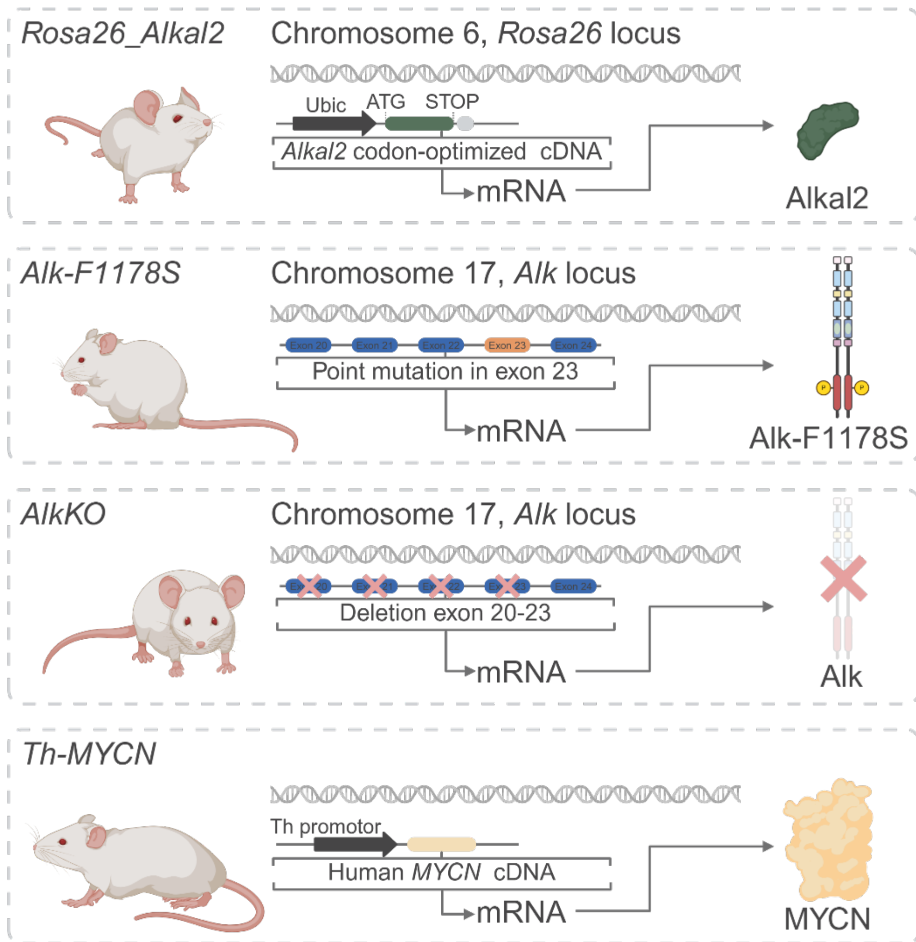

Figure 16. Overview of mouse strains utilized in this thesis. Created in BioRender. Borenäs, M. (2024) BioRender.com/ n69y125.

ALK inhibitors 10mg/kg (lorlatinib (RLor-10-21), Reagency (Australia) or selleckchem (Cat. #S7536)) and ATR inhibitors 25mg/kg (elimusertib (HY-101566) and ceralasertib (HY-19323), MedChemTronica (Sweden)) were administered by oral gavage dissolved in 2% DMSO (Sigma-Aldrich, Cat. #D4540) and 30% PEG300 (Aldrich Cat. #202371). Anti-mouse CD8α, 2 mg/kg (BioXcell, #BP0061), and the STING inhibitor H-151 (TargetMol, T5674) was delivered through intraperitoneal injection (Haag et al., 2018).

3.2 TUMOR MONITORING

Mice were screened with a Vevo 3100 imaging system (FUJIFILM VisualSonics, Toronto, Canada) to detect early tumor formation followed by follow up screens or 3D scans after treatment to determine tumor response. 3D scans were accompanied by anesthesia through isoflurane and parallel monitoring of ECG and respiration rate. 3D acquisition was done through usage of a step motor and image gating linked to respiration rate. Ultrasound acquired images were examined in VevoLab (Fujifilm VisualSonics, Canada) where tumor volume calculations were performed through either measuring the diameter of the tumor in three dimensions and using the formula for an ellipsoid or by Vevolabs open multi-slice method. Tumor volumes were also calculated through obtaining the diameter by direct measurement at sacrifice using a caliper.

Tumors were collected in 10% neutral buffered formalin (HT501128, Merck KGaA, Germany) for fixation followed by immunohistochemistry analyses, RNAlater (AM7024, Fisher Scientific, Sweden) for RNA extraction and subsequential sequencing, liquid nitrogen for methylation sequencing and proteomics, or kept at -20°C for DNA extraction and analyses.

3.3 IMMUNOHISTOCHEMISTRY

In short, tumors were fixed in formalin followed by washing in PBS. The samples were dehydrated followed by embedding in paraffin. Sections were acquired using a microtome followed by drying of the sections. Deparaffinization was followed by rehydration and heat induced antigen retrieval. After washing in TBS-T, samples were treated with hydrogen peroxide to block endogenous peroxidases. After washing in TBS-T a hydrophobic margin was drawn around the section with a water repelling pen. 5% goat serum diluted in TBS-T was used as blocking for one hour at room temperature. Primary antibodies were diluted in Signalstain® antibody diluent (Cell Signaling Technology, #8112S). After removal of blocking agent, diluted primary antibodies were added and incubated overnight at 4°C. After washing in TBS-T, sections were covered in Signalstain® Boost IHC detection reagent (HRP, Rabbit) (Cell Signaling Technology, #8114S) followed by TBS-T washing and exposure to Signalstain® DAB chromogen diluted in DAB diluent (Cell Signaling Technology, #8059S). After washing, samples were counterstained with hematoxylin, washed, dehydrated and mounted with a

cover slip. Slides were finally scanned in a Hamamatsu NanoZoomer-SQ Digital slide scanner for further analyses.

3.4 CELL CULTURE

Several neuroblastoma cell lines were cultured, treated and analyzed. Neuroblastoma cell lines utilized were NB1, IMR32, CLB-BAR, CLB-GE, CLB-GAR, SK-N-BE(2) and in house murine derived neuroblastoma cell lines. Cells were subjected to ALKAL2 stimulation, ATR inhibition, ALK inhibition, retinoic acid and etoposide with downstream analyses including western blotting, RNA sequencing, cell viability assays, cell differentiation assays, proteomics and phospoproteomics.

3.5 OMICS

In Paper I and II transcriptomics (by bulk RNA sequencing), proteomics, phospho-proteomics and genomics were applied. In short, in Paper I, RNA was extracted (Promega Total RNA Isolation Kit (Promega, Cat. #Z6111)) from two samples per tumor, to account for any possible heterogeneity. For *Alk-F1178S;Th-MYCN* and *Rosa26_Alkal2;Th-MYCN* three tumor were analyzed while two *Th-MYCN* tumors were analyzed. Isolated RNA was sent to Novogene for sequencing. Whole genome sequencing was also performed for these samples on Illumina instruments at NGI (SciLife Laboratories, Sweden). RNA-seq paired-end reads were aligned to the reference genome GRCm38 by employing hisat2, annotated using M22, quantified by HTSeq and differential gene expression determined by DESeq2 (Anders et al., 2015; Harrow et al., 2012; Kim et al., 2015; Love et al., 2014). Furthermore, RNA reads from *Rosa26_Alkal2* were mapped to the codon optimized Alkal2 cDNA to determine *Rosa26_Alkal2* expression using the R GenomicAlignments package. Moreover, the murine tumor RNA signature for all three genotypes, *Rosa26_Alkal2;Th-MYCN, Alk-F1178S;Th-MYCN* and *Th-MYCN,* were compared with six human cancers, including neuroblastoma, by a principal component analysis using R packages Limma, Facto-MineR and factoextra (Lê et al., 2008; Ritchie et al., 2015). In Paper II, RNA data from Paper I and previous studies as well as RNA from cerlasertib treated (3-day treatment, 25mg/kg, n=3) were sequenced and analyzed as described above (Borenas et al., 2021; Szydzik et al., 2021).

Phosphoproteomics were carried out on neuroblastoma cell lines NB1 (subjected to ALKAL2 stimulation with or without lorlatinib) and CLB-BAR (subjected to elimusertib, ceralasertib or DMSO proceeding cell synchronization by thymidine block) in Paper I and Paper II respectively. In brief, samples were lysed and treated with phosphatase inhibitors. Next, samples were reduced to break disulfide bridges followed by alkylation, preventing cysteine reactivity. Digestion with trypsin was followed by labelling of peptides with tandem mass tags. Separation of peptides was done through liquid chromatography followed by data-dependent MS/MS analyses on an Orbitrap mass spectrometer. For a subset of samples in Paper II, data independent acquisition, without tandem mass tag labelling, was performed. For the tandem mass tagged samples, the MS/MS data was analyzed regarding relative quantification using Proteome Discoverer version 2.2-2.4 (Thermo Fischer Scientific) and matched against Homo sapiens Swiss-Prot database for identification.

4 RESULTS AND DISCUSSION

Paper I

ALK ligand ALKAL2 potentiates MYCN-driven neuroblastoma in the absence of ALK mutation (Borenas et al., 2021)

In this study we wanted to characterize a potential role for ALKAL2/Alkal2 in neuroblastoma, using both neuroblastoma cell lines and neuroblastoma mouse models. First, we stimulated NB1 (amplified *ALK*) and IMR32 (ALK wild type receptor) with recombinant ALKAL2 ligand. ALK activation was examined by immunoblotting for activation of downstream targets of ALK (pERK and pAKT) as well as ALK-pY1278. Activation was confirmed upon ALKAL2 stimulation, which was blocked when treating with lorlatinib. To investigate the transcription response upon ALKAL2 stimulation, NB1 and IMR32 cells were investigated 1 hour after stimulation with ALKAL2 with or without lorlatinib. By overlapping RNA sequence data, six genes (*FOSB, FOS, ARC EGR3, EGR2* and *EGR1*) were identified to be upregulated and subsequently reduced upon lorlatinib inhibition with EGR1 and FOS being validated by immunoblotting. By gene set enrichment analysis, the Serum Response Factor (SRF) was identified as a potential transcription factor for all six genes. Indeed, ALKAL2 stimulation with or without ALK inhibition suggested that SRF might be a target of ALKAL2-ALK signaling. To further characterize ALKAL2 downstream signaling, NB1 cells were stimulated with ALKAL2 with or without lorlatinib, and subsequently subjected to phosphor- as well as total proteomics analyses. One of the more interesting proteins upregulated upon ALKAL2 stimulation was VGF which was concomitantly downregulated upon lorlatinib treatment. Some of the more prominent phosphorylated targets were STAT3, FOXO3 and adaptor protein CRK in line with our previous knowledge of ALK signaling.

Several other groups have previously shown that activating point mutations of Alk potentiate MYCN-driven tumor formation. The *Alk-F1178S* mouse line generated in this study was based on, and is orthologous to, an ALK mutation (F1174S) that had been reported in a relapsed neuroblastoma patient. Alk-F1178S mice do not form spontaneous tumors, however, hyperplasia is observed in celiac ganglions among young mice. Once crossed with *Th-MYCN* mice, MYCN-driven tumor penetrance is increased, which is in line with previous findings by other groups. The second mouse neuroblastoma model generated in this study, the *Rosa26_Alkal2* line, also does not form

spontaneous tumors, however when crossed with *Th-MYCN* mice tumor penetrance and survival is very similar to that observed in *Alk-F1178S;Th-MYCN* mice. ALKAL2 protein was detected in these mice and *Alkal2* cDNA was confirmed by RNA sequencing. Immunohistochemistry staining for neuroblastoma markers as well as comparing the RNA signature with human cancers confirmed murine neuroblastoma in our mouse neuroblastoma models. The *Rosa26_Alkal2;Th-MYCN* tumor RNA signature was similar to the *Alk-F1178S;Th-MYCN* RNA signature, though less pronounced. Interestingly, *Vgf* expression was increased in *Rosa26_Alkal2;Th-MYCN* and *Alk-F1178S;Th-MYCN* when compared to *Th-MYCN* tumors, though immunohistochemistry revealed no striking difference in Vgf levels within the tumors. Importantly, *Rosa26_Alkal2;Th-MYCN* tumors were sensitive to Alk inhibition, a finding that was also verified in murine derived *Rosa26_Alkal2;Th-MYCN* cell lines.

Our findings in this paper highlight the similarity between ALKAL2 signaling and ALK signaling in the context of Th-MYCN-driven neuroblastoma. This is not so surprising given v-Sis oncogenic capabilities. ALKAL2s oncogenic signaling, theoretically allows for inhibition of the extracellular domain of ALK. Suppression of ALK signaling by employing anti-ALK antibodies towards the extracellular domain has been proven possible in neuroblastoma cells, raising the question whether this approach would be effective in *Rosa26_Alkal2;Th-MYCN* neuroblastoma or in a clinical setting.

Findings of potential downstream targets of ALKAL2/ALK signaling, such as VGF and SRF, require additional future investigation. The important finding that Alkal2 potentiates MYCN in mouse models, together with the demonstration that these tumors are ALK inhibitor sensitive, open for potential treatment opportunities for a subset of neuroblastoma patients such as 2p gain patients. A patient presenting with 2p gain and a germline *ALKAL2* variant together with evidence of ALK kinase activation (as well as TRK activation) was recently reported to respond to entrectinib, further emphasizing the potential role of aberrant *ALKAL2* expression (Treis et al., 2022).

Paper II

ALK signaling primes the DNA damage response sensitizing ALK-driven neuroblastoma to therapeutic ATR inhibition (Borenas et al., 2024)

Previous findings reporting a remarkable effect of combined ALK and ATR inhibition on murine Alk/MYCN driven neuroblastoma spurred us to further

investigate this (Szydzik et al., 2021). We had previously detected ATR as a phosphotarget of ALK signaling in a study analyzing the phosphoproteome landscape of neuroblastoma cells in response to treatment with ALK inhibitors (Van den Eynden et al., 2018). In this study we undertook a phosphoproteomics study of NB1 cells stimulated with ALKAL2 ligand, identifying phosphorylation of ATR on S435 as well as S280 on CHK1 (which differs from the ATR target S/T-Q site on CHK1) downstream of ALK. The effect of ALK signaling on CHK1 was verified in two neuroblastoma cell lines, and phosphorylation of S280 was diminished upon lorlatinib treatment. Since phosphorylation of CHK1 on S280 is associated with priming the DDR we investigated DNA damage upon ALK-inhibition. Indeed, ALK inhibition increased DNA damage suggesting that ALK signaling is needed to maintain DDR integrity. To further support this, we showed that a DDR gene signature is decreased in ALK dependent cell lines upon inhibition of ALK.

We continued our investigation of ATR inhibition in a neuroblastoma setting by comparing elimusertib and ceralasertib in neuroblastoma cell lines. Although similar effects were noted for both elimusertib and ceralasertib, 20 times higher concentration of ceralasertib was consistently required to achieve this. Phosphoproteomic profiling after elimusertib or ceralasertib treatment revealed similar profiles with decreased mTOR and ATR signaling along with an upregulated ATM and DNA-PK response. However, the ceralsertib concentration needed to achieve this was 50 times higher compared to elimusertib. Not surprisingly, in mouse nueroblastoma models, elimusertib was superior to ceralsertib as a monotherapy as well as in combination with lorlatinib, compared to elimusertib/lorlatinib treatment, when survival was analyzed after treatment cessation. However, early tumor response between the groups was similar. We verified the remarkable effect of combination treatment with elimusertib and lorlatinib in murine Alk/MYCN driven neuroblastoma with six out of seven mice displaying sustained response for over 290 days after treatment cessation. In addition, we could conclude that combination treatment with ALK and ATR inhibition is superior to monotreatment with an ATR inhibitor. Surprisingly, neither blocking Cd8 positive cells nor the STING pathway had any effect on the early tumor response. However, tumor bearing mice that received 14-day elimusertib/lorlatinib combination treatment displayed a greater relapse frequency when the STING pathway was blocked during the treatment period, suggesting an important role of the inherent immune system. Furthermore, both our RNA data and immunohistochemistry suggested that tumors treated with elimusertib undergo a differentiation response, altering tumor cells to a

more differentiated Schwann/neuronal cell like state. This is further emphasized by the finding that elimusertib is able to potentiate retinoic acid differentiation in neuroblastoma cells.

Our findings underscore the potential of elimusertib/lorlatinib (ATRi/ALKi) combination treatment in murine Alk/MYCN driven neuroblastoma, which, together with the putative importance of the inherent immune system and the induced differentiation by ATRi treatment, suggests a viable treatment regime for high-risk neuroblastoma patients.

Paper III

ALK/ATR combination inhibition in neuroblastoma mouse tumors driven by MYCN (Manuscript)

Our results indicate an important and previously underappreciated role of Alk signaling as well as ALK/ATR inhibition in murine Th-MYCN driven neuroblastoma. For further discussion of these results, the reader is referred to the manuscript within this thesis.

5 CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, several important findings have been presented in this thesis.

Alkal2 potentiates murine Th-MYCN driven neuroblastoma similar to that of activating point mutations in Alk. Importantly, *Rosa26_Alkal2;Th-MYCN* tumor bearing mice are sensitive to Alk inhibition. Thus, ALK signaling through ALKAL2 could still be important among patients with ALK wild type receptor neuroblastoma, especially in subgroups of neuroblastoma patients such as those with 2p gain which may benefit from ALK inhibition therapy. More research within the field needs to be conducted before implementing ALK inhibition on ALK wild type neuroblastoma patients. However, a recent case report underscores the potential of ALK signaling through aberrant Alkal2 expression when a neuroblastoma patient presented with a germline *ALKAL2* variant and 2p gain together with evidence of ALK kinase activation (as well as TRK activation) and displayed sustained response to entrectinib (Treis et al., 2022).

Furthermore, our findings of superior long lasting tumor response in elimusertib/lorlatinib (ATRi/ALKi) treated over elimusertib (ATRi) treated murine neuroblastoma mouse models suggest a potential viable and potent treatment regime for high-risk neuroblastoma patients. This is further emphasized by the finding of differentiation induction by ATR inhibition and the importance of the endogenous immune system.

Our findings of the effect of ALK signaling on components of the DDR raises the question if a subgroup of neuroblastoma patients, already harboring somatic DDR defects or high replication stress through for example *MYCN* amplification, might be especially susceptible to ALK/ATR inhibition. If this is the case, patient work up in regard to identifying potential somatic DDR defects and replication stress in the tumor as well as the ruling out of such defects in the germline would ensure accurate tumor targeting.

The challenges for the future will be to identify those patients that might respond to tailored ALKi or ALKi/ATRi precision therapy and to design clinical trials involving several drug companies allowing for evaluation of the most promising combinational inhibitor regimes.

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