Using genetics to identify epigenetic and signal transduction targets in cancer

Akademisk avhandling

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Av

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This thesis is based on the following studies, referred to in the text by their roman numerals.

I. **Bhadury J**, López MD, Muralidharan SV, Nilsson LM, Nilsson JA*. Identification of tumorigenic and therapeutically actionable mutations in transplantable mouse tumor cells by exome sequencing. Oncogenesis. 2013 Apr 15;2:e44. doi: 10.1038/oncsis.2013.8. PubMed PMID: 23588493; PubMed Central PMCID: PMC3641362.

II. Einarsdottir BO, Bagge RO, **Bhadury J**, Jespersen H, Mattsson J, Nilsson LM, Truvé K, López MD, Naredi P, Nilsson O, Stierner U, Ny L, Nilsson JA*. Melanoma patient-derived xenografts accurately model the disease and develop fast enough to guide treatment decisions. Oncotarget. 2014 Oct 30;5(20):9609-18. PubMed PMID: 25228592; PubMed Central PMCID: PMC4259423.

III. **Bhadury J***, Einarsdottir BO, Podraza A, Olofsson Bagge R, Stierner U, Ny L, Dávila López M, Nilsson JA*. Hypoxia-regulated gene expression explains differences between melanoma cell line-derived xenografts and patient-derived xenografts. Oncotarget. 2016 Mar 18. doi: 10.18632/oncotarget.8181. [Epub ahead of print] PubMed PMID: 27009863.

IV. **Bhadury J**, Nilsson LM, Muralidharan SV, Green LC, Li Z, Gesner EM, Hansen HC, Keller UB, McLure KG, Nilsson JA*. BET and HDAC inhibitors induce similar genes and biological effects and synergize to kill in Myc-induced murine lymphoma. Proc Natl Acad Sci U S A. 2014 Jul 1;111(26):E2721-30. doi: 10.1073/pnas.1406722111. Epub 2014 Jun 16. PubMed PMID: 24979794; PubMed Central PMCID: PMC4084424.

V. Muralidharan SV, **Bhadury J**, Nilsson LM, Green LC, McLure KG, Nilsson JA*. BET bromodomain inhibitors synergize with ATR inhibitors to induce DNA damage, apoptosis, senescence-associated secretory pathway and ER stress in Myc-induced lymphoma cells. Oncogene. 2016 Jan 25. doi: 10.1038/onc.2015.521. [Epub ahead of print] PubMed PMID: 26804177.

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Using genetics to identify epigenetic and signal transduction targets in cancer

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ABSTRACT

Cancer arises mostly due to the stepwise acquisition of untamed growth capabilities by various means, ranging from genetic, epigenetic to environmental factors. With the advancement made in molecular biology and associated fields, the complex biological circuits leading to these pathological conditions have now started to be deciphered in-depth. In the present thesis I have shown that mouse exome sequencing may be used to guide targeted therapy in animal models (Paper I). In this study, we for the first time made makeshift genomes of two very popular mouse strains namely BALB/c and DBA/2J.

In a subsequent paper, we could translate the concept of genetics and mouse modeling for guiding patient enrollment into future clinical trials (Paper II). Thereafter, we used RNA sequencing to decipher similarities shared between cell line-derived xenografts (CDXs) and patient-derived xenografts (PDXs) developed in Paper II. Despite similar mutational profiles, CDXs and PDXs were very different irrespective of their genotype. Here, we unravel hypoxia and specifically hsa-miR-210 as a key player orchestrating the differences (paper III). To our dismay, abrogating the regulation dictated by miR-210 using a miR decoy; makes this cells become less sensitive to MEK inhibition *in vivo*, suggesting a possible role of hsa-miRNA-210 in conferring resistance to MEK inhibitors.

Myc proto-oncogene is deregulated in vast majority of cancers types but unfortunately remains to be inhibited by pharmacological means to date. Recently, Bromodomain and extra-terminal (BET) protein inhibitors (like JQ1) have been shown as an indirect means to inhibit Myc. We set out to test the new and orally bio-available BET inhibitor (RVX2135) in a transgenic mouse model of Burkitt Lymphoma (λ-MYC Mouse), where pathogenicity of the disease may be solely attributed to the over-expression of MYC. To our surprise, the data suggested an effect of BET inhibition independent of Myc inhibition using either the prototype JQ1 or the novel compound in our systems (Paper IV). Moreover, we not only show a possible mechanistic insight of BETi but also unravel a synergistic combination of BET and HDAC inhibitors. In a follow up paper, we show lethal synergistic combinations of BET inhibitors and inhibitors of the replication stress kinase ATR in lymphomas (Paper V).

Taken together, this thesis unravels the use of various genetic and epigenetic targets as suitable candidates for therepeutical invervention either as standalone and/or in combination; deciphered using different methods as an effective strategy for combating various cancer types both *in vitro* and *in vivo*.

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