Göteborg, 2022

Genetic determinants of lung cancer and their application toward therapeutics

The role of Zfp148 transcription factor and anaplastic lymphoma kinase (ALK) fusion proteins in non-small cell lung cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg.

Onsdagen den 14 september 2022, klockan 09:00

av

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Avhandlingen baseras på följande delarbeten

I. Zhiyuan V. Zou[1], Nadia Gul[1,2,3], Markus Lindberg4, **Abdulmalik A. Bokhari**[4], Ella M. Eklund[2,3], Viktor Garellick[1], Angana A. H. Patel[2,3], Jozefina J. Dzanan[2,3], Ben O. Titmuss[2,3], Kristell Le Gal[2,3], Inger Johansson[1], Åsa tivesten[1], Eva Forssell-Aronsson[5,6], Martin O. Bergö[7,8], Anna Staffas[9], Erik Larsson[4], Volkan I. Sayin[2,3*] & Per Lindahl[1,4*], "Genomic profiling of the transcription factor Zfp148 and its impact on the p53 pathway," *Scientific Reports*, vol. 10, no. 1, p. 14156, 2020, doi: 10.1038/s41598-020-70824-2.

II. **Bokhari AA[1]**, Lai WY[1], Le AT[2], Gabre JL[1,5], Chung, T-P[1], Fransson, S[3], Bergman B[4], Djos, A[3], Martinsson T[3], Van den Eynden J[5], Doebele RC[2], Palmer RH[1]*, Hallberg B[1]*, Umapathy G[1]*. Novel Human-derived EML4-ALK Fusion Cell Lines identify ribonucleotide reductase RRM2 as a target of activated ALK in NSCLC (Lung cancer journal, under revision).

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

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Abstract

Lung cancer causes severe morbidity and mortality in millions of patients globally each year. Anaplastic lymphoma kinase (ALK) mutations mediate initiation and progression of lung cancer in adults and young adults. However, the ways in which ALK interacts with genetic factors to trigger a variety of signaling pathways remain poorly understood. We investigated the transcription factor Zfp148, which represses activation of tumor suppressor p53, and downstream signaling targets of ALK fusion proteins in patient-derived non-small-cell-lung-cancer (NSCLC) cell lines. In addition, we investigated the efficacy of the United States Food and Drug Administration (FDA)-approved ALK inhibitors brigatinib, alectinib, lorlatinib, crizotinib, and ceritinib as modes of therapy in patients with lung cancer. The cumulative data reported in this thesis shed light on the interplay between ALK mutations and the signaling pathways triggered by ALK in the process of cancer development. Our goal is to understand underlying molecular mechanisms in patient-derived cell lines and to identify drug combinations to treat ALK-driven NSCLC. To increase our understanding of differences between two clinical variants of ALK fusion proteins (EML4-ALK variant 1 and variant 3) in NSCLC, we investigated how these variants influence the activity of downstream signaling. We showed that triapine inhibitors of the RRM2 have synergistic effects preventing DNA repair, cell cycle regulation, and ALK activation when given in combination with ALK inhibitors in patients with NSCLC expressing EML4-ALK fusion proteins.

Keywords: Zfp148, TP53, ALK, EML4-ALK, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, RRM2.

ISBN 978-91-8009-813-7 (PRINT)
ISBN 978-91-8009-814-4 (PDF)
http://hdl.handle.net/2077/71520