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Epigenetic aspects of antineoplastic activities from drugs affecting mevalonate metabolism

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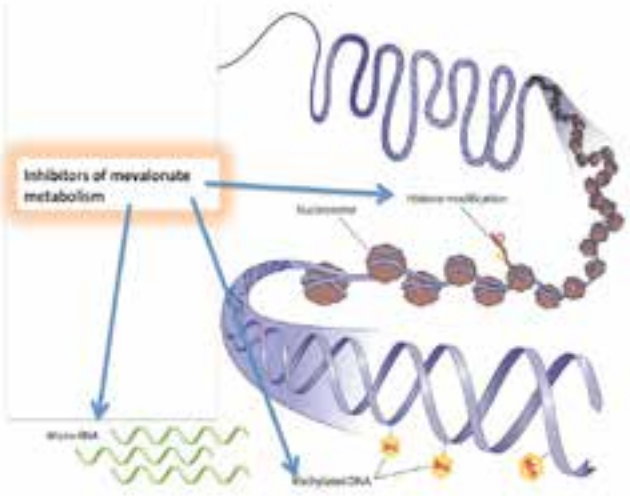
Statement of the Problem: Inhibitors of the mevalonate pathway are increasingly recognized as anti-cancer drugs. Thus, the aim of our work is to identify the molecular mechanisms and biological pathways associated with the anticancer effects of statins and bisphosphonates, which are known to downregulate the farnesylation and geranyl-geranylation of essential membrane-associated signal-transducers such as RAS and RHO proteins.

Purpose: It is to perform transcriptomic, proteomic and methylomic analyses from the neoplastic cell lines MDA-MB-231 breast cancer, PC-3 prostate carcinoma, MG-63 and U2-OS osteosarcoma and HMC-1 mast cell leukemia being treated for 6 days with pharmacologic doses with a representative statin (simvastatin) and a bisphosphonate (ibandronate). Bioinformatic analyses involve the gene set enrichment analysis (GSEA) and PathVisio software as pathway recognition algorithms.

Findings: Statin-treatment regulates more than double as many genes as a bisphosphonate. With the statin, there is an up to 90% reduction in gene expression of 3 genes namely topoisomerase (TOP2A), thymidylate synthase (TYMS) and anillin (ANLN). A stimulation of sestrin2 (SESN2) is observed both with ibandronate and statin. All these 4 genes are known for their association with a regulation of cell cycle. The downregulations of TOP2A, TYMS, and ANLN and the upregulation of SESN2 are most significant in epithelial-like cancer cell lines (MDA-MB-231 and PC-3), which also show a significant statin-associated increase in the oxidation of NADPH to NADP and associated metabolic and epigenetic consequences. In addition, treatments with simvastatin or ibandronate downregulate the epigenetic enzymes DNMT1 and the histone deacetylases (HDACs) and regulate some micro RNAs (MIR21, MIR520E, and MIR612). This provides some explanations for clinical observations, by indicating both shared and differential mechanisms for the anti-cancer and bone-preserving activities of statins and bisphosphonates in different types of malignancies. Image illustrating the epigenetic impact of statins and bisphosphonates



Recent Publications:

1. Karlic H, Herrmann H, Varga F, Thaler R, Reitermaier R, Spitzer S, Ghanim V, Blatt K, Sperr W R, Valent P and Pfeilstöcker M (2014) The role of epigenetics in the regulation of apoptosis in myelodysplastic syndromes and acute myeloid leukemia. Critical Reviews in Oncology/Hematology 90(1):1-16.

2. Karlic H, Thaler R, Gerner C, Grunt T, Proestling K, Varga F (2015) Inhibition of the mevalonate pathway affects epigenetic regulation in cancer cells. Cancer Genetics 208(5):241-252.
3. Ghanim V, Herrmann H, Heller G, Peter B, Hadzijusufovic E, Blatt K, Schuch K, Cerny-Reiterer S, Mirkina I, Karlic H, Pickl WF, Zöchbauer-Müller S and Valent P (2012) 5-azacytidine and decitabine exert proapoptotic effects on neoplastic mast cells: role of FAS-demethylation and FAS re-expression, and synergism with FAS-ligand. Blood. 119(18):4242-5
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5. Varga J, Varga F, Thaler R and Karlic H. Epigenetically active drugs target metabolic gene-regulation in leukemic cells. Webmed Central HAEMATO- ONCOLOGY 2013 4(8): WMC004342

Biography

Heidrun Karlic has her expertise in research on leukemia-associated oncogenes, metabolomics and epigenetics as well as cancer- and leukemia stem cells, and working as a Senior Researcher at the Ludwig Boltzmann Cluster Oncology (named until 2007: Ludwig Boltzmann Institute for Leukemia Research) located in the Hanusch Hospital, (Vienna, Austria), where she is employed since the year 1987. From 1981 to 1987, she worked at the Medical University in Vienna as a Research Assistant for Cell Biology in the departments of Molecular Biology and Gynecology (reproductive science and oncology). From 1974 until 1980, she studied Biology and Biochemistry at the University of Vienna, where she completed her PhD in Eco-Physiology, where systems biological approaches share some basic similarities with her recent studies on the interactions of metabolism and epigenetics.

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