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GLI2, a Hedgehog signaling pathway effector, is a transcription activator of survivin expression in human tumor cells

Jiri Vachtenheim

Charles University in Prague, Czech Republic

GLI transcription factors are effectors of the Hedgehog/GLI signaling pathway but can act also independently of the upstream signals due to their activation by several signaling pathways deregulated in cancer cells. They have an important role in the maintenance of the tumor stemness. Survivin (a “tumor protein”) levels in tumors cells are invariably high, whereas its expression is absent or extremely low in normal tissues. The general mechanism of its high and specific expression in tumor tissue remained unclear. Here, we identified survivin as a target of GLI2 and found many putative consensus binding sites for GLI transcription factors in the survivin promoter. Inhibitors of the Hedgehog/GLI pathway, cyclopamine and GANT61, decreased the survivin promoter activity in reporter assays. GANT61, a low molecular weight GLI1/2 inhibitor, repressed endogenous survivin protein and mRNA expression levels in most cells across a large panel of tumor cell lines, while expression of genes such as SRC or BCL2 were not changed. Chromatin immunoprecipitation showed GLI2 binding to the survivin promoter. Moreover, after transfection of ectopic GLI2 into normal human fibroblasts IMR90 which reveal no survivin or GLI2 expression, the endogenous survivin was evoked in these cells. The immunohistochemistry of human lung adenocarcinomas and other tumors revealed a correlation between the tissue regions showing strong GLI2 and survivin positivity. As the Hedgehog pathway is upregulated in all types of cancer cells, these findings substantially contribute to the explanation of uniform survivin expression in tumors.

Biography

Jiri Vachtenheim has completed his MD studies in 1981 and PhD in 1985 at Charles University in Prague. Part of his Post-doctoral studies was performed in Great Britain and Belgium. He is currently the Department Head and Principal Investigator at the Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University. He has published more than 40 papers in reputed journals and has been serving as a Reviewer of many papers and grants.

jiri.vachtenheim@lf1.cuni.cz

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