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Growth hormone and glucocorticoid-induced JAK2-STAT5-GR signalling for liver function, liver carcinoma development and control of peripheral lipolysis

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Abstract

Growth hormone (GH) receptor activation rapidly activates the JAK2-STAT5 pathway, which is a core cancer pathway that can drive other essential core cancer pathways such as survival and cell cycle progression. STAT5 is a weak transcription factor that needs glucocorticoid (GC) receptor (GR) cofactor function for potent gene regulation. GH signalling can also promote differentiation and it is an important cytokine for metabolic function throughout the whole body. The liver has several ways to communicate with neuroendocrine control and if hepatic GH and GC signalling is impaired it can mobilize fuel from muscle or adipose tissue to convert it to glucose. Overall, these processes are important to understand development of type II diabetes, obesity or metabolic liver cancer development. Imbalanced GH levels are involved in diseases such as dwarfism or chronic inflammation with polycystic kidney disease and liver cancer formation. Thus, we conditionally deleted the STAT5a/b and/or GR transcription factors or JAK2 tyrosine kinase in liver epithelial cells to understand these diseases in a physiologic context better. We compared their phenotypes for normal liver function or upon inflammatory hyper GH-induced hepatocellular carcinoma development. We found that STAT5 is a more prominent tumour suppressor then JAK2 and we undertook a careful genetic, biochemical and key protein analysis to explain differences in liver disease. The key role of STAT5 as an oncogene in hematopoietic cancers is well established, other cancer types like carcinomas lack behind. We found that STAT5 and GR function in adipocytes were crucial for development of metabolic liver cancer. Therefore, we followed a conditional approach do genetically deplete STAT5 or GR proteins in white and brown adipose tissue. We dissected their key function for lipolysis or other metabolic processes controlled by adipocytes. Surprising defects were manifested in the beta-oxidation pathway and catecholamine signalling. Despite that we know today from the cancer genome that ~90% of the mutations happen in tumour suppressor genes, we still have an incomplete understanding if JAK2-STAT5 activity is good or bad. Our data for loss of STAT5 and GR proteins pinpoint to tight regulation of many metabolic pathways and loss or disturbance of the STAT5-GR axis caused severe metabolic disturbances with rapid development of liver cancers.

Biography

Moriggl graduated at the age of 28 from the University Freiburg, Germany on cytokine signaling, moved to postdocs to St. Jude Children´s Research Hospital, USA, and Institute of Molecular Pathology, Austria, on immunology and hematopoietic cancer projects. He made important contributions to cancer research or the essential interaction of the hepatic glucocorticoid receptor with STAT5 controling body growth or metabolism. He heads the Ludwig Boltzmann Institute for Cancer Research since 2005. His research is focused on the JAK-STAT core cancer pathway and he published >90 peer reviewed publications.