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Meeting abstract

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Correlation of malignancy parameters in colorectal carcinoma with up- and downstream signalling partners of STAT3

A Müller*[1], M Schmitz[1], SA Tsareva[1], C Zugowski[1], F Stein[2], R Moriggl[3], SM Feller[2] and K Friedrich[1]

Address: [1]Friedrich Schiller University of Jena, Institute of Biochemistry, Jena, Germany, [2]University of Oxford, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK and [3]Medical University of Vienna, Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria

* Corresponding author

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STAT3 (Signal Transducer and Activator of Transcription 3) is persistently activated in about 90% of colorectal carcinoma (CRC) cases. However, CRC cell lines show variability in their degree of constitutive and cytokine-inducible STAT3 tyrosine phosphorylation. We have employed both surgical biopsies from CRC patients and a large collection of permanent CRC cell lines to address (1), which tyrosine kinases are involved in aberrant STAT3 activation in CRC, and (2) in which ways dysregulated STAT3 activity contributes to malignancy-associated cell behavior in CRC.

Western blot data obtained from analyzing CRC tumor specimens as well as vicinal normal tissue were quantified and statistically analysed. These studies revealed correlations between activated STAT3 on one hand and Src and JAK2 activity on the other (in particular in non-tumorous border tissue), and between Src and JAK1 activity (particularly in malignant tumor tissue). STAT3 activation shows a clear decrease in later stages of tumor progression. With regard to potential parameters of malignancy (here: invasiveness), we could show a striking coincidence of STAT3 activitation and strong expression of matrix metalloproteinases MMP-1 both by biochemical and histological analysis.

For detailled studies, we chose from an extended panel of CRC cell lines as examples (1) HT-29, in which STAT3 activity is inducible by IL-6, and (2) C-10, in which a strong constitutive STAT3 phosphorylation is observed. In C-10 cells, blockade of STAT3 dimerization by an inhibitor peptide specifically led to cell death, whereas experimental activation of STAT3 in HT-29 cells via IL-6 resulted in enhanced cell growth, MMP-1 expression and invasiveness.

In HT-29 cells, we investigated the role of IL-6-evoked STAT3 activity in the control of MMP-1 expression. Reporter gene experiments showed a direct influence of STAT3 activation on transcription from the human MMP-1 promoter. By analyzing both protein-protein and DNA-protein interactions within this promoter we obtained evidence for a complex mode a cooperative transcriptional regulation through STAT3 and AP-1. Additional STAT3 dimerization inhibitor compounds and CRC cell lines are currently being analyzed and the results will be discussed.