Advances in management of malignancies

Breast cancer

1 JAK/STAT signaling in cancer

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Interleukins (IL), growth factors and interferons exert their action on target cells via homo- or heterodimeric surface receptor complexes. Our laboratory has elucidated the molecular mechanism by which IL-6, IL-11, IL-31, oncostatin-M and leukemia inhibitory factor signal from the plasma membrane to the cell nucleus [1]. In this respect we have first described the transcription factor acute phase response factor (APRF)/signal transducer and activator of transcription 3 (STAT3) activated by tyrosine phosphorylation through receptor-associated tyrosine kinases of the Janus kinase family [2]. The tyrosine phosphorylated STAT3 is released from the receptor complex, dimerizes and translocates to the cell nucleus, where it binds to enhancer elements of IL-6-type cytokine target genes resulting in gene expression, differentiation, migration, survival and proliferation depending on the cell type.

Whereas in normal cytokine signaling STAT3-activation is transient, there is increasing evidence from different laboratories for constitutively activated STAT3 in numerous cancers including breast cancer where it has been shown to be required for malignant cellular transformation.

There are several possible mechanisms which can lead to a persistent STAT3 activation:

- by inhibition of downstream negative regulators such as suppressors of cytokine signaling (SOCS) and protein inhibitors of activated STATs (PIAS).

Regardless of the mechanism responsible for constitutive STAT3 activation, the consequence is a dysregulated expression of genes involved in the control of cell survival, proliferation and angiogenesis.

Data from a collaboration [3] will be presented showing that inhibition of gp130 signaling in breast cancer blocks constitutive activation of STAT3 and inhibits in vivo malignancy.

Furthermore, in order to block the above mentioned paracrine or autocrine stimulation by cytokines we developed a fusion protein consisting of the ligand binding domains of the IL-6-receptor subunits, IL-6R-α and the signal transducer gp130, that acts as a highly potent IL-6 inhibitor [4].

References


Real time analysis of oncogenic STAT3 in single cells

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