JAK/STAT signaling pathways and cancer[*]
Minireview

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Recent highlights in understanding molecular nature of signaling pathways that mediate biological effects of various external stimuli and control number of normal physiological processes of cells such as growth, differentiation, senescence and apoptosis, defined three major groups of proteins which apparently play an essential role in transmitting external signals from surface membrane to target genes in the nucleus. These include Janus kinases (JAKs), signal transducers and activators of transcription (STATs) and their endogenous inhibitors of SOCS family. Their inappropriate functioning and defective cross-talking associate with several human disorders including cancer. There is an increasing evidence that perturbances in STAT proteins are involved in the pathogenesis of some human malignancies. Moreover, cancer-related defective JAK/STAT/SOCS pathways may negatively affect tumor response to the cytokine-based immunotherapy.

This article provides an overview of the current knowledge about JAK/STAT/SOCS intracellular signaling cascades with special emphasis on their abnormalities in cancer.

Key words: STATs, SOCS, signal transduction, cancer, interferons.

Interferons and cancer management

Several recent statistics of cancer incidence and mortality showed that besides moderate increasing incidence of the most common cancers, the mortality has declined dramatically for only few malignancies. These data are indicative for the unsatisfactory results of current treatment approaches and denote an appeal to intensify the search for new modalities to control malignant tumors more effectively. Of various biological approaches such as neoangiogenesis inhibitors, apoptosis inducers, gene manipulation etc., only cytokine-based therapy has reached wider clinical application. The rationality of using cytokines for cancer management stands on their capability to magnify relatively weak host immune reactions to growing tumor and to render tumor cells more "foreign" for tumor bearer. In addition, some cytokines, which may be exemplified by a group of interferons (IFNs), exert varied direct effects on tumor cell or its immediate environment. Thus, for example, IFNs exhibit antiproliferative and tumoricidal activity, up-regulate the expression of adhesion proteins and MHC class I. antigens, inhibit tumor-induced neoangiogenesis and may also entail induction of apoptosis [2, 13, 14, 25, 52]. These, mostly non-immunological activities of IFNs are thought to play a significant role in their antitumor effects.

When introduced some years ago, IFNs generated the expectation to improving therapeutical results in some cancer diagnoses. Whereas the effectiveness of IFNs in hairy cell leukemia, cutaneous T-cell lymphoma and chronic myelogenous leukemia is well established, the response of "solid tumors" which represent over 90% of all human malignancies has been less than expected or hoped for. It fluctuates between 15–20% only, regardless the type of IFN used, dosage schedule and mode of application [44]. In addition, it is still not evaluated thoroughly to what extent IFN treatment affects median survival of responders.

Until recently, the unexpectedly low therapeutical re-

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