

The transforming growth factor beta 1/SMAD signaling pathway involved in human chronic myeloid leukemia

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ABSTRACT

Transforming growth factor beta 1 (TGF- β 1) is the prototypic member of a large family of structurally related pleiotropic-secreted cytokines. The TGF- β 1/SMAD signaling pathway usually participates in a wide range of cellular processes such as growth, proliferation, differentiation and apoptosis. Upon binding on TGF- β 1, the dimerized TGF- β type II receptors recruit and phosphorylate the TGF- β type I receptors, which phosphorylate the receptor-regulated SMAD (SMAD2 and SMAD3) presented by the SMAD anchor for receptor activation.

The phosphorylated receptor-regulated SMAD form heterologous complexes with the common-mediator SMAD (SMAD4) and subsequently translocate into the nucleus, where they interact with other transcription factors to regulate the expression of target genes. This multi-functional signaling pathway modulated by various elements with complex mechanisms at different levels is also inevitably involved in cancer. We herein present data on the role of the TGF- β 1/SMAD signaling pathway in human chronic myeloid leukemia and explain the potent biological effects of TGF- β 1 on leukemia cells. The paper is based on a review of articles selected from Cancerline and Medline data bases.

The constitutively active tyrosine kinase produced by the specific Bcr-Abl fusion gene on the Philadelphia chromosome can enhance the resistance of malignant cells to TGF- β 1-induced growth inhibition and apoptosis, which contributes to enhancement of proteasomal degradation of p27. However, overexpression of the EVI1 gene, which is also caused by Bcr-Abl, can recruit the C-terminal binding protein and histone deacetylase to prevent the MH2 domain on SMAD3. The later is essential for transcription activation on target genes and leads to blockage of the TGF- β 1/SMAD signaling pathway.

Some studies have indicated that certain therapeutic agents applied in clinical treatment can inhibit proliferation and promote differentiation of leukemia cells by way of modulation of the TGF- β 1/SMAD signal pathway. For example, arsenic trioxide can promote specific degradation of the AML1/MDS1/EVI1 oncoprotein and inhibit the proliferation of leukemia cells. However, specific histone deacetylase inhibitors can interrupt the effect of histone deacetylase to alleviate EVI1-mediated suppression of TGF- β 1/SMAD signaling. The tyrosine kinase inhibitor in the target therapy of chronic myeloid leukemia can effectively inhibit the tyrosine kinase activity of Bcr-Abl and induce suppression on the TGF- β 1/SMAD signaling pathway.

The TGF- β 1/SMAD signaling pathway plays an important role in chronic myeloid leukemia cells and leads the leukemia cells to growth inhibition, differentiation and apoptosis. The positive influence of the TGF- β 1/SMAD signaling pathway in chronic myeloid leukemia is fairly significant, and its potential effects in clinical treatment will bring about definite benefits.

Since it is a complex signaling pathway widely involved in many aspects of cellular activities, further study and comprehensive analysis of the TGF- β 1/SMAD signaling pathway are imperative and will have a guiding significance in research and clinical applications. It is an exciting area for future research. Free full text available at www.tumorionline.it

Key words: chronic myeloid leukemia, transforming growth factor beta 1, SMAD, BCR-Abl.

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