

# Transcription response in the TGF-beta pathway

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Transforming growth factor beta (TGF- $\beta$ ) is a signaling molecule involved in the regulation of numerous cellular responses, such as cell growth and cell death (apoptosis). Escaping from TGF- $\beta$ -induced apoptosis is one of the hallmarks that characterizes cancer cells. TGF- $\beta$  plays important roles in tumor development. Originally TGF- $\beta$  acts as a tumor suppressor and inhibits cell growth in most cell types, but once the tumor has been established, most cells become resistant to TGF- $\beta$  and TGF- $\beta$  turns pro-oncogenic (i. e. helps tumor growth).

TGF- $\beta$  binds to and activates receptors, small molecules present in the surface of the cell whose roles are to bind other molecules. Those receptors bind and activate Smads proteins, a family of proteins that directly mediate TGF- $\beta$  signaling. Once activated, the Smads proteins are transported to the nucleus, where they regulate the expression of certain genes through the interaction with other proteins that stimulate or inhibit expression of these genes. Such genes mediate the biological effects of TGF- $\beta$ . Some of the activated genes stimulate tumor development, while others suppress it. Hence it is of great importance to study those genes, to deepen the knowledge about the molecular mechanism underlying cancer.

The aim of this project was to identify genes regulated by Smad2 and Smad4, which directly mediate TGF- $\beta$  signaling, in a human liver-cancer cell line. For that purpose I used a state-of-the-art method to analyze protein interactions with DNA. Using this method I could determine what genes were regulated in TGF- $\beta$ -treated and untreated cells and by comparing these conditions determine what genes were specifically regulated by TGF- $\beta$ .

In order to validate the data obtained I confirmed that binding of Smad4 to well known target genes of the TGF- $\beta$  pathway occurred. Analysis of these data together with information from previous studies revealed interesting insights about a possible regulation mechanism for some TGF- $\beta$ -related genes. Moreover, a list of genes potentially regulated by TGF- $\beta$  was obtained. Such candidate genes represent unexploited potential targets for cancer treatment. Emerging gene-based therapies, such as gene regulation by enhancing or suppressing expression or gene insertion (tumor suppressors, apoptosis-inducing genes, etc.) targeting cancer cells are in a growing number of clinical trials worldwide. Those innovative approaches combined with conventional therapies such as chemotherapy, radiotherapy and surgery can lead to a more effective and less invasive ways of cancer treatment.

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