【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Biological Sciences)

Title of Project : Transcriptional Regulation by TGF-β Signaling and its Relation to Progression of Cancer

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Research Project Number : 15H05774 Researcher Number : 90209908
Research Area : Tumor biology
Keyword : Signaling, Biochemistry, Cancer microenvironment, Cancer stem cell, Genome research

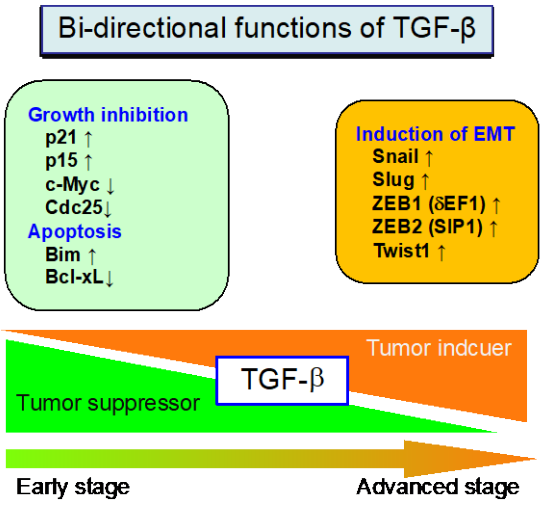
【Purpose and Background of the Research】

Transforming growth factor-β (TGF-β) was identified in the early 1980s as a factor that induces the anchorage-independent growth of normal fibroblasts. TGF-β was subsequently found to inhibit the growth of most types of normal cells, including epithelial cells and lymphocytes. In the mid-1990s, TGF-β was shown to induce the epithelial-mesenchymal transition (EMT) in certain epithelial cells. TGF-β is now known to exhibit bi-directional effects, i.e. tumor-suppressive effects and tumor-promoting effects, during cancer progression (figure below).

In this project, we will investigate how TGF-β loses its tumor-suppressive effects and acquires tumor-promoting effects during cancer progression. We will uncover the molecular mechanisms underlying the bi-directional effects of TGF-β on tumors using next-generation DNA sequencers, analyze EMT cell phenotypes using proteins and/or genes expressed in the cells undergoing EMT, and identify some TGF-β targets with therapeutic potential for certain types of cancer.

【Research Methods】

Project 1. Investigate dynamic changes in the transcriptional machinery as regulated by the



TGF-β-Smad pathways.

Project 2. Analyze cellular phenotypes regulated by the TGF-β-induced EMT, focusing the function of ZEB1 (δEF1) and other transcription factors.

Project 3. Determine the mechanisms of cancer invasion and metastasis induced by the TGF-β through analyzing new Smad2/3 target genes identified by RNA sequencing and other methods.

【Expected Research Achievements and Scientific Significance】

The biological importance and complicated mechanisms of action of TGF-β make them especially interesting to study. Much effort has been devoted to developing antagonists against TGF-β family proteins and their receptors, and some are in clinical trials. However, a better understanding of the TGF-β signaling pathways would facilitate the clinical development and application of such antagonists. The EMT is involved in the invasion and metastasis of cancer, but the underlying mechanisms are still not fully understood. Drugs that regulate the EMT have yet to be developed, and such drugs may be useful for treatment of certain types of cancer in the future.

【Publications Relevant to the Project】

・Isogaya K, *Koinuma D, Tsutsumi S, Saito RA, Miyazawa K, Aburatani H, *Miyazono K. A Smad3 and TTF-1/NKX2-1 complex regulates Smad4-independent gene expression. **Cell Res.** 24 (8): 994-1008, 2014.

・Shirakihara T, Horiguchi K, Miyazawa K, Ehata S, Shibata T, Morita I, *Miyazono K, *Saitoh M. TGF-β regulates isoform switching of FGF receptors and epithelial-mesenchymal transition. **EMBO J.** 30 (4): 783-795, 2011.

【Term of Project】

FY2015-2019

【Budget Allocation】

153, 800 Thousand Yen

【Homepage Address and Other Contact Information】

http://beta-lab.umin.ac.jp