Title: TGF-β signaling in cancer

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Speaker

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CAREER HISTORY

1981: M.D. degree, Faculty of Medicine, Univ. of Tokyo

1988: Assistant of Professor, Third Dept. Int. Med., Univ. of Tokyo

1989: Doctor of Medical Science, Faculty of Medicine, Univ. of Tokyo

1990: Assistant Member, Ludwig Institute for Cancer Research, Uppsala, Sweden

1995: Member and Chief, Department of Biochemistry, The Cancer Institute, Japanese Foundation for Cancer Research

2000: Professor, Department of Molecular Pathology, Graduate School of Medicine, Univ. of Tokyo

2011: Dean, Graduate School of Medicine, Univ. of Tokyo

AWARDS

1999: Honorary Doctor of Medicine of Uppsala University, Sweden

2000: Princess Takamatsu Cancer Research Award

2009: Medal of honor with purple ribbon from the Japanese government

2011: Japan Academy Prize

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ABSTRACT:

TGF-β elicits both pro-tumorigenic and tumor suppressive functions during progression of cancer. We present our recent findings on TGF-β signaling in progression of cancer, focusing on induction of epithelial-mesenchymal transition (EMT) by TGF-β. TGF-β induces EMT through activation of Smad and non-Smad signaling pathways. Inhibition of TGF-β signaling by Smad7 or small molecular weight TGF-β inhibitor(s) results in prevention of cancer metastasis in mouse models. Multiple transcription factors, including δEF1/ZEB1, SIP1/ZEB2, and Snail, play critical roles in TGF-β-induced EMT.
TGF-β induces EMT in normal and transformed cells. We have found that FGF-2 enhanced TGF-β-induced morphological changes and activation of ECM degradation. Normal mouse epithelial NMuMG cells treated with TGF-β and FGF-2 enhanced the invasion of co-cultured breast cancer cells into collagen gels in vitro. Thus, TGF-β and FGF-2 may cooperate with each other to produce activated fibroblasts in tumor microenvironment, and the activated fibroblasts in turn secrete some substances, e.g. MMPs, to induce invasion and metastasis of cancer.
TGF-β-induced EMT involves isoform switching of FGF receptors by alternative splicing. We have found that TGF-β induces broad alteration of splicing profiles by downregulating epithelial splicing regulatory proteins (ESRPs).
Thyroid transcription factor-1 (TTF-1/Nkx2-1) is expressed in lung cancer, but its functional roles remain to be elucidated. TTF-1 that inhibited TGF-β-mediated EMT and restored epithelial phenotype in lung adenocarcinoma cells. This effect was accompanied by down-regulation of TGF-β target genes, including Snail and Slug. Genome-wide analyses by ChIP-seq revealed that TTF-1 co-localized with Smad3 on the chromatin and altered the binding patterns of Smad3 throughout the genome. We also propose a new model of regulation of TGF-β-Smad signaling by TTF-1.