Crosstalk among TGF-β, Hedgehog and Wnt signaling pathway during EMT

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***Short Abstract* — Epithelial to mesenchymal transition (EMT) is a key step in cancer metastasis. It involves cooperation of signaling pathways, such as Transformation growth factor-β (TGF-β), Wnt and Hedgehog (HH) pathways. These signaling pathways cooperate together and converge to Snail upregulation to turn on the core switches of EMT. The functional roles of multi-signaling pathway crosstalks in EMT remain to be explored. In this project, we use integrated computational modeling and quantitative experimental studies to investigate TGF-β induced signaling crosstalk to promote Snail expression and EMT.**

***Keywords* — TGF-β, Hedgehog, Wnt, EMT, signal trasduction.**

I. Purpose

THE process of cells transformed from health to cancer cells and the promotion of cancer cell metastasis involves multi-steps, such as evading growth suppressors, avoiding immune destruction, enabling replicative immortability, genome instability and mutation, activating invasion and metastasis, and so on [1]. EMT, which transforms the regular-shaped epithelial cells with tight cell-to-cell attachment to spindle-like mesenchymal cells with loose or no cell-to-cell attachment, plays a key role in cancer metastasis. Previous studies showed that EMT can be induced in most of the mammalian cell lines by exogenesis signals, such as TGF-β, epithelial growth factor (EGF), HH, *etc.*, and is regulated by a delicate signaling network [2].

TGF-β is a major inducer of EMT. The core process of the transformation involves two transcription factors, Zeb and Snail, and two families of microRNAs, miR-34 and miR-200. These four components form two coupled double-negative feedback loops that enable EMT process following two steps, first transition to partial EMT then to full EMT [3, 4]. The canonical TGF-β signal transduction pathway involves TGF-β receptor (TGFBR) to SMAD family and finally to Snail [5, 6]. However, many bypasses also exist in response to TGF-β signaling, resulting crosstalk to other signaling pathways. For instance, SMAD3 and SMAD4 that are promoted by TGF-β also induce Gli1/2. As two are major transcription factors in HH signaling pathway, Gli1/2 also regulate Snail expression. Meanwhile, TGF-β also activates β-catenin, which is associated to the Wnt pathway and binds to the promoter region of Gli to upregulate its expression [7]. The question then lay on the reason behind the fact that a single signal input promotes actually more than one signaling pathways and how they operate together to regulate Snail1 and EMT.

II. Experiment procedure

We constructed a mathematical model based on experimental results that were collected from previous studies. After systematical analysis of the model, we found that the the three pathways are coordinately regulate Snail1 and EMT. Now we are confirming our predictions qualitatively by traditional biochemistry experiments (flow cytometry, qPCR and western plot) and combined with cut-edge technology such as CRISPR for quantitatively verification.

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