Deciphering the cellular integration of contradictory BMP and TGFβ signals

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Underlying question: How do cells encode combinatorial information from their signaling environment to control their cell fate determination?

Cells continuously interpret various signals in their surroundings, integrating them to create an intracellular representation of the extracellular milieu. Despite our extensive knowledge of the molecular intricacies of individual pathways, a comprehensive understanding of how cells process multidimensional information remains elusive. In our lab, we employ a combination of systematic experiments and quantitative modeling to decipher the principles governing information processing within cells. In particular, we study the BMP and TGFβ pathways, which play crucial roles in a wide range of biological processes, from early embryonic development to pathological conditions such as cancer. Extensive research has explored the individual impacts of these pathways on specific differentiation processes. Frequently, these two pathways exert opposing effects on cellular processes. During the epithelial-to-mesenchymal transition, for example, TGFβ acts as a strong inducer of the transition towards a mesenchymal state, while BMP supports an epithelial state. Despite their contrasting roles, in many biological contexts, cells are simultaneously exposed to ligands from both the BMP and TGFβ families. These pathways provide a compelling model system for studying the combinatorial effects of opposing ligands on cellular behavior.

To unravel how cells manage contradictory signals, we employ synthetic reporters to quantify the activity levels of both pathways. Our analysis spans a broad spectrum of stimuli, revealing novel molecular mechanisms within the signaling networks. Notably, we identify an unexpected asymmetric crosstalk biased towards the TGFβ pathway, reducing ambiguity in pathway activity compared to the extracellular environment. This effect proves to be generalizable across genes, ligand variants, and cell types. Employing mathematical models, we predict and experimentally validate a combinatorial interaction between the pathways. Specifically, through combinatorial dimerization of pathway mediators, BMP pathway proteins are redirected to activate TGFβ targets, highlighting the computational capabilities of signaling pathways in interpreting cellular environments.

Our study extends beyond elucidating cellular responses to conflicting signals, offering a broader perspective on signaling pathways as computational entities shaping cellular decisions during cell fate determination. This research opens new avenues for exploring and controlling cellular behaviors in diverse contexts.

References:

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