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EDITORIAL

A special issue on TGF-β signaling

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TGF-β-initiated signaling is undoubtedly one of the most important and well investigated signaling events as TGF-β controls cell proliferation, differentiation, death and motility, and therefore plays an essential role in embryonic patterning and homeostasis of adult tissues. Deregulation of TGF-β signaling has been shown to be associated with several major diseases. Much has been learnt about the Smad-mediated canonical TGF-β signaling pathway in the last decade. However, modulation of this pathway via regulation of protein stability and subcellular localization, the crosstalk between the TGF-β/Smad pathway and other signaling pathways, and Smad-independent TGF-β signaling pathways just starts to become clear. This special issue presents 10 review articles covering current understanding of these major issues as well as the physiological and pathological roles of TGF-β in stem cell self-renewal, cell differentiation, angiogenesis and cancer metastasis.

A well established TGF-β signaling pathway is the Smad-dependent pathway. TGF-β binding to its two cell surface signaling receptors results in the formation of the receptor heterocomplex and activation of the type I receptor, which in turn activates the cytoplasmic receptor regulated-Smad (R-Smad) proteins via phosphorylation at their C-terminal tails. Once phosphorylated by the receptors, R-Smad associates with the common Smad, Smad4, and together they are transported to the nucleus where they regulate the expression of target genes in collaboration with other factors. In addition to receptor-mediated activation, Smad activity can be modulated by different means, such as dephosphorylation, protein stability regulation, interaction with other proteins, cytoplasmic/nuclear localization, etc. In the past 3 years, several Smad phosphatases have been identified that remove the phosphates added to serine residues at the C-terminal tails or to serine/threonine residues in the middle linker regions of R-Smad proteins. Xin-Hua Feng and colleagues summarize how phosphorylation-dephosphorylation modulates the activity of TGF-β receptors and Smad proteins. Aristidis Moustakas and colleagues review ubiquitination/sumoylation and stability of TGF-β receptors and Smad proteins. Caroline Hill describes the continuous shuttling of Smad proteins between the nucleus and the cytoplasm, the underlying mechanisms and the role of the shuttling in TGF-β signaling. Julien Deheuninck and Kunxin Luo summarize recent findings on the biological functions of Ski and SnoN, two negative regulators of TGF-β signaling, and the mechanisms of their action. Furthermore, Ye-Guang Chen presents evidence of how endocytosis regulates TGF-β signaling in both positive and negative manners.

One mechanism underlying the multi-functionality and complexity of TGF-β action is that TGF-β can signal via other non-Smad pathways, such as through activation of small GTPases, MAPK and PI3K/Akt, which is reviewed by Ying Zhang. Another addition to the complexity of TGF-β action is the crosstalk between TGF-β signaling and other signaling pathways. Xing Guo and Xiao-Fan Wang describe the different modes of cross-talk between TGF-β/BMP and the signaling pathways of MAPK, PI3K/Akt, Wnt, Hh, Notch and IL/IFNγ/TNFα and the underlying molecular mechanisms.

TGF-β is a multifunctional cytokine. With the current understanding of the molecular details and the regulatory mechanisms of TGF-β signaling, the molecular bases of TGF-β action in a specific physiopathological context have started to emerge. Tetsuro Watabe and Kohei Miyazono summarize recent findings on the roles of TGF-β family signaling in stem cell self-renewal and differentiation. Rik Derynck and colleagues will review the role of TGF-β in epithelial to mesenchymal transition (in the coming February issue). Peter ten Dijke and colleagues present recent advances in our understanding of the role of TGF-β signaling in vascular biology and related diseases. TGF-β possesses

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the well known tumor-suppressing activity at early stages of tumorigenesis, but promotes tumor development in late stages. David Padua and Joan Massagué review current understanding of the role of TGF-β in tumor metastasis.

Although this special issue is far from covering every aspects of the TGF-β functions, we do hope that the review articles presented here can offer our readers an appreciation of the current development in our understanding of TGF-β signaling and the complex physiology regulated by this important pathway.