

Conserved in Structure but Diverse in Recognition

The crystal structure of BMP7 in complex with the type II activin receptor shows a different receptor binding site on the ligand compared to that observed in the TGF- β 3 and receptor complex. The result highlights the potential diversity in ligand recognition among members of the TGF- β superfamily.

Members of the transforming growth factor β (TGF- β) superfamily of cytokines signal through recruitment of their type I and type II receptors by a mechanism that requires the bound type II receptor, a serine and threonine kinase receptor, to phosphorylate a GS box region of the type I receptor and thereby activate its type I counterpart. The activated type I receptor, also a Ser and Thr kinase receptor, then initiates a signaling cascade through SMADs and other signaling components, leading to transcriptional activations. A unique feature of the TGF- β superfamily signaling that eluded the pursuit of structural biologists for years is how the cytokines orchestrate the heterodimeric receptor activation through binding. Parts of this signaling complex have been worked out recently by the determination of two binary receptor-ligand complexes: BMP2 in complex with its type I receptor ligand binding domain, and TGF- β 3 in complex with its type II receptor ligand binding domain [1, 2].

The work by Greenwald and colleagues published in the March issue of *Molecular Cell* [3] describes the crystal structure of BMP7 in complex with a type II activin receptor (ActRII), which is known to bind and deliver signals from BMP molecules. This is the second structural example of a type II receptor complexed to a member of the TGF- β superfamily of cytokines. Through sequence homology and mutational analysis, Greenwald et al. have demonstrated that the type II BMP receptor would share the same binding site on BMP7 as ActRII. This work contributes an important piece of the puzzle toward the ultimate goal of solving the structure of the ternary complex between cytokine and type I and II receptors. Of particular interest is the fact that the current BMP7/ActRII complex reveals a different binding site for the type II receptor on BMP compared to a homologous TGF- β 3 and its type II receptor complex (TGF- β 3/TBRII). As a result, a different model for a ternary complex between BMP and its type I and II receptors is proposed by Greenwald et al. (Figure 1). In the TGF- β ternary complex model, the type II receptor makes direct contacts to its type I receptor in addition to TGF- β , explaining the prerequisite of the type II receptor for the binding of the type I receptor. A note of caution with the TGF- β ternary complex model is the assumption that the type I receptor binds to a similar site on TGF- β as does the type I BMP receptor on BMP. The validity of this assumption is questionable from current work showing the type II activin receptor bound to a topologically distinct location on BMP as does the type II TGF- β receptor on TGF- β . In the BMP-receptor ternary complex model, however, there is no direct contact between the type I and II receptors, consistent with the fact that both types of BMP receptors bind their ligands indepen-



Figure 1. Proposed Ternary Receptor-Ligand Binding Model for TGF- β and BMP Signaling

The type I and II receptors are shown to bind TGF- β and BMP in two different ternary complex models. In the TGF- β receptor binding model, the type I receptor would interface with the type II receptor in addition to TGF- β . In contrast, the BMP receptor model predicts no direct contact between the two receptors.

dently. The lack of appreciable cooperativity in binding to BMP by its receptors is also confirmed in a BIAcore-based solution binding experiment by Greenwald et al.

Perhaps even more importantly, the structural difference between the TGF- β 3/TBRII and BMP7/ActRII complexes illustrates a potential diversity in ligand recognition among members of TGF- β superfamily of cytokines. As noted by the authors, despite the well-preserved structural folds among both the cytokines and their type II receptors, individual type II receptors may recognize their cytokines in distinct manners, as illustrated in the BMP7/ActRII and TGF- β 3/TBRII structures. It would be interesting to see whether this diversity in recognition also applies to the type I receptors, as their sequences are no more conserved than those of type II receptors. One question yet to be resolved, however, is how receptor cooperativity is achieved in activin and activin receptor signaling if the cytokine-receptor ternary complex resembles that proposed by Greenwald et al. for BMP and the type II BMP receptor complex. Activin, like TGF- β , displays a similar functional preference to its type II receptor as its distinct high-affinity receptor. However, the presumed BMP receptor-ligand ternary complex model for activin lacks direct contacts between its type I and type II receptors, leaving the receptor cooperativity unexplained, at least not through the extracellular receptor-ligand interactions. To further understand the structure-based receptor cooperativity in both TGF- β and activin signaling, the key clearly resides in the solution to the crystal structures of the ternary receptor-ligand complexes for members of TGF- β superfamily.

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Selected Reading

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