A new β-catenin/Tcf binding site in DNA mediates robustness in gene regulation

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Fate patterning in embryonic development relies on activation of specific genes at the right time, place, and dose. One important mode of regulating gene expression in development is through activation of signaling pathways. A major signaling pathway in early development is the Wnt/β-catenin pathway. Activation of Wnt signaling in early *Xenopus* embryo leads to *siamois* expression, which is necessary and sufficient to specify the dorsal-anterior cell fate. We have previously observed that dorsoanterior patterning in *Xenopus* and *siamois* expression are buffered against variation in the biochemical parameters of the Wnt pathway (e.g., concentration of Axin, concentration of GBP, activity of GSK3β) (1). Here we demonstrate that the buffering can be recapitulated by a 1-kb region upstream of *siamois*. Using promoter bashing and directed mutagenesis, we identified a distal 11-bp element that is necessary for the buffering. Using electrophoretic mobility assay, biochemical assays, and chromatin immunoprecipitation, we demonstrate that the 11-bp element competes with the canonical Tcf sites by binding directly to the β–catenin/Tcf complex. Thus, a new, dynamic circuit interprets Wnt signaling: β-catenin/Tcf acts through a new DNA binding site that interacts with the established canonical site in an incoherent feedforward fashion, and mediates the robustness in gene expression and *Xenopus* development. In the context of our previous work (1,2), this circuit serves as a putative mechanism of Weber's Law detection, by which cells compute the ratio of β-catenin level after to before stimulation. As Weber's Law has now been found in a growing number of metazoan signaling pathways (3-5, and our unpublished results in Tgfβ pathway), this finding may have broad implications.

References

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