Modeling the regulation of β-catenin by Wnt stimulation and GSK3 inhibition

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Background: Wnt/β-catenin signaling is crucial for cell renewal and differentiation. Aberrant signaling caused by specific mutations plays an important role in oncogenesis. A better understanding of these signaling mechanisms is therefore crucial. We have constructed a Petri net model of Wnt/β-catenin signaling that captures the regulation mechanisms of the transcriptional co-activator β-catenin. Main components included are the Wnt receptors, the destruction complex and three of its crucial components AXIN, AXIN2 and GSK3. We included an important feedback loop of upregulated AXIN2 expression by β-catenin.
Description: We simulated the model with Wnt stimulation (i.e. normal signaling) and GSK3 inhibition (i.e. aberrant signaling). β-catenin increased earlier and to higher levels for aberrant signaling compared to normal signaling. We experimentally validated these observations by western blot and TCF/LEF luciferase reporter assay. In addition, our simulations show that the feedback from AXIN2 expression has a negative effect on normal signaling, but no effect during aberrant signaling.
Conclusions: During aberrant signaling β-catenin increases earlier and to higher levels compared to normal signaling. The feedback from AXIN2 has a negative effect on β-catenin during normal signaling, where AXIN is the limiting factor, and not during aberrant signaling. Using this model we predicted the β-catenin behavior from other important mutations found in breast and colorectal cancer. In summary, our model can be used to explain plausible underlying mechanisms for oncogenic signaling.