

The IRAK Regulatory Module in IL-1 Signaling

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Recruited to plasma membrane by activated receptors through interaction with MyD88, the IRAK4/IRAK1 complex undergoes multi-step phosphorylation to produce activated IRAK1 proteins. Activated IRAK1 protein can complex with TRAF6 and activate the MAPK and NF-kappaB cascades to induce cytokine production. The activated IRAK1 protein is also subjected to ubiquitin-mediated degradation (for details see Oda and Kitano, 2006). This regulatory module is essential for the signaling of IL-1, IL-18, a subset of Toll-Like Receptors (TLRs). IL-1 signaling is implicated in many inflammatory and auto-immune diseases. In this study, we focus on integrating pre-existing biological knowledge to understand the role of the IRAK regulatory module in IL-1 signaling of epithelial cell-types.

The model for the IL-1 signaling network was constructed in SBML using the Systems Biology Workbench (SBW) (Fig. 1). The focus of the model is on the IRAK regulation module which is consisted of sequential activation followed by elimination of excessive active IRAK1 through degradation. During the model construction, we came across a recent discovery on the importance of IRAK module in IL-8(CXCL8) signaling to NF-kappaB. Additional literature analysis confirmed the existence of an IL-8 autocrine loop in the epithelial cell-types. Since IL-1 signaling can activate the transcription of IL-8 through AP-1 or NF-kappaB, the existence of a positive feedback loop downstream of IL-1 signaling can greatly impact the dynamic behavior of the network.

Network analyses were performed on the model with various parameter sets. Without the IL-8 autocrine loop, a short IL-1 stimulation lead to a pulse of the active IRAK1/TRAF6 complex then inactivated by the rapid IRAK1 degradation. When the positive feedback of the autocrine loop is coupled with the damping of active IRAK1, the network can achieve very stable steady states of constitutive IL-8 expression that are robust against any change in IL-1 level. In other words, the IL-8 expression will persist even after the IL-1 signal disappears. Constitutive expression of IL-8 expression has been reported in several epithelial-related diseases, for example severe asthma and inflammatory bowel disease. It is possible that these disease-inflicted cells are those stuck in the alternative steady states. To rescue these cells from constitutive IL-8 expression, different parameters in the network were perturbed. We identified parts of the network that are potential candidates for therapeutic interventions.