Network-based Systems Pharmacology Model to Identify Novel Treatment Strategies for Bortezomib-induced Peripheral Neuropathy.

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Objectives: To develop a systems pharmacology model of neuronal signal transduction and gene regulatory processes involved in the development of chemotherapy-induced peripheral neuropathy, and to utilize network-based systems analyses to identify potential therapeutic interventions for the treatment of bortezomib-induced peripheral neuropathy (BIPN).

Methods: A Boolean network model of intracellular signaling and gene regulation in neurons was constructed from literature and pathway mapping in KEGG. The network was validated by comparing model predictions with a microarray dataset of oxidative stress effects in ATF4 knockout neurons. Network simulations were performed for the (1) absence of drug, (2) presence of bortezomib, and (3) bortezomib plus antioxidant therapy. A minimal intervention analysis was performed in CellNetAnalyzer to identify single and combination treatment strategies that prevent neuronal apoptosis in the presence of bortezomib. An attractor analysis was conducted with BoolNet to identify stable states of the system and to evaluate the effectiveness of select single and combination treatment strategies for decreasing neuronal apoptosis.

Results: We constructed a neuronal signaling network that contains 131 nodes and 252 regulatory interactions (Figure 1). Network simulations showed that bortezomib increases apoptosis, which is prevented by antioxidant therapy. Minimal intervention analysis identified 226 potential treatment strategies to prevent neuronal apoptosis, consisting of 2 one-target, 109 two-target, and 115 three-target interventions. The inhibition of PARP was identified as a single target intervention. Inhibition of TNFα signaling was identified in all two-/three-target interventions. Attractor analysis identified 276 stable states in the network and revealed that antioxidant therapy in combination with TNFα inhibition should completely prevent the activation of apoptosis.

Conclusions: The development and analysis of a network-based systems pharmacology model of neuronal signaling pathways led to the identification of potential treatment strategies for BIPN. TNFα was identified as an important target, and its inhibition in combination with antioxidant therapy could serve as a potential therapy for BIPN. The model presented here can be easily extended to investigate peripheral neuropathy associated with other chemotherapeutics.