Computational Simulation and Verification of HMGB1 Signaling Pathway

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Recent cancer studies have found that overexpression of the High-mobility group box-1 (HMGB1) protein, in conjunction with its receptors for advanced glycation end products (RAGEs), is associated with proliferation in breast and pancreatic cancers. We have developed a rule-based model of crosstalk between HMGB1 signaling and other key cancer signal pathways. The model has been simulated using both ordinary differential equations (ODEs) and discrete stochastic simulation. Then, we apply an automated verification technique, Statistical Model Checking, to validate formally interesting temporal properties of our model. Our simulations show that, if HMGB1 is overexpressed, then the oncoproteins CyclinD/E, which regulate cell proliferation, are activated or overexpressed, while tumor suppressor proteins which regulate cell apoptosis (programmed cell death), such as p53, are repressed. The discrete, stochastic simulations show that p53 and MDM2 oscillations continue even after 10 hours. This property is not exhibited by the deterministic ODEs simulation. Moreover, the models also predict that mutation of RAS, ARF and P21 in the HMGB1 signaling pathway could influence the cancer cell's fate – apoptosis or survival – through the crosstalk of different pathways.