A logical model for the bimodal p53 switch in cell-fate control

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The p53 pathway is activated in response to DNA damage, leading to different cell fate decisions, as cell cycle arrest and the possibility of DNA repair, senescence or apoptosis. Recent experimental works have suggested that is not just the strength of damage that controls cell fate, but rather the dynamics of p53. Chen et. Al (2013) have studied U-2 OS cells under DNA damage generated by etoposide which is a chemotherapeutic compound that induces DNA damage and is also know to activate the kinase p38MAPK. They identified a bimodal switch of p53 dynamics due to MDM2 upregulation that is important for cell-fate control. Low levels of damage (low concentration of etoposide) primarily induce p53 pulses and the cell undergo cell cycle arrest, whereas high level of damage (high concentration of etoposide) might induce a p53 monotonic increase and the cell eventually enters apoptosis. Given this background, in this work we propose a logical model for the switch behavior in p53 dynamics that contemplates the upstream kinases induced by DNA damage that regulate p53 as ATM/ATR and other important p53 regulators like p38MAPK, Wip1 and MDM2 (nuclear and cytoplasmic). In a logical model the proteins have discrete state values and the interactions are represented by the logical operators AND, OR and NOT. The input of the model is the level of DNA damage. Simulations of the model were generated using the tool GINsim 2.9.4. We found that for high DNA damage the model presents bistable dynamics, where one of the stable states presents p53 in its highest activation level corresponding to apoptosis, while the other state has p53 in its lower activation level corresponding possibly to senescence. Both stable states present inhibition of nuclear MDM2 which is observed experimentally. For the intermediate level of damage, the model presents a terminal cycle, where p53 oscillates between levels 0 and 1, never reaching level 2, and p21 and MDM2 also oscillate. In the model, knockdown of nuclear MDM2 leads to stable states and completely abrogates the terminal cycle, independently of the DNA damage level, showing the crucial influence of MDM2 on p53 dynamics.

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