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Quantitative model of the Mdm2-mediated p53 ubiquitination network

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Short Abstract: Stability of the “guardian of the genome” tumor suppressor protein p53 is regulated predominantly through its ubiquitination. Here a data-driven computational dynamic systems model of the Mdm2-mediated p53 ubiquitination network is presented. The model predicts existence of the HAUSP regulated switch from auto- to p53 ubiquitination by Mdm2.

Long Abstract:

Cell fate under conditions of different stresses is largely determined by the tumor suppressor protein p53. Activated in response to DNA damage-induced stress, p53 arrests the cell division cycle, initiates DNA repair mechanisms, and, if the damage is not fully repaired, stimulates apoptosis. If deregulated, p53 fails to stop proliferation of aberrant cells and often leads to tumor development. P53 mutation is found in more than 50% of human cancer.

P53 responses are cooperative (involve a number of other proteins), dynamically complex (from switching to oscillatory or pulsatile), and are not easy to comprehend. They cannot be understood by study of simple genomic events, because the gene coding for the p53 protein is constitutively expressed in normal cells. The activity of this important transcriptional regulator is tightly controlled by post-transcriptional modifications (phosphorylation, ubiquitination, acetylation, etc), interactions with other proteins, and by changes in subcellular localization.

Ubiquitination of p53 interferes with its activation and leads to protein degradation. It can be accomplished by several proteins, among which Mdm-mediated ubiquitination is considered to be the most important mechanism of regulation of abundance of p53. Many tumors with wild type p53 exhibit supra-physiological levels of Mdm2. The issue of regulation of the p53 protein stability via Mdm2 mediated ubiquitination have recently received a new twist with the discovery that the ubiquitin-specific protease HAUSP can de-ubiquitinate p53 and Mdm2.

In this presentation we report a quantitative computational analysis of dynamics of the Mdm2 mediated p53 ubiquitination network. In brief:

(1) Our quantitative analysis shows that currently available experimental data on p53 ubiquitination can be caste in a consistent data-driven chemical kinetics model that fits relevant experimentally observed behavior.

(2) The model reproduces (as a validation case) the recently observed differential responses of p53 to changes in HAUSP: gradual decrease of the p53 level in response to the partial removal of HAUSP and a sharp p53 activation in the case of complete HAUSP knockout.

(3) Our in silico modeling suggests that the aforementioned behavior is due to a HAUSP-regulated switch from auto-ubiquitination of Mdm2 to p53 ubiquitination by Mdm2.

(4) Our analysis suggests that HAUSP can be a downstream target of the DNA damage signaling pathway.
(5) By fitting experimental data, we make predictions for values of several rate constants which have not yet been measured experimentally.
(6) Our model constitutes an important experimental-data verified building block for advanced models aimed to address complex p53 responses.