Two feedback loop model of p53|Mdm2 signaling pathway

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1. INTRODUCTION

p53 is a transcriptional factor kept in healthy cells at low level under the control of its inhibitor Mdm2, but activated (phosphorylated) in response to DNA damage. When activated and present in high concentration, it induces the transcription of numerous genes involved in cell cycle arrest and DNA repair. If the last fails p53 final job is to trigger the cell-death program called apoptosis. For this reasons p53 is often called “the guardian of the genome”.

2. RESULTS

In order to analyze the p53|Mdm2 system we expanded and improved the two-feedback loop model introduced by Ciliberto et al.

The first feedback is negative and couples Mdm2 with p53. Namely, the phosphorylated p53 triggers production of Mdm2, which is activated, enters the nucleus and ubiquitinates p53 what results in its rapid degradation.

The second feedback is positive in this sense that it blocks the negative loop. Since it involves additional three proteins PTEN, PIP3 and Akt it works on a much slower time scale than the negative feedback. Explicit introduction of PTEN--PIP3--Akt pathway adds time delay (neglected by Ciliberto et al.) and results in a novel model with substantially different dynamics. In short; p53 induces transcription of PTEN, PIP3, and Akt it works on a much slower time scale than the negative feedback. Explicit introduction of PTEN--PIP3--Akt pathway adds time delay (neglected by Ciliberto et al.) and results in a novel model with substantially different dynamics. In short; p53 induces transcription of PTEN then PTEN triggers PIP3 deactivation. Active PIP3 is needed to activate Akt, which in turn is activator of Mdm2 enabling its nuclear entry. Thus, deactivation of PIP3 blocks activation (phosphorylation) and nuclear entry of Mdm2 and in turn rescue p53.

The system is activated by DNA damage (or oncogene stimulation), which results in p53 phosphorylation. In turn phosphorylated p53 induces synthesis of proteins responsible for DNA repair.

Fig. 1. Diagram of p53|Mdm2 signaling pathway. Notice two feedback loops: negative involving p53 and Mdm2 proteins and positive involving p53, PTEN, PIP3, Akt and Mdm2.

Analysis of the system indicates existence of 3 distinct states; two steady points and limit cycle.

1) Without DNA damage system remains in stable point (healthy cell). The negative feedback loop assures that p53 remains at low level under the control of its inhibitor Mdm2 (see Fig. 2, t<0).

2) When DNA is persistently damaged, but the slow positive feedback is blocked (e.g. no PTEN) the system converges to stable limit cycle (Fig. 2A).

3) When DNA is persistently damaged and the slow positive feedback is intact the system after several oscillations converges to second stable point (apoptotic cell), characterized by high p53 level and low Mdm2 level (Fig. 2B). This

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second stable point is absent in Ciliberto et al. model.
In real situation, there is a competition between DNA repair due to elevated level of p53 and action of the positive feedback. If DNA repair proceeds sufficiently fast, and the DNA damage is removed before Mdm2 phosphorylation is blocked by the slow positive loop, the system converges to the first steady state (healthy cell, Fig. 2D). However, if DNA damage is irreparable (Fig. 2B) or the DNA repair proceeds to slow (Fig. 2C) p53 rises to high level what potentially leads to apoptosis (not modeled explicitly in this work).

3. CONCLUSIONS

Recently, the dynamic of fluorescently tagged p53 and Mdm2 was observed over several days after radiation in living cancer cells. The experiment by Geva-Zatorsky et al., showed irregular oscillations, with period of about 5.5 hours continuing for as long as 72 hours. The fraction of oscillated cells increased with gamma dose reaching 60% following 10Gy. Even at that dose, the analyzed cells proliferated and do not exhibited apoptosis. The prolonged (persistent) oscillations are observed in our model only when the positive feedback loop is at some point blocked, and DNA is irreparable. This supports Geva-Zatorsky et al. conjecture that human breast cancer epithelial cells, they studied, “might be deficient in some aspects of p53 regulation and downstream apoptotic responses”.
Based on our analysis we would expect that normal untransformed cells after about 24 hours of unsuccessful DNA repair, would commit to apoptosis.

REFERENCES


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