Gene Copy Number in p53 Signaling Pathway

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***Short Abstract* — p53 is a transcription factor controlling genes involved in DNA repair, cell cycle arrest and apoptosis. DNA damage triggers oscillations of p53 and Mdm2 levels, which were visualized in individual living cells with help of fluorescently tagged proteins. In these cells the p53 or Mdm2 gene copy number was elevated, which in principle, may alter cell responses. We analyzed several models of the p53/Mdm2 regulatory core (including our own) to conclude that oscillations resulting from cooperation of positive and negative feedbacks are very sensitive to the number of p53 and Mdm2 gene copies.**

***Keywords* — p53, Mdm2, Hopf bifurcation, transfected cells, haploinsufficiency.**

I. Introduction

As demonstrated in single cell experiments [1, 2], DNA damage results in sustained oscillations of p53 and Mdm2 levels. These oscillations were attributed to cooperation of positive and negative feedbacks [3]. We found however, that all four models proposed in [3] are very sensitive to the gene copy number of p53 or Mdm2 elevated in experiments [1, 2] they attempted to explain. The aim of our study is to analyze how p53 and Mdm2 gene copy number may influence cell responses to DNA damage, assuming that these oscillations result from cooperation of positive and negative feedbacks.

II. Methods

We illustrate our study based on a simple model of p53 regulatory core involving positive and negative feedback loop introduced in [3]. The negative feedback arises since p53 positively regulates production of Mdm2, while the nuclear Mdm2 enhances p53 degradation. The positive feedback arises since p53 blocks Mdm2 nuclear import. The pathway is described by the system of equations for total p53, cytoplasmic Mdm2 and nuclear Mdm2,

$$\frac{d(p53)}{dt} = m\,s_1 - d_1\,p53(Mdm2_{nuc})^2,$$

$$\frac{d(Mdm2_{cyt})}{dt} = n\left(s_2 + s_{20}\frac{(p53)^3}{(p53)^3 + s_{200}{}^3}\right) - \frac{k_1}{p53 + k_2}Mdm2_{cyt},$$

$$\frac{d(Mdm2_{nuc})}{dt} = \frac{k_1}{p53 + k_2}Mdm2_{cyt} - d_2\,Mdm2_{nuc},$$

where m and n denote p53 and Mdm2 gene copy number. DNA damage destabilizes Mdm2 and stabilizes p53 that causes oscillations. This agrees with our model, in which transition from stable point to stable limit cycle is a consequence of increased Mdm2 degradation or decreased p53 degradation rate.

III. Results

We investigate how transition from stable state to stable limit cycle depends on the number of p53 and Mdm2 gene copies (**Fig. 1**). We show that lack of Mdm2 allele promotes oscillations even when DNA is intact, and the lack of p53 allele may inhibit oscillations even when DNA is damaged what may explain p53-haploinsufficiency resulting in cancer. Mdm2 transfection decreases, and p53 transfection increases parameter range of oscillations.

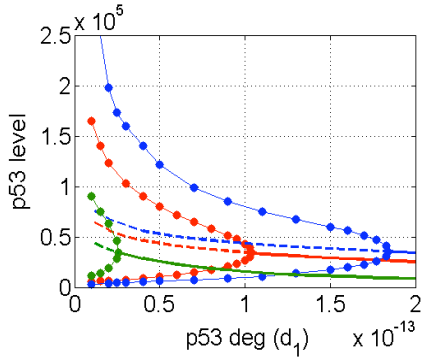

Fig. 1. Red, green and blue colors denote bifurcation diagrams, respectively, for normal diploidal cells ($m = n = 2$), Mdm2-transfected cells ($m = 2$, $n = 4$) and p53-transfected cells ($m = 4$, $n = 2$).

Analysis of Zhang et al. models [3] and also of our own, simple, but more robust model, suggests one of two possibilities:

1) The observed oscillations are due to cooperation of positive and negative feedback, but behavior of normal cells is qualitatively different than that of transfected cells.

2) The positive feedback does not play any role in the oscillations, which results from negative feedback and time delay and are thus less sensitive to the number of Mdm2 and p53 gene copies.

References

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Acknowledgements: This work was funded by Polish Committee for Scientific Research Grant No. 4 T07A 001 30.

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