Activation and regulation of p53 in single cells

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***Short Abstract* — The p53 protein is activated whenever the genome integrity of a cell is attacked. In such cases, the cell responses through the p53-mediated transcriptional activation of several cascades of proteins that directly or indirectly lead either to cell cycle arrest or programmed death. With the perspective of p53-controlled cell fate decision between survival and death we simulate *in silico* p53 activation and regulation in individual cells. We show that experimentally observed p53 oscillations can be reproduced by considering compartmental distribution of cellular events between the nucleus and the cytoplasm together with p53 activation by the ATM kinase and its regulation by the Wip1 and Mdm2 proteins.**

***Keywords* — p53, DNA damage, ATM, Mdm2, Wip1, cell proliferation, cell arrest, apoptosis**

I. Motivation

THE cell population based pharmacokinetic and pharmacodynamic (PK–PD) therapies are recently broadly used in cancer treatment to fully obtain absorption, distribution, metabolism, excretion and toxicity of anticancer drugs. This is simply because clearly measurable effects of drugs can be seen on populations of cells (tissues, organs), healthy and tumor. However, the actual targets of drug administration, i.e. the targets where drugs exploit their activity are the cells themselves [2]. Drugs in use either cause nonrepairable DNA double strand breaks (DBSs) and subsequently initiate programmed cell death (apoptosis) or block cell proliferation mainly by inhibiting factors that enable the transition from one cell cycle phase to another in the cell division cycle (cell cycle arrest).

Following the presence of DSBs, activated p53 can either accumulate in the mitochondria and directly launch apoptosis [7], or p53 acts as a transcription factor of both proarrest and proapoptotic proteins, which transcription runs independently on p53 affinity to the proteins' genes. These proteins can either arrest the cell cycle (temporarily with parallel DNA repair, or permanently), or initiate irreversible apoptosis [6]. Thus, involving processes occurring in individual cells to PK–PD models with the dominant role of p53 can contribute to establishing new cancer therapies, bearing in mind that p53 is inactive due to its gene mutations in around 50% of tumor cells.

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II. p53 Kinetics, Basics for Modeling

In response to DSBs, p53 can be activated by phosphorylation of the serine 15 (Ser15) site by the ATM kinase, which masks p53 from its main regulator. The regulation of p53 is dominantly achieved through its interactions with the Mdm2 ligase, which is itself a transcription target of p53. Mdm2 regulates p53 through (multiple-)ubiquitination, followed by nuclear export and subsequent degradation. Such regulation by Mdm2 is possible due to previous p53 deactivation, i.e. Ser15 dephosphorylation by the Wip1 protein, which also dephosphorylates ATM rendering the proteins in inactive forms [4,7].

In individual cells, the proteins p53, Mdm2 and ATM are observed to oscillate for several days in response to γ-irradiation [5]. In addition, it is experimentally observed that p53/Mdm2 negative feedback is not sufficient to produce p53 oscillations without the presence of ATM pulses in the cell [1]. In simulations, oscillatory dynamics of proteins needs to distinguish between the reactions occurring either in the nucleus or in the cytoplasm [3].

III. Conclusions

The ATM/p53/Mdm2/Wip1 dynamics is modeled as the initial process in the subsequent p53 signalling towards its proarrest and proapoptotic proteins in response to DNA DSBs at the single cell level. We show that the p53 → Mdm2 ⊣ p53 and ATM → p53 → Wip1 ⊣ ATM control feedbacks together with the compartmentalization of these cellular events can reproduce experimental observations.

References

[1] Batchelor E, et al. (2008) Recurrent Initiation: A mechanism for triggering p53 pulses in response to DNA damage. *Molecular Cell* **30**, 277--289.

[2] Clairambault J (2009) Modelling physiological and pharmacological control on cell proliferation to optimise cancer treatments. *Mathematical Modelling of Natural Phenomena* **4**, 12-67.

[3] Dimitrio L, Clairambault J, Françoise JP (2013) "Bifurcation in the p53 system: a compartmental approach," in preparation.

[4] Eliaš J, et al. (2013) The p53 protein and its molecular network: dynamic modelling of a missing link between the effects of anticancer cytotoxic drugs on DNA damage and cell proliferation in healthy and cancer cell populations. *BBA - Proteins and Proteomics*, submitted.

[5] Geva-Zatorsky N, et al. (2006) Oscillations and variability in the p53 system. *Molecular Systems Biology* **2**, 1-13.

[6] Kracikova M, et al. (2013) A threshold mechanism mediates p53 cell fate decision between growth arrest and apoptosis. *Cell Death & Differentiation* **20**, 576-588.

[7] Murray-Zmijewski F, Slee EA, Lu X (2008) A complex barcode underlies the heterogeneous response of p53 to stress. *Nature, Rev. Mol. Cell Biol.* **9**, 702-712.