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MATHEMATICAL MODEL OF p53 GENE WITH DNA DAMAGE IN APOPTOSIS

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The tumor suppressor protein, p53, is a transcription factor that regulates the activity of hundreds of genes involved in cell growth and death. Over 50% of human cancer cells contain mutations in p53, because of which it has become a key target in cancer research. A wide variety of stress conditions result in the accumulation and activation of p53-among others : DNA damage, hypoxia, heat shock, nutrient deprivation and oncogene activation. The aim of this research is to investigate the design principles behind the precise regulation of p53 activation. We develop a mathematical model using differential equations that incorporate the most recently found molecular interactions and genes regulated by p53, such as p53 activation of MdmX and Wip1, in the core regulation of p53 in normal proliferating cells and cells under DNA damage stress. In this model the p53 core regulatory feedback mechanisms are analyzed and that control p53 levels.

INTRODUCTION

The p53 gene is responsible for proteins that can either repair damaged cells, or cause damaged cells to die, a process called apoptosis. When the gene is not working due to a mutation, these proteins that repair cells or eliminate damaged cells are not produced, and abnormal cells are allowed to divide and grow. If the p53 gene is damaged, tumor suppression is severely reduced. People who inherit only one functional copy of p53 will most likely develop tumors in early adulthood, a disease known as Li-Fraumeni syndrome. p53 can also be damaged in cells by mutagens (chemicals, radiation or viruses), increasing the likelihood that the cell will begin uncontrolled division. More than 50 percent of human tumors contain a mutation or deletion of the p53 gene [3].

p53 protein was first identified in 1979 as a transformation-related protein and a cellular protein which accumulates in the nuclei of cancer cells and binds tightly to the simian virus 40 (SV402) large T antigen. The gene encoding p53 was initially found to have weak oncogenic activity as the p53 protein was observed to be over expressed in mouse and human tumor cells[2]. p53 belongs to an unique protein family which includes three members: p53, p63 and p73 . Although these proteins are structurally and functionally related to each other, p53 seems to have evolved in higher organisms to prevent tumor development, whereas p63 and p73 have clear roles in normal developmental biology [1]. Because p53 plays a pivotal

role in regulation of the cell cycle and induction of apoptosis, there has been enthusiasm about its potential for therapeutic application [3]. The p53 gene is a tumor suppressor gene, *i.e*., its activity stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from one of their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood [2]. p53 is a protein that is able to block the cell cycle if DNA is damaged. p53 acts as a sequence–specific transcription factor it localizes to the cell nucleus and initiates the transcription of target genes (DNA repair, apoptosis). The p53 gene is mutated in about 60% of all human cancers [1]. Activation of p53 can induce several responses in cells, including differentiation, senescence, DNA repair and the inhibition of angiogenesis, but best understood is the ability of p53 to induce cell cycle arrest and apoptotic cell death . These two responses allow p53 to inhibit the growth of stressed cells either by a cycle arrest, which may be irreversible or transient to allow repair and recovery before further rounds of replication, or by permanent removal of these cells from the organism by apoptosis [4]. p53 is a sequence-specific transcription factor that can mediate many of its downstream effects by the activation or repression of target genes.

MATHEMATICAL MODELLING

Under normal conditions the amount of p53 protein in the cell is kept low by a genetic network built of the mdm2gene, the mdm2 protein and the p53 protein itself. p53 is produced at a essentially constant rate and promotes the expression of the mdm2 gene [2]. On the other hand, the mdm2 protein binds to p53 and promotes its degradation, decreasing its concentration.

The p53 and mdm2 network having the following system of equations [1]

$$\frac{\partial p}{\partial t} = S - a.pm - bp \qquad \ldots(1)$$

$$\frac{\partial m}{\partial t} = c\frac{p(t-\tau) - pm(t-\tau)}{k + p(t-\tau) - pm(t-\tau)} - d.m \qquad \ldots (2)$$

$$pm = \frac{1}{2}\left((p+m+k) - \sqrt{(p+m+k)^2 - 4p.m}\right) \qquad \ldots(3)$$

Integrating equation (1), with respect to '*t*' can get the value of p53 is

$$p = \frac{s - a.pm}{b + 1/t} \qquad \ldots (4)$$

p53 GENE AND DNA DAMAGE

When DNA is damaged by the irradiation or chemical agents, the damage signal activates the tumor suppressor protein p53 followed by the stimulation of the transcriptions of many related genes such as p21, 14-3-3, Bax, Bcl-2 and so fourth. These genes may determine the destination of the cell whether the cell cycle arrest or apoptosis induction. Thus, p53 is responsible for the conflict between the cell cycle arrest and apoptosis induction. The p53 upregulated modulator of apoptosis (PUMA) also known as Bcl-2-binding component 3 (BBC3), is a pro-apoptotic, member of the Bcl-2 protein family. In humans, the Bcl-2-

binding component 3 protein is encoded by the *BBC3* gene. The expression of PUMA is regulated by the tumor suppressor p53. PUMA is involved in p53-dependent and –independent apoptosis induced by a variety of signals, and is regulated by transcription factors, not by post-translational modifications. The majority of PUMA induced apoptosis occurs through activation of the tumor suppressor protein p53. p53 is activated by survival signals such as glucose deprivation and increases expression levels of PUMA. This increase in PUMA levels induces apoptosis through mitochondrial dysfunction. p53, and with it PUMA, is activated due to DNA damage caused by a variety of genotoxic agents. Levels of p53 protein increase in cells following exposure to DNA damage and other stresses, leading to cellular responses such as cell cycle arrest or programmed cell death.

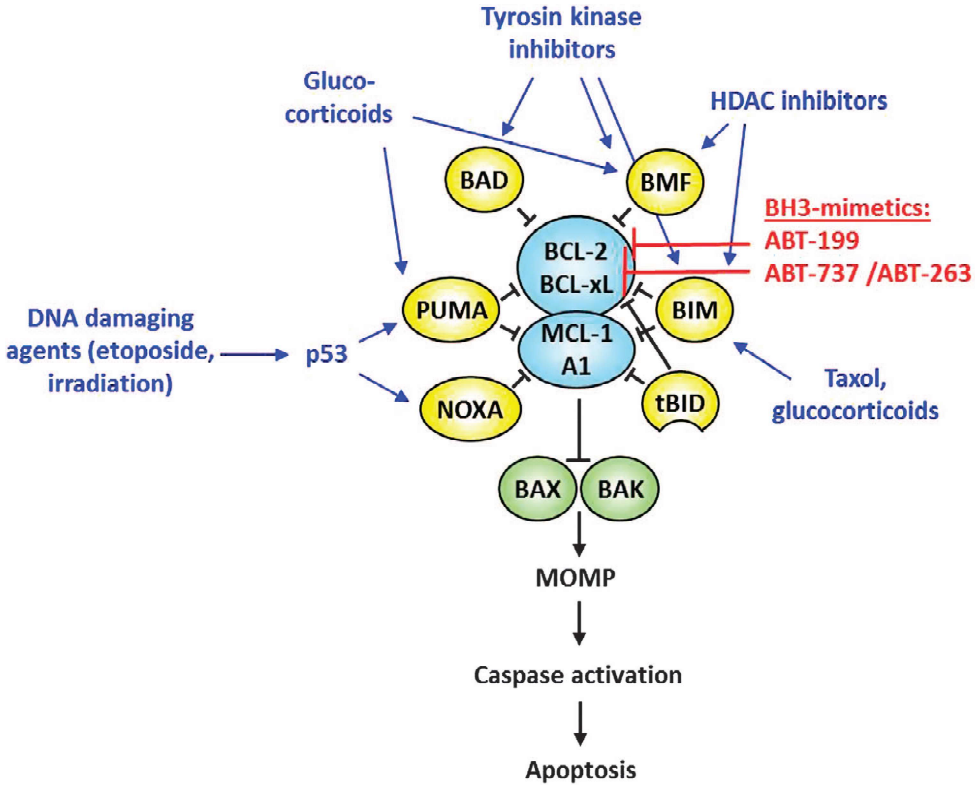


Fig. DNA damage caused by a variety of genotoxic agents and the levels of p53 protein increase in cells leading to cellular responses such as cell cycle arrest or programmed cell death.

DNA damage is represented in the following differential equation [4].

$$\frac{d[Dam]}{dt} = -k_{13}.[Dam].[p53] \quad \ldots (5)$$

The damage level can get easily from Equation (5), where the value of k_{13} is taken from the following table of parameter values[4].

Increases in p53 protein levels after DNA damage have been largely attributed to increases in the half-life of p53 protein. Cellular exposure to DNA damage results in an inhibition of Mdm2-mediated degradation of p53 protein, contributing to an increase in p53 protein half-life and increased cellular levels of p53 protein. The high levels of basal DNA damage are responsible for generating sustained pulses of p53 in the tumor cells [6]. The Bax

activation switch can count p53 pulses through PUMA accumulation and transfer it into death signal. Our modeling provides a plausible mechanism about how cells generate and orchestrate p53 pulses to tip the balance between survival and death. Three modules of p53 network (ATM activation module, p53-MDM2 oscillation module and the Bax activation module) were interconnected [5]. The ATM switch can turn off the p53 pulses when damage is repaired and thus elicit digital p53 pulses. A mutant switch with high basal DNA damage, however, can never turn off the downstream oscillation.

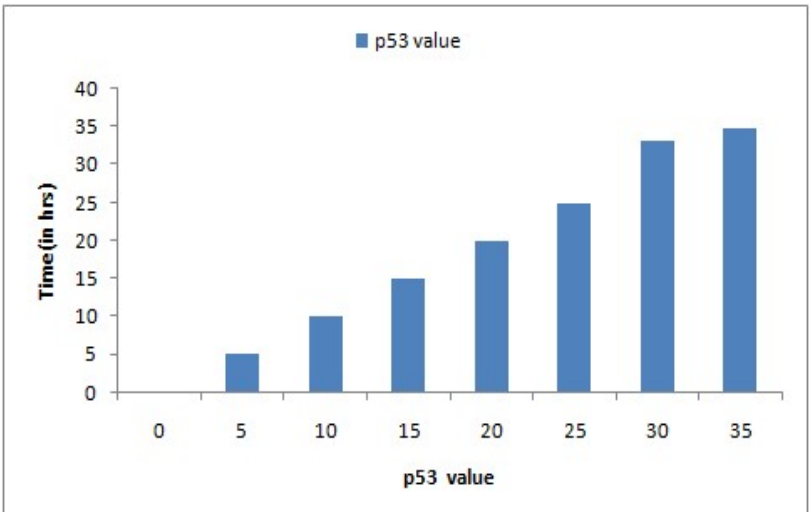
Table 1: Parameter values for ATM and p53 module

ATM module	p53-MDM2 module
$k1 = 1\ min^{-1}$	$katm' = 0.01\ s^{-1}$
$k2 = 0.01$ mM	$kmd' = 0.03\ min^{-1}$
$k3 = 0.005\ min^{-1}$	$dp53 = 0.01\ min^{-1}$
$k4 = 2.5\ min^{-1}$	$dMDM2 = 0.002\ min^{-1}$
$k5 = 1$	$Ka = 0.3$ mM
$k6 = 0.1\ min^{-1}$	$Kb = 0.3$ mM
$k7 = 0.5$ mM	$Kc = 0.3$ mM
$k8 = 1\ min^{-1}$	$Kd = 0.5$ mM
$k9 = 0.01$ mM	$Ke = 0.5$ mM
$k10 = 0.005\ min^{-1}$	$kind = 0.02\ mM \cdot min^{-1}$
$k11 = 0.8\ mM \cdot min^{-1}$	$ktrans = 0.1\ mM \cdot min^{-1}$
$k12 = 0.1$ mM	$mp53 = 0.003\ mM \cdot min^{-1}$
$k13 = 0.02\ mM^{-1} \cdot min^{-1}$	$mMDM2 = 0.002\ mM \cdot min^{-1}$
[ATM]total = 1 mM	$m = 4$
[MRN]total = 1 mM	$n = 3$ $np = 3$

Result

The value of p53 molecules and the corresponding time interval is listed from equation (4). From this table values , the apoptosis level is shown in the following graph, when the time increases the p53 value also increases. P53 will induce the cells to apoptosis.

Time (in hours)	p53value
0	0
5	4.988505
10	9.972028
15	14.9655
20	19.9241
25	24.8927
30	33.1628
35	34.90



PDCD5 is known as Programmed Cell Death 5 to interact with p53 and functions as a regulator in the p53 pathway during responses to DNA damage. The cell fate was governed by the number of p53 pulses during DNA repair. After DNA damage starting from the survival state a cell transitions to the apoptotic state with an increase in the amount of cytochrome *c* release and caspase-3 activation [6].

Dependence of cell fate on the DNA repair time t_c and PDCD5 level P_0 are given in the following table.

P53 pulses	Time required for repair DNA damage	Caspase activation	Progress in Apoptosis
7 pulses	48hours	Caspase-3 level increases	Apoptosis is induced
4 pulses	30hours	Caspase is maintained at low level	The cell recovers to normal growth

The effects of PDCD5 on p53 dynamics, we fixed the DNA repair process at tc = 48h and varied the PDCD5 level to examine the cell response.

P0 value	**P53 pulses**	**Progress in Apoptosis**
0.4	6 pulses for DNA repair	Normal growth in cells
<0.4	P53pulses are repressed	Cells recover to normal growth
0.2	P53 level is attenuated	Cells fails to induce apoptosis

Conclusion

The conclusion is that when the time increases the p53 value also increases. P53 will induce the cells to apoptosis. These results suggest that p53 dynamics and cell fate can be modulated by PDCD5 in a dose-dependent manner. The high levels of basal DNA damage are responsible for generating sustained pulses of p53 in the tumor cells. The Bax activation switch can count p53 pulses through PUMA accumulation and transfer it into death signal. This model provides a plausible mechanism about how cells generate and orchestrate p53 pulses to tip the balance between survival and death. This model successfully provided p53

pulses in governing DNA damage-induced cell death decision. The p53-MDM2 module can be analyzed and the oscillation in apoptosis will be discussed in future.

REFERNCES

1. Tiana, G., Jensen, M.H. and Sneppen, K., "Time Delay as a key to apoptosis induction in the p53 network" (2002).
2. Wang, Hua and Peng, Guang, "Mathematical Model of Dynamic Protein Interactions Regulating p53 Protein Stability for Tumor Suppression" (2013).
3. Steele, R.J.C., Thoompson , A.M., Hall, P.A. and Lane, D.P., "The p53 tumor suppressor gene" (1998).
4. Tingzhe Sun, Chun Chen, Yuanyuan Wu, Shuai Zhang, Jun Cui and Pingping Shen" Modeling the role of p53 pulses in DNA damage- induced cell death decision" (2009).
5. Ma, Lan, Wagner, John, Rice, John Jeremy, Hu, Wenwei, Levine, Arnold J. and Stolovitzky, Gustavo A., "A plausible model for the digital response p53 to DNA damage" (2005).
6. Zhugea, Changjing, Sunb, Xiaojuan, Chenc, Yingyu, Leid, Jinzhi, "PDCD5 interacts with p53 and functions as a regulator of p53 dynamics in the DNA Damage response" (2015).
7. Haupt1, Susan, Berger2, Michael, Goldberg2, Zehavit and Haupt2, Ygal, "Apoptosis – the p53 network" (2003).
8. Haupt1, Susan, Berger2, Michael, Goldberg2, Zehavit and Haupt2, Ygal, "Tp3 gene and p53 p protein as Targets in Cancer Management and Therapy".
9. Suzuki, Kazufumi and Matsubara, Hisahiro, "Recent Advances in p53 Research and Cancer Treatment" (2011)
10. Labi, V. and Erlacher, M., "How cell death shapes cancer" (2015).
11. Chen, Jing and Kastan, Michael B., "59–39-UTR interactions regulate p53 mRNA translation and provide a target for modulating p53 induction after DNA damage" (2010).
12. Bai, Ling and Zhu, Wei-Guo, "p53 : Structure, Function and Therapeutic Applications" (2006)

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