CHAPTER 2

Oscillations by the p53-Mdm2 Feedback Loop

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Abstract

The p53 network is perhaps the most important pathway involved in preventing the initiation of cancer. p53 levels and activity are upregulated in response to various stresses including DNA damage, hypoxia, and oncogene activation. Active p53 initiates different transcriptional programs that result in cell cycle arrest, cellular senescence or apoptosis. p53 also activates the transcription of Mdm2, which in turns target p53 for degradation, therefore creating a negative feedback loop on p53. Previous studies showed that the level of p53 increased dramatically after exposure to damaging radiation, then declined in a series of damped oscillations. Recent quantitative studies examined p53 responses in individual living cells, using time-lapse fluorescent microscopy and showed that—on an individual cell level—the oscillations are not damped. Instead, one cell may have only one pulse of p53, while its neighbor may show several repeated pulses. As the amount of irradiation increased, the percentage of cells showing a high number of p53 pulses also increased. The mean height and width of the pulses was constant and did not depend on the damage level. These observations opened new questions regarding the mechanism and function of p53 oscillatory dynamics. In this chapter I will review the different models that have been suggested for p53 oscillations, including proposed reasons for variation between cells, and will discuss potential functions for oscillatory dynamics in the p53 signaling pathway and in stress responses in general.

Introduction

The tumor suppressor protein p53 is the protein most frequently inactivated in human cancer. More than half of all human cancers contain mutations in the p53 gene, and in almost all cancers the p53 regulatory circuit is functionally inactivated. The protein is known as the “guardian of the genome” because it is activated when cells are under stress. For example, when cells suffer DNA damage (as skin cells do when they are exposed to excessive radiation), both the level of p53 and its transcriptional activity are increased. This may cause the cell to delay DNA replication to give extra time to repair the DNA. Sometimes, however, p53 triggers a cell death pathway instead, preventing the chance that the damaged cell may later become cancerous. If p53 is not functional, the cell cycle might continue unrestrained, leading to uncontrolled cell proliferation and cancer.

Under normal, unstressed conditions p53 is kept at low levels, primarily through a mechanism in which the negative regulator Mdm2 targets p53 to degradation. Mdm2 is one of p53’s target genes and thus any increase of p53 normally leads to an increase in Mdm2 levels, which

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then pushes p53 back down to a low steady state level. But in various stress conditions, up­
stream mediators are activated and induce post-translational modification on p53 and Mdm2.
For example, DNA damage activates the protein kinases ATM, ATR, Chk1 and Chk2, which
phosphorylate p53 and Mdm2. These modifications disrupt the p53-Mdm2 interaction, lead­
ing to stabilization of p53 and an increase in p53 transcriptional activity. p53 then activates
several stress response programs including cell cycle arrest (both reversible and irreversi­
bly), DNA repair and programmed cell death (apoptosis)2-4 (Fig. 1).

Double-strand breaks (DSBs) are an important type of DNA damage, which lead to sta­
bilization and activation of p53. They are mainly caused by ionizing radiation and radio-mimetic
chemicals, and can also occur by mechanical stress on chromosomes and during DNA replica­
tion. DSBs are repaired by two main mechanisms, homologous recombination and
nonhomologous end-joining. In both cases, phosphorylation of histone H2AX is an early

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Figure 1. The p53 network. In response to DNA damage, ATM and ATR transfer the damage signal
directly, and through Chk2/Chk1, to p53. p53 level and transcriptional activity increase, leading
to activation of several programs including: cell cycle arrest, DNA repair and apoptosis.