Cellular Signalling 33 (2017) 49–58

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Reverting p53 activation after recovery of cellular stress to resume with cell cycle progression

Pedro A. Lazo *

Experimental Therapeutics and Translational Oncology Program, Instituto de Biología Molecular y Celular del Cáncer, Consejo Superior de Investigaciones Científicas (CSIC), Universidad de Salamanca, Salamanca, Spain
Instituto de Investigación Biomédica de Salamanca (IBSAL), Hospital Universitario de Salamanca, Salamanca, Spain

ARTICLE INFO

Article history:
Received 19 November 2016
Received in revised form 23 January 2017
Accepted 6 February 2017
Available online 9 February 2017

Keywords:
p53
Kinases
Phosphatases
Deacetylase
Proteasome
Autophagy

ABSTRACT

The activation of p53 in response to different types of cellular stress induces several protective reactions including cell cycle arrest, senescence or cell death. These protective effects are a consequence of the activation of p53 by specific phosphorylation performed by several kinases. The reversion of the cell cycle arrest, induced by p53, is a consequence of the phosphorylated and activated p53, which triggers its own downregulation and that of its positive regulators. The different down-regulatory processes have a sequential and temporal order of events. The mechanisms implicated in p53 down-regulation include phosphatases, deacetylases, and protein degradation by the proteasome or autophagy, which also affect different p53 protein targets and functions. The necessary first step is the dephosphorylation of p53 to make it available for interaction with mdm2 ubiquitin-ligase, which requires the activation of phosphatases targeting both p53 and p53-activating kinases. In addition, deacetylation of p53 is required to make lysine residues accessible to ubiquitin ligases. The combined action of these downregulatory mechanisms brings p53 protein back to its basal levels, and cell cycle progression can resume if cells have overcome the stress or damage situation. The specific targeting of these down-regulatory mechanisms can be exploited for therapeutic purposes in cancers harbouring wild-type p53.

Contents

Abbreviation: AMPK, AMP - activate kinase alpha 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; CHK2, checkpoint kinase 2; CHK1, checkpoint kinase 1; CDK, cyclin-dependent kinase; CDKN2A, cyclin dependent kinase inhibitor 2A; DNA-PK, DNA-activated protein kinase; DRAM, damage-regulated autophagy modulator; DUSP4, dual specificity phosphatase 4 (MKP2); DUSP6, dual specificity phosphatase 6 (MKP3); DYRK2, dual specificity tyrosine phosphorylation regulated kinase 2; ERK2, extracellular signal-regulated kinase 2 (MAPK1); GRWD1, glutamate rich WD repeat containing 1; HDAC, histone deacetylase; Hdm2, human double-minute 2; HIPK2, homeodomain interacting protein kinase 2; JNK2, c-jun n-terminal kinase 2 (MAPK9); LSD1, lysine demethylase 1 (KDM1A); MAPK1, mitogen-activated protein kinase 1; Mdm2, murine double-minute 2; MKP2, mitogen-activated protein kinase phosphatase 2 (DUSP4); PKCδ, protein kinase C δ; PP, phosphatase; PPM1D, protein phosphatase, Mg2+/Mn2+ Dependent 1D (WIP1); RPL11, ribosomal protein L11; RUNX2, runt related transcription factor 2; SIRT1, sirtuin 1; TBK, TANK binding kinase 1; VRK1, vaccinia-related kinase 1; WIP1, wild-type p53-induced phosphatase (PPM1D).

* Centro de Investigación del Cáncer, CSIC, Universidad de Salamanca, Campus Miguel de Unamuno, E-37007 Salamanca, Spain.
E-mail address: pedro.lazo@csic.es.

http://dx.doi.org/10.1016/j.cellsig.2017.02.005

1. Introduction

Cells undergoing any type of stress, including DNA damage, have to react individually, and independently, of cell cycle progression and these reactions are mediated by p53 that functions as an integrator of multiple cellular responses to cellular stresses [1,2]. The cellular responses mediated by p53 can have an effect at both the cellular and organism levels. First, each individual cell within a tissue has to react on its own to the specific stress to which it is exposed. The initial protective response consists in the arrest of the cell cycle to allow specific repair processes to solve the problem. In those cells that cannot cope with cellular stress or damage, the p53 response triggers cell death and in that way protects the organism from the expansion of a damaged cell population, which is an important component in cancer development. Thus, mutations or deletions of *TP53* can facilitate tumour development [3]. The p53 protein has a regulatory role in all biological processes that contribute to cancer hallmarks [4], including cell proliferation, genomic stability, cell death, senescence, hypoxia, angiogenesis, and tumour metabolism in which it plays different roles [5]. The complexity of these roles requires very fine regulatory mechanism controlling p53 protein levels and functions. The activated p53 protein channels distress signals towards the selection of the appropriate response pathway in order to initiate specific cellular reactions, aiming either to protect either the individual cell or the organism. Therefore, the p53 protein is an intermediate switch, which is activated by multiple signalling pathways and mediates selection of specific cellular responses, which represent their biological outputs [6]. The change in p53 protein level and its pattern of posttranslational modifications regulate and determine the specific biological responses mediated by the activation of p53. These p53 changes determine the selection of interacting proteins, transcriptional cofactors and gene promoters [7]. In normal growth conditions, the level of the p53 protein undergoes temporal fluctuations that may be important for specific roles within a tissue, normal or tumoral, and it can also vary among cells forming the affected tissue, which reflects the individual cell situation [8,9]. In response to cellular stress, the level of the p53 protein raises immediately because of its stabilization by phosphorylation. This increased in p53 level triggers its biological effects, mostly as a consequence of p53-dependent activation of gene transcription [10,11], so that cells are able to start an immediate and specific response [12–14]. These fluctuations are underlined by a complex network of autoregulatory loops [15].

The 53 activation, if sustained in time, will cause a stable accumulation of p53 protein that is incompatible with cell life. When the cellular protective response to stress is completed, p53 has to return to its basal protein level so that cells can resume with their normal functions. Therefore, once the protective actions have been successfully performed, cells need to have active mechanisms that will revert the accumulation of p53. These p53 down regulatory mechanisms are late events in the cellular response to stress, and are a direct consequence of an activated p53. Because of these roles, the accumulation of p53 protein has to be necessarily transient, so that cell viability can be maintained. In this context, mechanisms that participate in p53 downregulation have not received as much attention as its activation, but they play a fundamental role in the cycling behaviour of p53 and form a complex network of regulatory mechanisms.

2. P53 activation mechanisms

2.1. Importance of p53 levels to trigger different biological effects

Any response to stress has an immediate initial phase that cannot depend on de novo gene transcription and translation, because this will require several hours, and by that time the consequences of cell damage will accumulate, and might become irreversible. However, all cells in order to initiate an immediate response to any type of stress must have a basal p53 level. In the basal situation of non-stressed cells, the level of p53 protein is very low, and in this readiness state p53 is forming a stable basal complex with VRK1 [14], the most abundant nuclear kinase [16]. The level of p53, its posttranslational modifications and protein-protein interactions determine the specificity of the cellular response to stress. Within a tissue, the individual cell situations are different, but they will have to react to a common type of stress. In a tissue there are dividing and non-dividing cells might react differently, and cells differ in their local microenvironment and cellular interactions that can be homotypic or heterotypic or stroma. There are also known variations in the context of cell cycle phases [17]. Therefore, even in a tissue exposed to a common stress signal, for example in skin exposure to UV damage, each cell has to respond individually. The different mechanisms contributing to p53 regulation are summarized in Table 1.

2.2. Structural bases of p53 activation and its selection of transcriptional cofactors

The p53 protein has two different binding modes whose roles are determined by the phosphorylation state of the N-terminal trans-