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Review

Interaction of p53 with prolyl isomerases: Healthy and unhealthy relationships☆

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ABSTRACT

Background: The p53 protein family, comprising p53, p63 and p73, is primarily involved in preserving genome integrity and preventing tumor onset, and also affects a range of physiological processes. Signal-dependent modifications of its members and of other pathway components provide cells with a sophisticated code to transduce a variety of stress signaling into appropriate responses. *TP53* mutations are highly frequent in cancer and lead to the expression of mutant p53 proteins that are endowed with oncogenic activities and sensitive to stress signaling.
Scope of review: p53 family proteins have unique structural and functional plasticity, and here we discuss the relevance of prolyl-isomerization to actively shape these features.
Major conclusions: The anti-proliferative functions of the p53 family are carefully activated upon severe stress and this involves the interaction with prolyl-isomerases. In particular, stress-induced stabilization of p53, activation of its transcriptional control over arrest- and cell death-related target genes and of its mitochondrial apoptotic function, as well as certain p63 and p73 functions, all require phosphorylation of specific S/T-P motifs and their subsequent isomerization by the prolyl-isomerase Pin1. While these functions of p53 counteract tumorigenesis, under some circumstances their activation by prolyl-isomerases may have negative repercussions (e.g. tissue damage induced by anticancer therapies and ischemia-reperfusion, neurodegeneration). Moreover, elevated Pin1 levels in tumor cells may transduce deregulated phosphorylation signaling into activation of mutant p53 oncogenic functions.
General significance: The complex repertoire of biological outcomes induced by p53 finds mechanistic explanations, at least in part, in the association between prolyl-isomerases and the p53 pathway. This article is part of a Special Issue entitled Proline-directed foldases: Cell signaling catalysts and drug targets.

1. Introduction

1.1. The p53 pathway

While displaying key roles in several pathological and physiological processes, the transcription factor p53 is undoubtedly one of the most relevant proteins restraining cancer initiation and progression. Recent whole-exome sequencing efforts have conclusively shown that *TP53* is the most frequently mutated gene in human cancers [1]. Germline *TP53* mutations are causative of the rare Li–Fraumeni cancer predisposition syndrome [2], and mice lacking one or both *TP53* alleles are prone to spontaneous tumor development [3].

Mechanistically, the p53 protein lies at the core of an intricate and highly interconnected pathway, whose multiple branches act to maintain genome integrity and prevent tumor onset. The ability of p53 to block tumor progression heavily depends on its anti-proliferative functions that are activated in response to many stress conditions arising during malignant progression and including DNA damage, oncogene activation, oxidative stress and hypoxia, among others. The particular biological response that is eventually executed in a given context ranges from transient or permanent cell cycle arrest to cell death, depending on both the extent and duration of the stress stimulus and on the cell type. In addition, because of its nodal position downstream to many cell-intrinsic and extrinsic cues p53 regulates a broad range of key cellular processes, some of which are emerging as important tumor-suppressor mechanisms besides proliferation arrest and cell death [4–6]. It is involved in DNA repair, metabolism, oxidative status and autophagy, endocytosis, stemness/reprogramming, differentiation, development, angiogenesis, inflammation and fertility [7–9].

p53 exerts its functions primarily as a transcription factor, regulating a vast array of coding and non-coding genes (including several microRNAs)

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by both activating and repressing transcription [10,11]. It also has extranuclear activities that implicate the interaction with cytosolic and mitochondrial proteins to regulate apoptosis, autophagy and necrosis [12], as well as energy metabolism [4,9] (Fig. 1). A further level of complexity is added by the fact that the human *TP53* gene encodes at least twelve protein isoforms, which are produced either by alternative promoter usage, splicing, or by initiation of translation [13]. In addition, *TP53* belongs to a family of related genes. The other two members of this family encode the p63 and p73 proteins and their isoforms. All these three show high sequence and structural homology, are similarly involved in tumor suppression, and perform additional non-overlapping functions (Fig. 2) [14].

Among the multifaceted activities of p53, those ensuring a prompt and appropriate response to conditions threatening the genome or cell integrity require activation by stress signaling pathways. This occurs through a code of post-translational modifications, structural changes and protein–protein interactions [15]. Typically, the activation of p53 may require partial or full relief of its poly-ubiquitination, of which the MDM2 ubiquitin ligase is responsible. Under normal conditions, poly-ubiquitination keeps the p53 protein levels low by inducing proteasome-dependent degradation. Stress-induced phosphorylation of specific Serine and Threonine residues within the N-terminal domain of p53 dampens its affinity for MDM2, and the acetylation/SUMOylation of various C-terminal Lysine residues produces the same outcome [16]. In addition, different stress cues induce several other activating modifications including phosphorylation, acetylation, methylation, SUMOylation and NEDDylation, some of which are either interdependent or act by enabling/disabling interactions with partner proteins or by affecting p53 conformation [17] and subcellular localization [15].

The functional flexibility of p53 is reflected by its structure. Consistent with its nature of transcription factor, p53 has a modular structure, consisting of folded DNA-binding and oligomerization domains, flanked by intrinsically disordered regions at both the amino- and carboxy-terminus [18]. The p53 core domain displays low thermodynamic stability that may allow for rapid transition between folded and unfolded states with important implications for protein turnover, interaction with partner molecules and function. p53 is highly susceptible to mutations and many amino acid substitutions that are associated to cancer development are deleterious for its structure and function. Indeed, the structural plasticity of p53 is modeled by post-translational modifications. In this review, we will focus on the relevance of specific modifications that heavily impact on the structure and function of p53 and its family members by acting on protein folding at the level of Prolines.

1.2. Structure-function relationship: the role of peptidyl-prolyl-isomerization

Protein structure is intimately linked to function. Among all amino acids that compose the primary structure, Prolines provide conformation-restrained peptide bonds. Indeed, while most amino acids show preference for the *trans* peptide bond conformation, the cyclic structure of Proline stabilizes the *cis* conformer so that both isomers are represented under biologically relevant conditions [19]. While the change from *cis* to *trans* occurs spontaneously, its achievement in a biologically relevant timeframe requires enzymes with prolyl-isomerase activity (PPIases). In this way, PPIases assist other proteins to shape

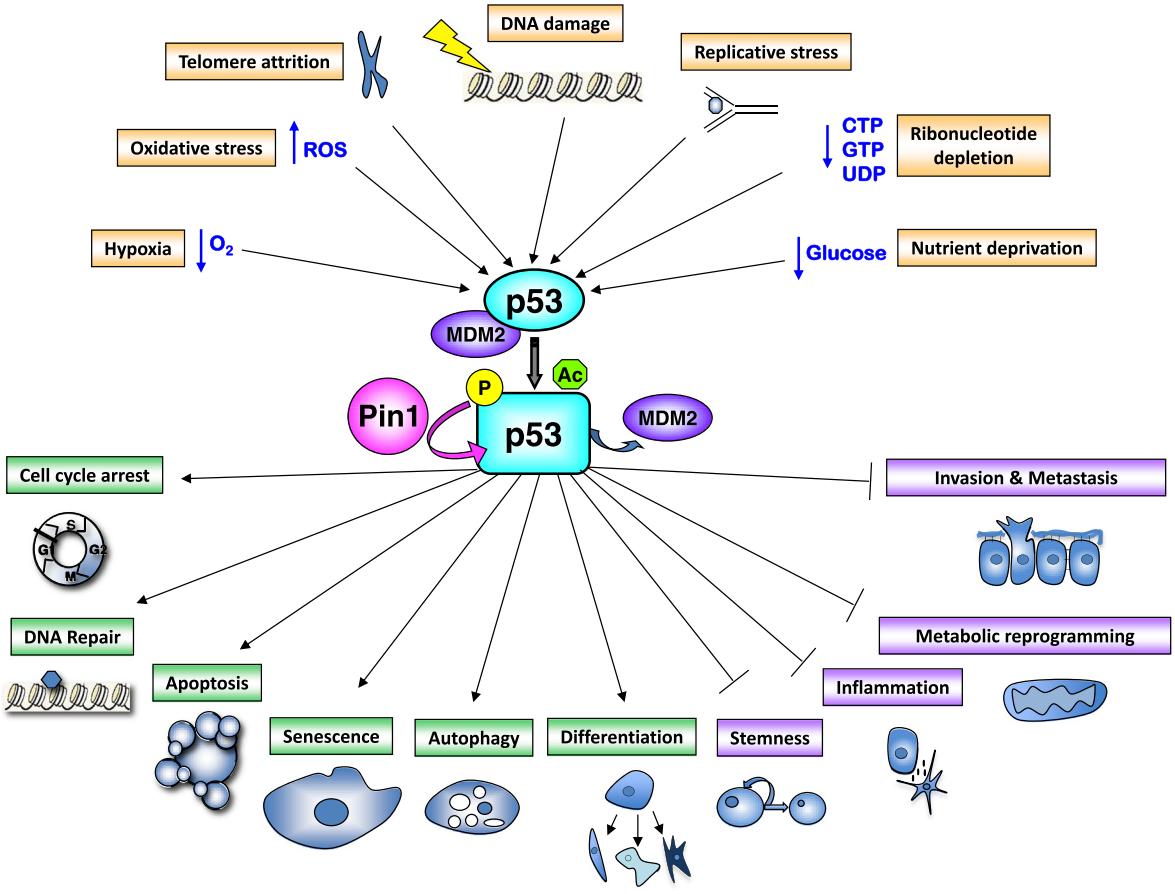

Fig. 1. The p53 pathway. p53 is activated by a variety of tumor-related stress conditions (orange boxes), that lead to its post-translational modification. Proline-directed phosphorylation (P) and subsequent prolyl-isomerization by the PPIase Pin1 (bent pink arrow) in particular lead to conformational changes and stabilization of p53 via detachment from MDM2, and to its acetylation (Ac) and activation of its transcriptional competence. As a function of the nature and duration of the inducing stimulus and of the cell context, p53 may then affect a wide variety of cellular processes, either positively or negatively (green and violet boxes, respectively).

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