Mutation Research 681 (2009) 118–133

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

P53 transcriptional activities: A general overview and some thoughts

Jean-François Millau, Nathalie Bastien, Régen Drouin *

Service of Genetics, Department of Pediatrics, Faculty of Medicine and Health Sciences, Université de Sherbrooke, 3001, 12th Avenue North, Sherbrooke J1H 5N4, QC, Canada

ARTICLE INFO

Article history:
Received 1 December 2007
Received in revised form 5 May 2008
Accepted 19 June 2008
Available online 27 June 2008

Keywords:
TP53
p53
Transcriptional activity
Response element
Gene regulation

ABSTRACT

P53 is a master transcriptional regulator controlling several main cellular pathways. Its role is to adapt gene expression programs in order to maintain cellular homeostasis and genome integrity in response to stresses. P53 is found mutated in about half of human cancers and most mutations are clustered within the DNA-binding domain of the protein resulting in altered p53 transcriptional activity. This illustrates the importance of the gene regulations achieved by p53. The aim of this review is to provide a global overview of the current understanding of p53 transcriptional activities and to discuss some ongoing questions and unresolved points about p53 transcriptional activity.

Contents

* Corresponding author. Tel.: +1 819 820 6827; fax: +1 819 564 5217.
E-mail address: regen.drouin@usherbrooke.ca (R. Drouin).

Abbreviations: EMSA, Electrophoresis Mobility Shift Assay; HR, Homologous Recombination; MMR, MisMatch Repair; NER, Nucleotide Excision Repair; NES, Nuclear Export Signal; NLS, Nuclear Localization Signal; NMR, nuclear magnetic resonance; RE, response element; ROS, Reactive Oxygen Species; UV, ultraviolet.

1383-5742/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrrev.2008.06.002

1. Introduction

P53 is a master transcriptional regulator which can be compared to the maestro of a symphony orchestra. The role of p53 is to maintain cell harmony and to provide specific and adapted responses to stresses by coordinating the expression of many effector genes (the musicians). P53 also regulates the cell cycle (the tempo) ensuring a perfect control of this important cellular event. When p53 transcriptional activities are deficient, the orchestra plays out of tune (wrong gene regulation) and out of tempo (poor regulation of the cell division): the normal cell may become malignant. Gene regulation achieved by p53 appears thus to be a very important cellular mechanism. In this article, we will review different aspects of p53 transcriptional activities. After a brief historical presentation of p53, we will describe the different domains of the protein, how p53 acts as a transcription factor and how its transcriptional activity is regulated. We will also describe some p53 effector genes reflecting the wide variety of regulated pathways. We will discuss about the consequences of p53 mutations found in cancer cells, evoke their possible use for diagnosis and prognosis. Finally, we will present some ongoing questions and unresolved points about p53 transcriptional activity dealing with how adapted responses are achieved.

2. P53 short story: from an oncogene to a tumor suppressor transcription factor

When p53 was simultaneously discovered by Arnold Levine, David Lane and Lloyd Old in 1979 [1–3], it was thought that this protein was an oncogene. Researchers were principally misled due to the p53 overexpression observed in rat, hamster, rabbit and human transformed cells, but p53 was in fact mutated [4]. It was only ten years later that Bert Vogelstein demonstrated that instead of being an oncogene, *p53* is a tumor suppressor gene mutated in cancer cells [5]. This finding greatly reinforced the interest of the scientific community in this protein and accelerated research. One year later, Weintraub et al. discovered the potential transcription factor function of p53 [6]. They showed an up-regulation of the *CPK* (Creatine PhosphoKinase) gene induced only by wild-type p53. However, the precise mechanism behind this regulation remained unclear until 1992 when Zambetti et al. discovered the binding of p53 to a specific DNA sequence located in the *CPK* promoter [7]. The same year, El-Deiry et al. defined the precise DNA consensus sequence of p53 response elements (RE) confirming definitively the transcription factor function of p53 [8].

3. Dissection of the p53 protein

In its basic form, p53 is composed of 393 amino acids arranged in four main domains (Fig. 1). The N-terminal region contains the transactivation domain divided into three sections: AD1 (residues 1–42), AD2 (residues 43–63) and a proline-rich domain (residues 64–97). The AD1 and AD2 domains are pivotal for p53 regulation because they are the site of numerous post-translational modifications and interactions with regulatory proteins such as MDM2 (Murine Double Minute 2), the acetyltransferases p300 and CBP (CREB-Binding Protein) [9–11]. The proline-rich domain contains five copies of the "PXXP" motif. This domain seems to be involved in different mechanisms but its precise function has not yet been clearly defined. The proline-rich domain has been shown to be implicated in growth suppression and in apoptosis [12–15]. Recently, Bergamaschi et al. showed that iASPP (inhibitory Apoptosis Stimulating Protein of P53) interacts with p53 through this domain [16]. There is also evidence implicating the proline-rich domain in the p53 interaction with the F-actin of the nuclear matrix in response to DNA damage [17]. Finally, the proline-rich domain has also been reported to include a negative autoregulatory domain reducing p53 DNA-binding abilities [18]. Next to the transactivation domain is the DNA-binding domain (residues 102–292). This domain is dedicated to DNA interaction and a zinc-binding activity is required for proper folding of the protein allowing DNA binding. However, it is worth mentioning here that two classes of proteins interact with p53 through this domain: the ASPPs (Apoptosis Stimulating Protein of P53) and the p53 homologues p63 and p73 [19,20]. On its side, the C-terminus region contains the oligomerization domain and the basic domain. The oligomerization domain (residues 323–356) allows p53 to dimerize during a cotranslational process and subsequently to self-associate to form tetramers [21]. Moreover, this domain contains a NES (Nuclear Export Signal). Finally, the basic domain, located at the extreme C-terminus end (residues 363–393), contains two NLS (Nuclear Localization Signal) and a second negative autoregulatory domain [22,23]. Interestingly, this region has been shown to bind DNA in a non-sequence-specific manner [24].

4. How the maestro controls its effector genes

P53 is essential for the cell to properly adapt its gene expression profile in response to stresses. P53 continuously receives information transmitted by cellular sensors relaying important cellular statuses. For example, DNA-PK (DNA-dependent Protein Kinase) senses DNA strand breaks, ATM (*Ataxia telangiectasia* Mutated) senses ionizing radiation induced damage, ATR (*Ataxia telangiectasia* and Rad3-related) sense UV induced damage, REDD-1 (REgulated in Development and DNA damage responses) senses ROS (Reactive Oxygen Species) level and AMPK (AMP-activated Protein Kinase) senses nutriment deprivation [25]. P53 integrates those signals by protein–protein interactions and post-translational modifications then triggers effector gene expression programs in order to preserve genome integrity and cellular homeostasis. P53 transcriptional activities are mainly promoted through direct DNA-binding to RE generally located in the promoters or first introns of effector genes [26,27]. Noticeably,

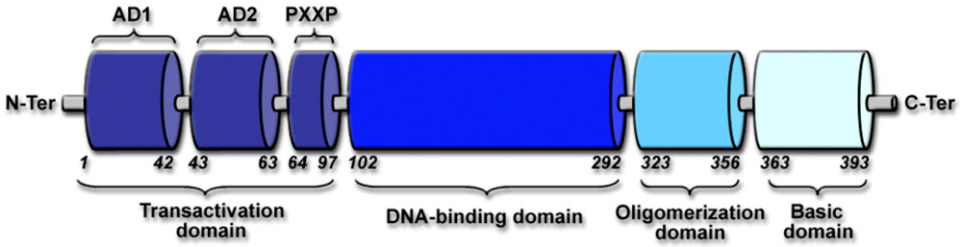

Fig. 1. The different domains of the p53 protein in its basic form.