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Functional implication of p73 protein stability in neuronal cell survival and death

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Abstract

p73, a newly identified member of *p53* family, locates at human chromosome 1p36.2-3, a region which is frequently deleted in a wide variety of human tumors including neuroblastoma. p73 is induced to be accumulated in response to a subset of DNA damaging agents such as cisplatin, and thereby promoting G1/S cell cycle arrest and/or apoptosis. Since the expression levels of p73 are kept extremely low under normal conditions, stabilization of p73 is critical for its effects on cell growth inhibition and apoptosis. Indeed, p73 is induced at protein level in SH-SY5Y neuroblastoma cells exposed to cisplatin. Several lines of evidence indicate that stress-induced post-translational modifications of p73 such as phosphorylation and acetylation lead to a marked extension of its half-life. p73 stability is regulated at least in part by proteasome-dependent degradation pathway, however, MDM2 which mediates ubiquitination and subsequent degradation of p53 by the 26S proteasome, does not promote the proteolytic degradation of p73, implying that the protein stability of p73 is regulated through a pathway distinct from that of p53. Although little is known about the regulation of p73 turnover, we are now beginning to understand the regulatory mechanisms by which p73 is induced to be stabilized in response to apoptotic stimuli, and exerts its pro-apoptotic activity. In this review, we discuss about the cellular proteins implicated in the stability control of p73.

Keywords: E3 ubiquitin ligase; MDM2; Neuroblastoma; p53; p73; p63; Proteasome; Ubiquitination; UFD2a

1. Introduction

p73 belongs to the tumor suppressor p53 family including p53, p73 and p63 [1,2]. As expected from their structural similarity, particularly in the central sequence-specific DNA-binding domain (over 60% amino acid sequence identity), p73 displays several p53-like properties. Analogous to p53, p73 can transactivate a large number of p53-responsive genes such as $p21^{WAF1}$ and *Bax*, and thereby inducing G1/S cell cycle arrest and/or apoptosis in a variety of cancerous cells [3]. *p73* gene has been mapped to human chromosome 1p36.2-3, a region which is frequently lost in neuroblastoma and other types of

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tumors [1]. In a sharp contrast to p53, however, p73 is rarely mutated in human tumors including neuroblastoma despite an extensive search [4], and the loss of p73 does not predispose mice to cancer [5], suggesting that p73 does not function as a classic Knudson-type tumor suppressor. Recently, it has been demonstrated that the p53-dependent apoptosis requires the indirect contribution of at least one of the other p53 family members, p73 or p63 [6], whereas p73 is sufficient to induce apoptosis in the absence of p53 [7,8]. Thus, it is likely that p73 cooperates with p53 to induce apoptosis and/or exerts its pro-apoptotic activity in a p53-independent manner. These findings have emphasized the functional importance of p73 in the regulation of apoptotic response, and attracted considerable attention. In particular, p73 is regarded as an important cell fate determinant of neuroblastoma in response to apoptotic stimuli, because wild-type p53 lacks its intact function due to its abnormal cytoplasmic localization in neuroblastoma [9].

Unlike p53, p73 is expressed as multiple variants with varying COOH-terminal extensions (TA isoforms) and lacking NH_2-terminal transactivation domain (ΔN isoforms), arising from alternative splicing and promoter usage, respectively (Fig. 1) [3]. Among them, ΔNp73 has an oncogenic potential [10], and exhibits a dominant-negative behavior toward TAp73 as well as p53 [5,11]. Consistent with this notion, the expression levels of ΔNp73 are closely associated with poor prognosis in human tumors including neuroblastoma [12,13]. Intriguingly, we and others found that p73 directly transactivates the expression of ΔNp73, suggesting that there exists a negative feedback regulation of p73 by ΔNp73 to modulate cell survival and death [14,15].

Steady-state expression levels of endogenous p73 are maintained at extremely low level under normal conditions, keeping this dangerous protein in an inactive state. In response to a subset of genotoxic stresses including oncotoxic drug cisplatin and ionizing radiation, however, p73 is induced to be accumulated at protein level, and the stabilization of p73 results in either G1/S cell cycle arrest or commitment to death through apoptosis [16]. Thus, stabilization of p73 is directly linked with its function. Several pieces of evidence suggest that the protein stability of p73 is regulated through a pathway distinct from that of p53 [8,17]. Although p73 protein stability is regulated at least in part by proteasomal degradation [17,18], it remains still unknown whether the proteasome-mediated degradation system is the main degradation route of p73. In this review, we will discuss about the cellular proteins regulating the p73 stability and how they affect its stability and activity.

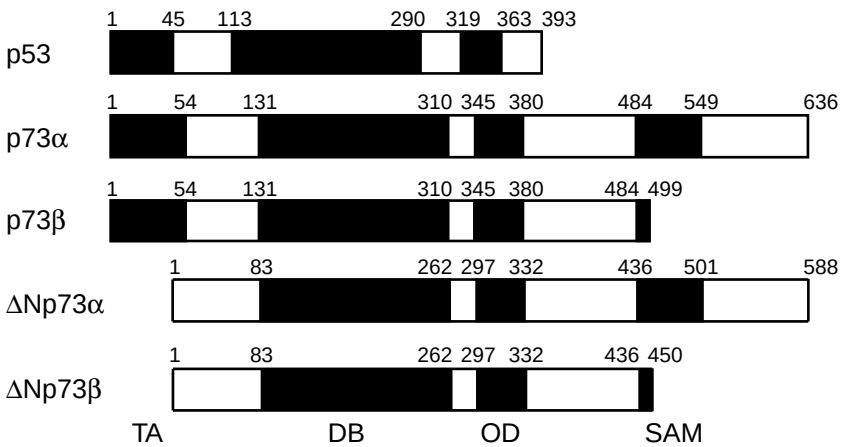

Fig. 1. Structural comparison between p53 and p73. p73α and p73β are generated by alternative splicing. Alternative promoter usage gives rise to ΔNp73α and ΔNp73β. The domains indicated are: a transactivation domain (TA), a DNA-binding domain (DB), an oligomerization domain (OD) and a sterile alpha motif domain (SAM).