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Review

Examination of the expanding pathways for the regulation of p21 expression and activity

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ABSTRACT

$p21^{Waf1/Cip1/Sdi1}$ was originally identified as an inhibitor of cyclin-dependent kinases, a mediator of p53 in growth suppression and a marker of cellular senescence. p21 is required for proper cell cycle progression and plays a role in cell death, DNA repair, senescence and aging, and induced pluripotent stem cell reprogramming. Although transcriptional regulation is considered to be the initial control point for p21 expression, there is growing evidence that post-transcriptional and post-translational regulations play a critical role in p21 expression and activity. This review will briefly discuss the activity of p21 and focus on current knowledge of the determinants that control p21 transcription, mRNA stability and translation, and protein stability and activity.

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Contents

1. Introduction

Deregulated cell proliferation is a hallmark of carcinogenesis [1]. To develop cancer therapeutic strategies, intensive studies have been carried out to identify key factors regulating the cell cycle in the past two decades. Cell cycle progression is controlled by a set of cyclin-dependent kinases (CDKs), which are activated by their associated cyclins, but inhibited by two classes of CDK inhibitors. One group is the INK4 family, including $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$, which specifically target CDK4 and CDK6 (reviewed in [2,3]). Another group is the CIP/KIP family, including $p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$, which inhibit a broad spectrum of CDKs (reviewed in [2,3]). p21, also named as Cip1, Waf1, Sdi1, and Cap20 [4–9], was discovered as a component of a quaternary complex consisting of cyclin D1, a CDK, the proliferating cell nuclear antigen (PCNA), and p21 in normal

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human fibroblasts [6]. Later studies found that p21 also associates with cyclin E-CDK2, cyclin A-CDK2, and cyclin B-CDK1 complexes, and has a universal inhibitory activity towards these CDKs [4,7,8,10]. In addition, p21 is a direct target of p53 tumor suppressor, and mediates p53-dependent cell cycle arrest in response to DNA damage [5]. When p21 was identified, the mechanism by which p53 suppresses cell growth was unclear. Therefore, the study provided first direct evidence that p53 exerts its activity through its downstream target genes. Consistent with the activity of p21 in growth suppression, p21 knockout mice are prone to accelerated tumor formation in response to genetoxic stresses, but the susceptibility to spontaneous tumors is delayed and mild [11–14]. However, p21 is more than an inhibitor of CDK. Indeed, p21 is implicated in cell death, DNA repair, cellular senescence, and aging [15–17]. Recent studies showed that p21 is found to be a barrier in reprogramming of induced pluripotent stem (iPS) cells [18]. Thus, the biological functions of p21 are far more complex than what we thought. As such a critical regulator of the cell cycle, p21 expression and activity are found to be tightly regulated by multiple mechanisms. In this review, we will discuss what is currently known about some of the key determinants in controlling p21 transcription and protein stability. We will also discuss the regulation of p21 by miRNA and RNA-binding proteins (RBMs), which has not been reviewed. The general information covering the function of p21 can be found in several recent reviews [19–21].

2. The biological functions of p21

2.1. p21 in cell cycle

p21 is accumulated in normal human fibroblasts arrested in G_0, whereas depletion of p21 expression by anti-sense RNA promotes cell cycle reentry and DNA synthesis [22]. Thus, p21 is a negative regulator that maintains cells in G_0 when the condition for cell cycle progression is not optimal [23]. Upon exposure to growth stimuli, a series of CDKs, including CDK4, CDK6, and CDK2, are sequentially activated during the cell cycle. In the late G_1, phosphorylation of the retinoblastoma protein (pRb) is found to be essential for G_1/S transition. pRb phosphorylation is initiated by cyclin D-CDK4/6 and phosphorylated pRb is separated from E2F transcription factors which transactivate genes necessary for the G_1/S transition and S phase, including cyclin E [24]. Activation of cyclin E-CDK2 complex further phosphorylates and completely releases pRb from interacting with E2Fs. However, association of p21 with cyclin D-CDK4/6 inhibits pRb phosphorylation and induces cell cycle arrest in G_1 (Fig. 1). p21 also associates with and inactivates E2F, leading to cell cycle arrest and cellular senescence [25]. During S phase, PCNA, which is expressed as a ring-shaped trimeric complex, is necessary for the formation of DNA replication complex by interacting with replicative DNA polymerase δ (polδ) and replication factor C (RFC) [26,27]. However, the p21 binding site in PCNA overlaps with the polδ- and RFC-interaction sites [28], and therefore the association with p21 blocks the ability of PCNA to activate polδ, leading to DNA replication block and intra-S arrest [29,30].

Upon exposure to γ-irradiation, cells deficient in p53 or p21 progress into mitosis but fail to undergo cytokinesis [31]. In addition, p21 inhibits both cyclin B1-CDK1 and cyclin A-CDK1/2 complexes, leading to permanent cell cycle exit in G_2 in normal human fibroblasts [32]. Consistent with this, overexpression of p21 is capable of inducing both G_1 and G_2-arrest, and p21-induced G_2 arrest appears to be more prominent in pRb-null cells [33]. Cyclin B-CDK1 complex, which phosphorylates and inhibits protein phosphatase Cdc25C, is a key regulatory factor for mitotic entry [34,35]. p21 cooperates with 14-3-

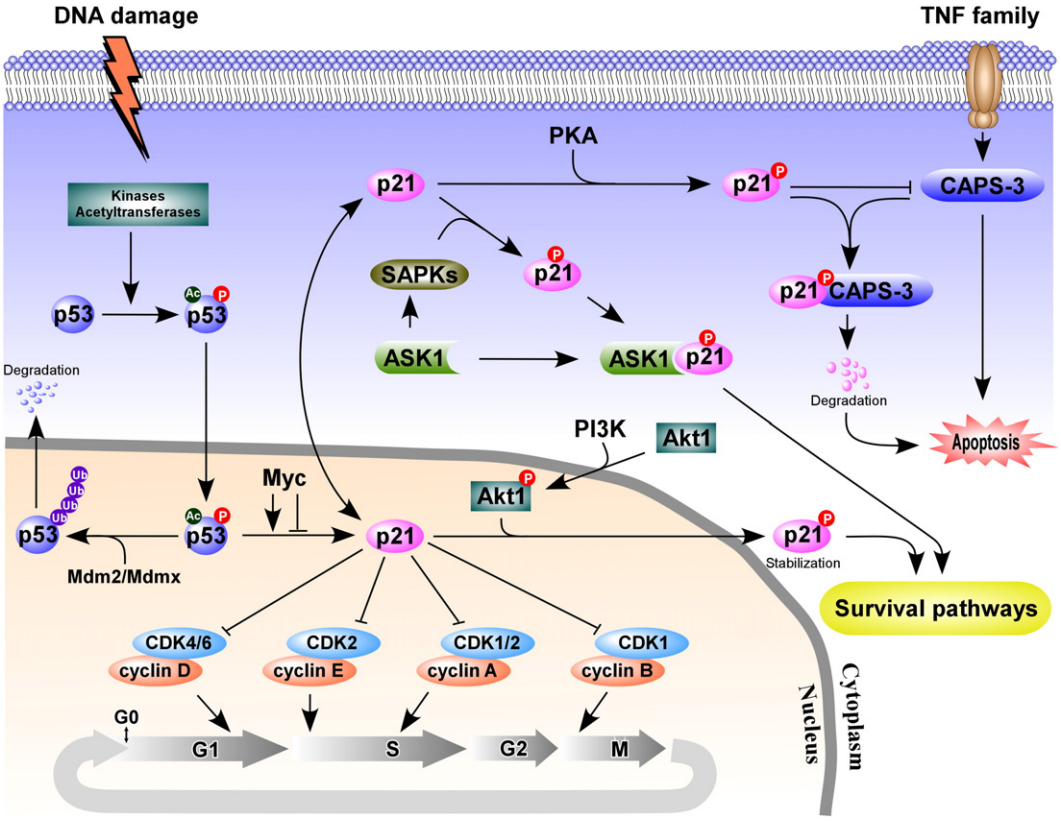

Fig. 1. The role of p21 in cell survival and death. Under non-stressed conditions, p21 is expressed at low levels and promotes cell cycle progression. Under stress conditions, p21 expression is increased through p53-dependent and -independent pathways. Increased p21 interacts with and inhibits cyclin–CDKs activity. In most tumor cells, the cell cycle checkpoint function of p21 is lost due to p53 mutations. Akt1 phosphorylates and then stabilizes p21 protein for cell survival. p21 inhibits apoptosis by interacting with pro-apoptotic molecules such as caspase-3 and ASK1.