p53-Cells’ Inbuilt Mechanism to Inhibit Cancer through Apoptosis

Rashmi Kumariya*, Amit K. Barui# and Smita Singh#

1Animal Biochemistry, Division National Dairy Research Institute, Karnal, Haryana, India
2Dairy Chemistry, Division National Dairy Research Institute, Karnal, Haryana, India
*These authors are contributed equally

Abstract

Cancer cells continue to grow and divide, without undergoing apoptosis. p53, a tumor suppressor protein, serves as a checkpoint in prevention of cancer by inducing the abnormal cells to commit apoptosis. p53 can induce both extrinsic and intrinsic pathways of apoptosis and can also induce apoptosis by directly acting on mitochondria. Regulation of p53 concentration in cell is very critical and is regulated by Mdm2 which triggers degradation through ubiquitylation. Keeping in view, the role of p53 in preventing cancer, many effective strategies can be developed to combat cancer by enhancing either function or stability of p53.

Keywords: p53; Cancer; Apoptosis; Tumor

Introduction

Cancer is a class of diseases characterized by uncontrolled growth of cells, which never die. Normal cells in the body follow an orderly path of growth, division, and death through apoptosis. Unlike regular cells, cancer cells do not experience apoptosis, which is the process of programmed cell death (PCD) that occurs in multicellular organisms, which involves a series of biochemical events that lead to a variety of morphological changes, including outward bulging of cell membrane, loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. So the cancer cells instead of undergoing apoptosis continue to grow and divide which leads to a mass of abnormal cells known as tumor that grows uncontrollably.

Apoptosis which plays a key role in inhibiting carcinogenesis is controlled by diverse range of cell signals either extracellularly or intracellularly. Extracellular signals must either cross the plasma membrane or transduce to affect a response. So, apoptosis can proceed through two pathways: extrinsic pathway and intrinsic pathway. p53 is a tumor suppressor protein which can activate both extrinsic and intrinsic pathways of apoptosis [1], leading to the activation of the aspartate-specific cysteine proteases (caspases) that mediate apoptosis and serves as a major barrier to carcinogenesis [2]. p53 is also known as protein 53 or tumor protein 53, encoded by the TP53 gene [3]. There are many isoforms of p53 known and the interactions between members of the p53 family and their isoforms have a profound effect on tumorigenesis and anticancer drug response [4]. It is known to regulate the cell cycle in multicellular organisms and thus functions as a tumor suppressor that is involved in preventing cancer through several mechanisms like, growth arrest, DNA repair and apoptosis. The growth arrest stops the progression of cell cycle, preventing replication of damaged DNA. During the growth arrest, p53 may activate the transcription of proteins involved in DNA repair. If the DNA damage proves to be irreparable, p53 can initiate apoptosis, which is the “last resort” to avoid proliferation of cells containing abnormal DNA [5,6]. Mutation in p53 leads to unrestrained cell cycle and reproduces the damaged DNA, leading to uncontrolled cell proliferation and cancer tumors [7]. Inactivation of p53 is responsible for majority of cancers as it is no longer functions as a tumor suppressor but also exert tumor-promoting effects [8]. The cellular concentration of p53 must be tightly regulated. While it can suppress tumors, high level of p53 may accelerate the aging process by excessive apoptosis. The major regulator of p53 is Mdm2, which can trigger the degradation of p53 by the ubiquitin system [9,10].

Role of p53 in Extrinsic Pathway of Apoptosis

p53 can activate the extrinsic apoptotic pathway through the induction of genes encoding three transmembrane proteins: Tumor necrosis factor receptor-1 (TNFR1), Fas and death receptor-5 (DR5), which on activation transducer signals to further activate the caspases responsible for apoptosis [11]. p53 induces Fas mRNA expression by binding to elements found in the promoter and first intron of the Fas gene. This induction along with the induction of DR5 and TNFR1 by p53 occurs in response to DNA damage and in turn promotes cell death through caspase-8 [12-17].

Apaf-1: Apoptotic protease activating factor-1); Bid: BH3 interacting-domain death agonist; Bax: Bcl-2-associated X protein; Cyt c: Cytochrome c; FADD: Fas associated death domain; Puma: p53-upregulated modulator of apoptosis; t-Bid: Truncated BH3 interacting-domain death agonist; Bax: Bcl-2-associated X protein; TRAIL: TNF-related apoptosis-inducing ligand [18].

Role of p53 in Intrinsic Pathway of Apoptosis

The intrinsic apoptotic pathway is dominated by the Bcl-2 family of proteins which comprises of anti-apoptotic proteins eg., Bcl-XL, Bcl-2, etc, and pro-apoptotic proteins eg., Bax, Noxa, Puma, Bid, etc., and are responsible for the release of cytochrome c from the mitochondria. Balance of pro- and anti-apoptotic bcl-2 proteins decides the sensitivity of cells to apoptotic stimuli like excess of pro-apoptotic proteins renders cells sensitive to apoptosis; while excess of anti-apoptotic proteins render cells more resistant to apoptosis. When there is an irreparable DNA damage, p53 induces the expression of Bcl-2 proapoptotic family members: Bax, Puma and Noxa, resulting in shifting of the balance towards pro-apoptotic effects [19-21]. p53...
subsequent release of apoptogenic factors [24]. These cause disruption of mitochondrial membranes and
mitochondria, antagonizing the anti-apoptotic effect of Bcl-2 and Bcl-
alpha. There are two categories of caspases: initiator caspases like,
caspase-9 and the induction of apoptosis (Figure 1).

p53 also participates in apoptosis induction by acting directly
at mitochondria. Localization of p53 to the mitochondria by using
mitochondrial-import leader peptides occurs in response to apoptotic
signals and precedes cytochrome c release and procaspase-3 activation
[23]. P53 also known to induce Bax and Bak oligomerization in the
mitochondria, antagonizing the anti-apoptotic effect of Bcl-2 and Bcl-
X1, and forms a complex with cyclophilin D in the mitochondrial inner
membrane. These cause disruption of mitochondrial membranes and
subsequent release of apoptogenic factors [24].

Caspase Activation

There are two categories of caspases: initiator caspases like,
caspase-9, caspase-2, caspase-8 and caspase-10 and effector caspases,
caspase-3, caspase-6 and caspase-7. Initiator caspases, caspase-9 and
caspase-2 respond to changes in mitochondrial potential, whereas
caspase-8 and caspase-10 sense activation of death receptors which

p53 family transcriptional targets have been identified as having the
capacity to modulate various cellular processes including growth arrest,
apoptosis, senescence, differentiation, and DNA repair. Deregluation
of p53 has enormous influence on carcinogenesis as mutant p53 can
induce an increased epigenetic instability of tumor cells, facilitating
and accelerating the evolution of the tumor. Based on p53’s critical role
in carcinogenesis, multiple effective strategies for treating cancer can
be developed by enhancing function of p53 or increasing p53 stability
[25].

As p53 plays an important role in the cellular response to stress,
it serves as a major barrier to carcinogenesis. This obstacle has to be
removed in order for tumor development to proceed and restoration
of p53 function is thus a potential key in anticancer therapies. Since
Mdm2 is an important negative regulator of p53, Mdm2 hyperactivity
may inhibit the function of p53 and lead to the development of a wide
variety of cancers. Because the apoptotic function of p53 is critical
for tumor suppression, induction of apoptotic pathways through
p53-induced apoptotic targets may be an attractive strategy for anti-
cancer treatment. Furthermore, the p53 apoptotic targets, unlike p53,
are rarely mutated in human cancers. There is a clear consensus that
restoration of the function of mutant p53 in tumor cells would also
be of potential therapeutic benefit. This strategy should be specific
to cancer cells, as normal cells contain no mutant p53. Understanding
the mechanisms of p53’s may ultimately provide novel targets and
approaches to therapeutic manipulation of the p53 pathway in the
treatment of cancer. Sound knowledge of p53 will help to develop
highly effective strategies and novel drugs for cancer prevention and
treatment with fewer side effects.

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