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FUNCTION AND REGULATION OF P53

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ABSTRACT: DNA damage checkpoint mechanisms are important for tumor suppression. P53 is a checkpoint protein that protects cell through transcriptional control of target genes. It plays an important role in the genome instability, including a transient cell cycle arrest, senescence and apoptosis. Different stress signals can mediate different responses and independent pathways to activate p53. All malignancies carry a p53 mutation or its function is inactivated by other mechanisms. Taken together, function of p53 lost in almost all tumors. Therefore, a greater understanding of function and regulation of the p53 will allow us to develop better strategies to treat cancer. Here, we summarize the functions and regulations of the p53 in cell through the stress signals.
Keywords: P53, Apoptosis, Tumor Suppressor, Cancer, Cell Cycle.

HISTORY

The p53 protein was described in 1979 as a transformation-related protein and associated with the SV40 DNA tumor virus large T antigen which was over expressed in tumor cells. Therefore, at first p53 seemed to being a proto-oncogene. A few years later, it was discovered that p53 was a tumor suppressor gene. (1) We now know that p53 is a member of a family of proteins that has three members: p53, p63 and p73. Although all three can induce apoptosis, there are many structural and functional differences between p53 and other family members.(1, 2) The p53 gene is located on the small arm of chromosome 17 (17p13.1) and have 11 exons and 393 amino acids that span approximately 20 kb.(3) The p53 is a nuclear phospho-protein with five conserved domains and four functional domains: an N-terminal transactivation domain (residues 1–42); a polyproline-rich region (residues 61–94); a central DNA-binding core domain (residues 102–292) , the oligomerization domain (residues 324–355) and a C-terminal regulatory domain (residues 311–393) (1, 4, 5)

ROLES OF P53

Transcription Factor

Damage to the p53 gene and disrupt the pathways that allow activation of the p53 protein is observed genetic alterations during tumorgenesis. The p53 acts as a multifunctional protein; therefore functions of p53 target genes are diverse. (1) Different stresses such as ionizing radiation, UV radiation, hypoxia, heat shock, growth factor withdrawal, ontogeny activation and the application of cytotoxic drugs can increase the levels of p53 within the cell.(6, 7) cellular functions such as gene transcription, DNA synthesis, DNA repair, cell cycle arrest, induction of permanent cell cycle arrest(senescence)and apoptosis are modulated by the p53 protein. (1, 8, 9)(Figure 1)

Transcription factors play a central role in cell biology through binding to target DNA elements and regulating gene expression. Since The p53 is as a transcription factor, it can binds to specific DNA response elements (REs) and exerts tumor-suppressive functions by regulating the expression of effectors genes.(8)

Two large target genes of p53 are: (1) negative regulators of cell cycle progression, such as the p21, cyclin-dependent kinase inhibitor 1A (CDKN1A), 14-3-3s, DNA damage-inducible gene (GADD45a); and (2) a number of pro-apoptotic proteins such as the BH3 only proteins Puma and Noxa and Bcl-2-associated protein X (BAX) and Bcl-2 antagonist/killer (BAK) IGF-BP3, DR5/KILL- ER, Fas/Apo-1, PIGs, PAG608, PERP, PIDD, DRAL, Apaf1, Scotin and p53AIP1.(7, 8, 10, 11) p53 specifically curbs the expression of anti-apoptotic genes such as Bcl-2, MAP4 and surviving.(1) Studies showed that the p53 can regulate pro-survival pathways because p53 modulate a variety of anti-apoptotic targets, such as DcR1, DcR2 , EGFR , Akt and NF-rB.(12, 13)

The outcome of p53 activation depends on a number of factors, such as the availability of interactive cofactors, different promoter strengths of the anti-apoptotic genes and its post-translational modifications. P53 also can bind to non-specific DNA and RNA, so it promotes annealing of single stranded DNA and RNA. In addition, p53 has been shown to localize to centrosomes.(14)

Induction the Apoptosis

One of the most important p53 functions is its ability to activate apoptosis. The p53 can mediate apoptosis through transcription- dependent and –independent mechanisms. In the transcription-dependent process, two distinct signaling pathways are involved: extrinsic and intrinsic pathways. Each of them can be regulated at multiple levels.

The extrinsic pathway, which consists of cell surface receptors, and their associated cytoplasmic proteins, can be modulated by altering the number of each type of receptor.(15) Indeed, in this pathway the transcription of death receptors of the tumor necrosis factor receptor (TNF-R) family: Fas, APO-1, CD95, DR5, and PERP are induced by p53. After a ligand binds to its receptor, the death-inducing signaling complex (DISC) is formed and it can accomplish recruitment of the Fas-associated death domain (FADD) and caspase-8 and -10, This caspase active the effector caspases (e.g., caspase-3 and -7) and finally apoptosis is started.(8, 16)

The intrinsic pathway centers on the mitochondria, which contain key apoptogenic factors such as cytochrome c, AIF, SMAC/DIABLO, Htra2/Omi , and endoG . Major regulators of the intrinsic pathway are the pro and anti-death members of the Bcl-2 family.(16, 17)

The p53 transactivates the pro-apoptotic genes Bax, Noxa, PUMA, and Bid.(18) Of these, the translocation and functional multimerization oF Bax depend on other pro-apoptotic family members.(19) Bax can be homo-multimerize or hetero-multimerize with Bak in the outer mitochondrial membrane and induce the release of cytochrome C, SMAC /DIABLO, and apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space to the cytosol. The cytochrome c interacts with APAF-1 (apoptotic protease-activating factor 1 is a p53-regulated gene) to initiate a protease cascade, leading to the activation of caspase9 and then caspase-3, -6, and -7. This process induces apoptosis.(8, 20)

Interestingly, caspase-8 can cleavage Bid to t-Bid that translocates to the mitochondria and activates the Bax and Bak, so in this way the intrinsic and extrinsic pathways can be connected.(18) The p53 accumulates in the cytosol or mitochondria under cellular stress, and leads to the direct activation of Bax and/or Bak.(21-23)

P53 can play a role in apoptosis via transcription independent pathway as well. The p53 protein has an activity permitting it to interact with the mitochondria directly and promotes apoptosis. In response to DNA damage, mitochondrial p53 translocation triggers a rapid apoptotic response that occurs prior to p53 target gene activation.(24, 25)

Transcription-independent proapoptotic activities of p53 may result from the interaction between p53 and proteins known to be critical for the cascade. Including the Fas/CD95 death receptor that is translocated to the plasma membrane by p53 and the p53- mediated translocation of Bax from the cytoplasm to the mitochondria, resulting in cytochrome C release.(25)

The apoptosis delete surplus cells and that is crucial for multicellular organisms. Interestingly, the phenotype of an apoptotic cell and the regulation of p53 by the ASPP family are conserved from nematodes to mammals.(1)

Induction of Cell Cycle Arrest

DNA damaging agents can induce arresting of S- and G2-phase and also entering into mitosis can be blocked by the G2 checkpoint mechanism.(26)

The inhibition of distinct Cdk/cyclin complexes prevents or slows G1/S transition, S-phase progression, G2/M transition, or all three.(27, 28) Many of the Cdks can be inhibited by Cdk inhibitors including, p21, p27, and p57. The p21 is the most significant target of p53 for inhibiting G1-phase, Cdk4/cyclin D and Cdk2/ cyclin E. This significance is reflected in the fact that p21 can induce G1-phase arrest(28), whereas other mechanisms inhibit S- and G2-phase Cdk activities.(29)During G2, the Cdc2-Cyclin B complex is kept inactive by phosphorylation of Cdc2 by the kinases Wee1 and Myt1 and it can be dephosphorylated by the phosphatase Cdc25 at the onset of mitosis. DNA damage stimulates the kinases Atm and Atr, which activate the Chk1 and Chk2 kinases, which phosphorylate Cdc25, causing it to bind to 14-3-3 proteins, which anchor Cdc25 in the cytoplasm, so it can't activate Cdc2.

P53 has other targets that not only affect Cdc2 but also contribute to G2 arrest.(9) Atm and Atr can also phosphorylate p53 in response to DNA damage so it accumulates and stimulates its ability to bind to specific DNA sequences, essential steps in activating p53 in response to stress.(9)

Centrosome Duplication is Controlled by P53

Ether loss or mutation of p53 induces abnormal amplification of centrosomes(hyperamplification), resulting in missegregation of chromosomes into daughter cells.(14) P53 controls centrosome duplication through multiple pathways, and p21 is one of them. In human cells, activation of CDK2/cyclinE is strictly controlled. The activation of CDK2/cyclinE at late G1 coordinates the initiation of centrosome and DNA duplication and it prepares a cell to progress from G-1 to S phase in the cell cycle.(25) p21 targets G1/S, CDK/cyclin complexes, including CDK2/cyclinE. The inactivation of p21 leading to uncoupling in the initiation of centrosome and DNA duplication (centrosomes initiate duplication early in G1 much before S phase entry). The activation of CDK2/cyclinE induces centrosome hyperamplification by loss of p53.(14)

Induction of Senescence

In addition to p53-dependent apoptosis, senescence is a powerful tumor-suppressive mechanism downstream of p53 as well. Many forms of stress stimuli, such as telomerase shortening, oncogenic stimuli, ionizing radiation, and DNA damaging agents can induce the senescence phenotype.(30) The irreversible cell cycle arrest is called cellular senescence. The senescence is considered as an additional tumor suppressive mechanism in benign or premalignant cancer lesions(31) because It can prevent cell immortalization and transformation to a genetically unstable phenotype.(32) Senescent cells remain metabolically active but have changes in cell size, chromatin condensation, and also in gene expression.

Mutations can inactive the p53 and/or p16 inhibitor of cyclin-dependent kinase4A (INK4A)/retinoblastoma (Rb) pathways in the most human tumors, which are crucial molecular constituents of the senescence response.(8) Stress induce the senescence via the ATM/ATR-Chk2/ Chk1-p53 pathway, and also several p53-dependent downstream molecular markers, such as p21, PML, PAI-1, and DEC1.(31)

INACTIVATION OF P53 BY MUTATION IN HUMAN CANCER

Nearly 50% of human tumors have mutations in p53.patients with the Li–Fraumeni syndrome have a inherited germline mutation in p53, so they have multiple tumors early in life including tumors of the brain, breast, connective tissue, hematological system and adrenal gland.(1) The most of p53 mutations is missense substitutions (75%). Other alterations include frameshift insertions and deletions (9%), nonsense mutations (7%), silent mutations (5%) and some infrequent alterations.(33, 34) The majority of these mutations are within the central region of p53 (residues 102–292). These residues are the most highly conserved region between p53, p63 and p73. These amino- acid residues are essential for contact p53 with DNA. The mutation in genes that encode positive regulators or effectors of p53 can inactive p53 function as well.(1, 10, 35, 36)

REGULATION OF P53 PROTEIN STABILITY

In normal condition cellular levels of p53 are kept at extremely low because its half-life is 20 min and it is rapidly degraded following synthesis.(26) Abundance and activity of the P53 are regulated by many different post-translational modifications including phosphorylation, acetylation, methylation, ribosylationm, O-glycosylation, ubiquitination and SUMOylation.(37, 38)

The proteasome is a multicatalytic enzyme complex that recognizes and degrades poly-ubiquitinated proteins.(39) suppression of the proteasome often leads to cell cycle arrest and apoptosis, because many of poly-ubiquitinated proteins are closely implicated in cell cycle regulation, cell death and cell proliferation.(40, 41)

The p53 is degraded via both of the proteasome by a ubiquitin-dependent mechanism or the proteasome by an ubiquitin-independent mechanism .

The Mdm2 is the important component of the p53 degradation pathway. This protein is one of the transcriptional targets of p53. Mdm2 can keep the physiological levels of p53 low, and contribute to the recovery phase at the end of a p53 response.(10) The Mdm2 is a ring finger protein that regulate p53. It can directly interact with the p53 protein and inhibit its activity. Mdm2 binds to the N-terminus of p53, and inhibits the normal function of this region of p53, so it can reduces the ability of p53 to activate gene expression but this is not the only way in which Mdm2 controls p53, Mdm2 also participates in the degradation of p53.(10)

The subcellular localization of p53 can play an important role in regulating its activity. It is a protein with both nuclear and cytoplasmic functions. Mdm2 carries p53 from the nucleus into the cytoplasm, where degradation occurs through cytoplasmic proteasomes. However, p53 itself has a nuclear export sequence that functions in the absence of Mdm2 and the two proteins could shuttle independently of each other. Nevertheless, degradation of p53 by Mdm2 depends directly on the ability of Mdm2 to shuttle from the nucleus to cytoplasm and another possibility is that shuttling of Mdm2 is necessary to activate the ubiquitin ligase function.(42, 43)

STABILIZATION OF P53

The stabilization of p53 involves mechanisms to protect p53 from Mdm2. This is a common response to many different and diverse forms of stress, including DNA damage, oncogene activation, metabolic changes, hypoxia and changes in pH or temperature.

The activation of p53 prevents the development and progression of malignant cells. Each of these stress signals inhibits Mdm2-mediated degradation of p53 through numerous independent pathways. (44)(Figure 2) different types of DNA damage can active various specific kinases such as; ATM, ATR, Chk1, and Chk2 that modify the p53 protein at different amino-acid residues .they can also phosphorylate p53 target sites, such as Ser15, Thr18, and Ser20, and this phosphorylation forces dissociation of p53 from the Mdm2–p53 complex. Therefore, the p53 can translocate to the nucleus and be enable to bind as a tetramer to specific DNA sequences and transactivate target genes.(26, 45, 46)(figure1) Phosphorylation of Mdm2 also enhances the degradation of this proteins by reducing their association with HAUSP (47)DNA damage in part by promoting acetylation within the C-terminus of p53 induced activation of p53 as a transcription factor as well.(10) A number of ribosomal proteins, in particular L5, L11and L23 can bind and inhibit Mdm2, so they are able to stabilize p53.(10, 48) Cancer associated mutations in Mdm2 can prevent the interaction with L11 and L5.(10)

If DNA damage is repairable, p53 functions as a modulator of the DNA but when it is persists or irrepairable, p53 may induce apoptosis specific genes leading to cell death. (10, 41) Physiological stimuli include serum starvation and cell–cell contact growth inhibition can induce p53 activation through the ribosomal stress pathway. (49) Another stimulus that leads to the stabilization of p53 is the loss of cell–matrix adhesion. (50) The loss of adhesion in non-transformed cells can induce apoptosis known as anoikis, The loss of p53 is critical for in tumor progression towards metastasis in some cell types.

Studies showed that not all p53 activating signals depend on direct phosphorylation. Some of them such as heat shock, oncogene activation or treatment with actinomycin-D, stabilize p53 without significant phosphorylation. They can inhibit the transcription of Mdm2, so they reduce Mdm2 protein levels and increase p53 stability.(44)

The best phosphorylation independent stabilization mechanism is activation of expression of a small tumor suppressor protein p14ARF in human. This protein can bind to Mdm2 in a region distinct from the p53 binding domain and inhibits the degradation of p53 without preventing the binding. (51) This protein also can sequester Mdm2 into the nucleolus, thus preventing nuclear export which is necessary for degradation.(44)

In the oncogenes, such as E2F-1, beta-catenin, myc, ras and adenovirus E1A increase level of p53 via the pl4ARF/ Mdm2/53 pathway which in turn inhibits the HDM-2 ubiquitin ligase.(25, 52)

Other proteins that bind to p53 or Mdm2 may also Stabilize p53.For example the pRB inhibit the degradation of p53 by binding to Mdm2 .It does not inhibit p53/Mdm2 interaction, so the p53 stabilized by pRB remains in contact with Mdm2. Another protein which can bind to the p53 is c-Abl. It can protect p53 from Mdm2-mediated degradation without inhibiting the p53/Mdm2 interaction. (44)

Collectively , these protein modifications alter the p53 protein in two ways: first of all they increase the half-life of the protein , from 6–20 min to hours, so this results in a 3–10-fold increased concentration of the p53 protein in a cell. Second prompting the ability of the p53 protein to bind to specific DNA sequences.(25)

CONCLUSION

The p53 is a transcription factor that binds to specific DNA response elements. It is a protein with both nuclear and cytoplasmic functions. The p53 is a multifunctional protein that can mediate transien cell cycle arrest, senescence and apoptosis so it plays an important role in the genome instability.p53 elevates the expression of some Proapoptotic genes and curbs the expression of antiapoptotic genes as well. In this way it can produce apoptosis. Depend on reparable or irreparable DNA damage p53 acts as a modulator of the DNA or inducer of apoptosis and cell death. Studies showed a variation in p53 mutation rates in different tumour types. The regulation of p53 stability is a complex process. Degradation of p53 via proteasomes occurs in cellular cytoplasm, therefore it must be carried from the nucleus into the cytoplasm. The phosphorylation, inhibition of Mdm2 synthesis, cytoplasmic sequestration of p53 or expression of inhibitors of Mdm2 function such as p14ARF are used for stabilizing of p53 in stresses. The Mdm2 protein targets p53 for degradation via the ubiquitin- dependent or ubiquitin-independent proteasome pathway. Increase in p53 protein level reduced degradation through the Mdm2 protein , so it can increase the p53 stability . Taken together, undoubtedly p53 has a key player in the inhibition of tumor development. Therefore it is clear that for developing strategies to treat cancer, more understanding of function and regulation of the p53 will be necessary.

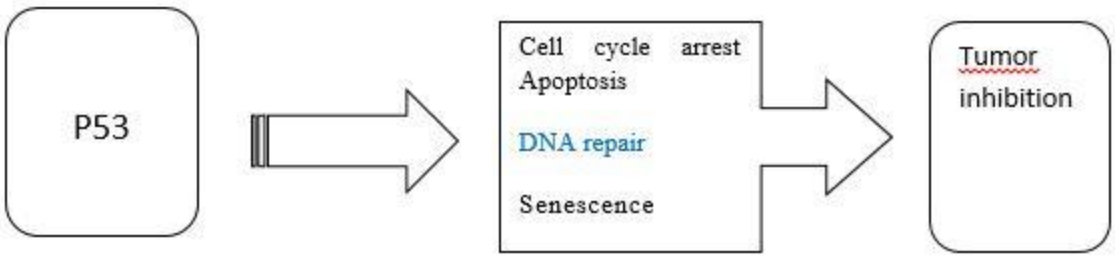

Figure1: p53 acts as a multifunctional protein and it can inhibit Tumors

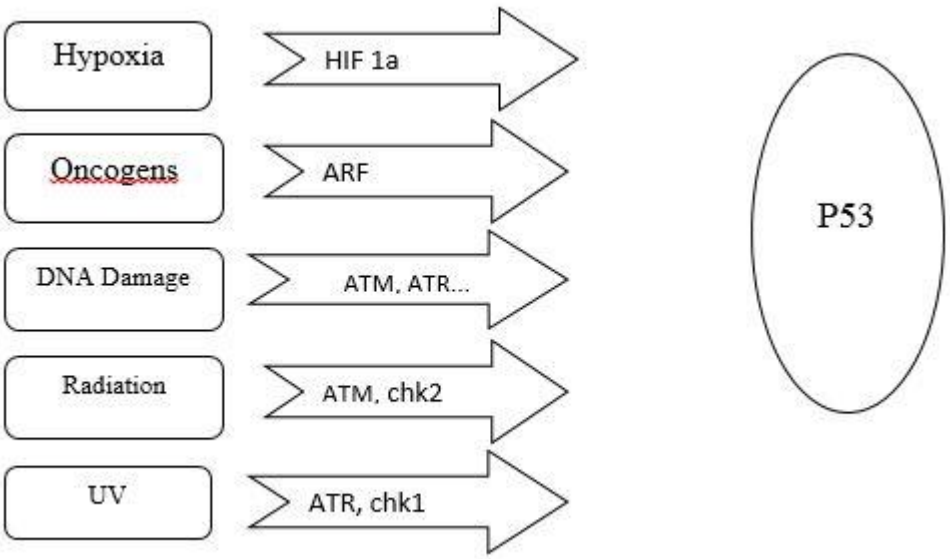

Figure2: Many different and diverse forms of stress stabilize p53

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