Egyptian Journal of Veterinary Sciences
https://ejvs.journals.ekb.eg/

Mechanism of p53 Action [Review Article]

Ghorbat Saleh Ali[1] and Basim S.A. Al-Sulaivany[2]
[1.] *Department of Biology, Faculty of Science, University of Duhok, Duhok, Iraq.*
Email: ghorbat.ali@uod.ac
[2.] *Department of Biology, Faculty of Science, University of Zakho, Duhok, Iraq.*
Email: basim.ahmed@uoz.edu.krd

P53 is a 393 residue protein in human made up of five proposed domains, with which the central DNA binding domain with 100-300 sequences very important for the direct binding of p53 in the promoters of its target genes to specific response elements. P53 is a tumor suppressor gene with cellular stress like oxygen deficiency, oxidative stress, radiation and carcinogens substances, and its stimulated has major roles in translational regulation and feedback processes. A wide assortment of harm signals that relate a stability, post-translational alteration and recruitment of p53 to binding sites in chromatin which activate the p53 pathway. As a transcriptional activation, p53 mediates transcriptional changes which facilitate cell death, senescence or reversing and protective arrest of the cell cycle. P53 is a protein under intense investigation because it is necessary to prevent tumor, in human tumors have been found to deregulation of p53 activity. On this article study focuses on the mechanism of suppressive p53 effects in the response to any stress and correlation of the mutation p53 with different tumours.

Keywords: P53, Cell arrest, Apoptosis, Senescence and Cancer.

Introduction

Firstly, protein 53 is identified by the discovery of the antibodies against SV40 expansive T antigen from creature carrying tumours produce by SV40-transformed cells is immune precipitated an apparent with mass about 53 kDa is identified as p53 [1]. Initially, gene encoding p53 showed low oncogenic action as a result of overexpression of the p53 protein in mice tumor cells [2]. In 1984, after the first cloning of p53 gene was reported that a discovering that fitted with the speculation that p53 was a cellular oncogene that might be enacted by transformation [1]. Following that, a number of important findings were soon discovered, including p53 may be inactivated by tumor viruses. In 1989, p53 was established as tumor suppressor gene after review verified the capacity of wild type 53 to suppress E1A and *Ras* mediated transformation. Until 1989, it was classified as a tumor suppressor [3]. The first set of such studies on mice expressing temporally regulated version has been proved inhibition tumor genesis of p53 when the exposure to acute DNA damage [4].

Structure of P53

P53 gene is located on chromosome 17, it contains 11 exons of human genome which coding the p53 protein. The natural p53 protein transcribed and translated consists of 393 amino acids with half-life between 6 to 20 min [5].The p53 is consisted of four major functional regions, as tetramer-like structure. The N-terminal region consists of the transactivation field (TAD). TAD is the fundamentally n-terminal area. Transcription factor TF11D acts in this location through connecting to TATA box in the promoter and initiate the transcription. TAD divided into TAD1 and TAD2. The follow part is the proline-rich with five PXXP motifs. Then the core Domain, which highly specialized region responsible for binding DNA sequence, where the inactivating mutations are most commonly identified. Lastly, there is a C-terminal domain, composed of NLS

*Corresponding author: Basim S.A. Al-Sulaivany, E-mail: basim.ahmed@uoz.edu.krd. Tel.: 009647504509701
(Received 16/04/2023, accepted 25/06/2023)
DOI: 10.21608/EJVS.2023.205434.1490

and NES, binding with nonspecific nucleic acid or other protein, target for regulation p53 and posttranslational alteration. The terminal tetramerization domain (TD) is situated between the C-terminal region and DNA-binding domain [6]**.** DNA binding domain is necessary for specific binding of p53 to its target promoters. In many human cancers the missense mutations within this central domain commonly happen [7]. The mostly mutations occur in disturbing of the p53 capacity to DNA binding or alteration in domain folding. Therefore, these mutation p53 prevents to perform its transcription factor activity [8].

Functions of p53 protein in the Cell Bodies

P53 tumour suppressor is susceptible for different genotoxic stress such as ionizing radiation, ultraviolet radiation, application of cellular toxicity drugs or chemotherapeutic agent and irresistible infection), warm stun, hypoxia, and oncogene overexpression and damage to DNA. Distinct signalling processes have evolved which in effect up regulate different pathways to increase health and survival of organism [9,10]. P53 can activate a variety of responses, including cell cycle arrest, altered metabolism, and restoration of DNA, antioxidant, anti-aging, senescence and apoptosis effects [11].

Mechanism of the Cell Cycle Arrest
Cell Cycle

The cycle of cell is divided into two phases; interphase, which consists from G1, S, and G2 phases, and the mitotic (M) phase. The end of cytokinesis in a previous division is named as G1 phase which the cell grows in preparation for DNA replication. In S- or synthetic-stage is replicated of chromosomal DNA and two strands of DNA produce by every chromosome. In phase G2, continues protein synthesis and prepares cell for the mitotic phase. There are checkpoints (G1/S or G2/M) to make sure the previous phase is complete prior to embarking on the next step checking DNA. Finally in phase M cell is divided [12].

A series of checkpoints where cyclins and Cyclin Dependent Kinases (CDK) form complexes and collaborating allow to controlling to each phase to Progression the next phase [11]. Signals that cause cell death excite cyclin-dependent kinase 4 (CDK4) and CDK6 and encourages the cell division. Initially, complexes CDK4 and CDK6 with cyclin D Phosphorylation of the tumor suppressor retinoblastoma protein (Rb) is a particular favourite of theirs which coordinated the function of the transcription factor family E2F. Whereas Rb has to be hyper-phosphorylated to proceed to the cell cycle's synthesis, stage and DNA replication is initiate. E-CDK2 adds phosphate groups to Rb during the G1 checkpoint phase. So, it will become gradually oxidized, allowing this to be detached from E2F, allowing E2F to start a transcriptional system that allows cells advance into S phase. Protein kinase inhibitor such as p21 and p27 that inhibit CDK2–cyclin complexes. During the normal cell division, after passing from G1/S start DNA synthesis. CDK1-Cylin A and CDK1-Cyclin B complexes phosphorylate their goals in the G2 stage. When there isn't any DNA damage, and after adequate chromosome duplication preparation will Progress towards mitosis [13]. Mutations in any of these regulatory pathways lead to mutated cells replication or irregular chromosome numbers, contributed in genomic instability [14]. The cell cycle includes several regulatory proteins, tumor-suppressor genes, oncogenes and mitotic proteins for proper cell replication [14].

G1 Checkpoint

When stress is inserted on the cell, p53 as a tumor suppressor gene, code transcription factors in G1-S phase checkpoint and prevent cell division. When DNA damage is observed, the activity of repair enzymes is stimulated at a time. DNA damage is beyond repair, the p53 protein will causes the destruction of the cell [5]. Most observations of the activities of p53 have based on p53 transcriptional sites, p53 protein up regulates endogenous production of p21 protein, which interacts with the cell division stimulating cyclin dependent kinase 2 and generate p21- cdk2 complex that cell unable to pass the next level. p53/p21 G1 restricted point have been activated by trauma such as radiation, DNA-damaging chemotherapy, or other stress, such as nutritional deficiency, trigger growth arrest before desirable condition [15].

P21 prevents cyclin-dependent kinase 2 (Cdk2)-complex lead to Rb inactivation, therefore inhibits to entrance cell to S phase. Thus, cell cycle is arrested in the G1 through inhibition Rb-mediated of E2Fdependent transcription [16]. In addition, p21 prevent the binding to E2F to phosphorylated pRB and check the activity of CdK2 [17]. Generally, P21 is recognized as an inhibitor of cyclin-dependent kinase, encoded by the gene CDKN1A situated on chromosome

6p21.2. It triggers cell cycle arrest by identifying with various stimuli and transfer factors such as p53, which by interaction with cell nuclear antigen proliferating, work as a regulator of cell cycle progression and induced G1arrest in cell until cell repair DNA-damage [18] [19].

G2 checkpoint

Multiple experiments were established in the G2 phase, p53 plays a crucial role to M regulation due to the loss of substrates required for DNA synthesis. Cells which have already completed transcription of DNA whereas possess impaired DNA, the G2 checkpoint is activated. Part of the mechanism is restricting cell at the G2/M barrier via p53 includes Cdc2 inhibition, which Cyclin-dependent kinase is essential for mitosis to occur. Three target p53 genes such as p21, Gadd45 and 14-3-3 sigma inhibit Cdc2 [20].

Genotoxic stress often causes p53-dependent pathways that prevent the activation of Cdk2. In human cells, p53-mediated arrest responsible for cell-cycle checkpoint which is critically cyclin B1/ Cdk2 complex. When DNA double-strand break by irradiation causes stimulation of the Ataxia telangiectasia mutated protein (ATM) and Ataxia telangiectasia and Rad3-related protein (ATR) activate the Chk1 and Chk2 kinases (Checkpoint kinase 1 and 2) phosphorylate Cdc25, allowing it to connect to 14-3-3 proteins that support Cdc25 in the cytosol where is unable to promote Cdc2 promote arrest of G2/M that prevents cell division [9] [21] [20]. Additionally, this modification is produced in 14-3-3δ regulatory protein at the binding site lead to aggregation separated in the cytoplasm and stop replication [21]. Additionally, p53 increase activation and expression of p21, p53-mediated p21 inhibit cyclin B/ Cdk2 prevent progression mitosis and contributes to inactivation of Cdk1 to the G2 checkpoint [22]. In other side, p53 is affected on target gene, a specific 14-3-3δ isoform. 14-3-3s, is up regulated after DNA mutation. Proper localization of nuclear for cyclin B1/CDC2 is inhibited by 14-3-3s. Other the *p53* target gene DNA damage-inducible 45 alpha gene (GADD45) interacts with Cdk2 and suppresses its kinase activity; dissociate cyclin B1/ Cdk2 which anchors Cdk2 in the cytosol that cannot induce mitosis. Further, induction of GADD45 consequences increased cytoplasmic cyclin B and in G2 arrest phase [23, 20].

P53 inhibits cell cycle arrest at G1 and G2 is delaying cellular disruption sustained from free radicals before entering the post synthesis and process mitosis [10]. With p53's the purposes of biochemical that promote nucleotide excision repair and base excision repair are two types of DNA repair, arrested cells will return to the proliferating condition [24].

Programmed cell death

According to numerous publications, the mechanism of p53 in the programmed cell death. The cells face p53-induced apoptosis, if the genomic repair cannot complete or the cells no programmed to respond to the stresses of sustainable cell cycle arrest [25]. P53 is activated a substantial number of genes in different levels of programmed cell death execution and signalling during the severe stress [26]. Processes of modulation control Apoptosis progression, the intrinsic pathway also named the mitochondrial pathway and the extrinsic pathway are the two best-understood activation mechanisms [27].

Intracellular signals produced when cells are stressed stimulate the intrinsic pathway and dependent on the release of proteins from the inter-membrane space of the mitochondria. In the other way, extracellular ligands bonding to cell-surface death receptors stimulate extrinsic pathway, which contributes to the death inducing signalling development [28]. In contrast, the intrinsic pathway is accelerated after the release of cytochrome C from mitochondria [29]. New research suggests that p53 not only controls the permeability of the outer membrane mitochondria, but also promotes inner permeability during oxidative stress [30]. The fundamental mechanism behind the correct action is unclear. There many genes code proapoptotic proteins which are BH3 domain-only (Noxa, Bad, Bax, Puma, Bak, p53AIP1); death receptors (Killer/ Dr, Fas, Dr4,); and execution factors for apoptosis (Apaf1, caspase 6, Bnip3L) in mitochondrial membrane. P53 induce the expression genes like Puma, Bad, Bax, Noxa, Bak, and Apaf 1 a variety of levels of the permeability of outer membrane mitochondria regulatory mechanism facilitate the apoptosis [31]. p53 induces activation of Fas and Dr5, stimulates mechanism of exterior apoptosis through facilitating death receptor dimerization such as procaspase 8 expression and executioner caspase 3 and 7 activation, then eliminate destroyed cells. In intrinsic apoptosis pathway in the severe damage, P53 causes the activation of the BH3-only proteins triggers permeability the outer membrane of mitochondria, in the intrinsic

apoptosis route, this is a crucial stage. That promotes the mitochondrial membrane potential disturbance and cytochrome c release result apoptosome complex formation. Apoptosomes recruit and activate procaspase 9, which further triggers executioner caspase 3 and 7 then finally death of the cell [31-33].

P53 proteins fusion to a signal peptide in the mitochondria is enough to induce apoptosis and does not involve activation of transcription factors. Biochemically, P53 will attach to Bcl2 and BclXL, encouraging Bax and Bak release and activation which are pro apoptotic proteins that incorporated into the extracellular matrix, and oligomerzed to take shape pore to relief cytochrome c as well as other proteins such as Smac and Omi from the inter membrane. Cytochrome c binds to adenosine triphosphate (ATP) and Apaf1, facilitating oligomerization of Apaf1 to create an apoptosome complex. The apoptosome employs and stimulates procaspase 9, which further activates caspase 3 and 7 to cause death of the cell [31].

Senescence

Cellular senescence is characterized as a condition of the cell with prolong and the acquisition of an irreversible cell-cycle arrest of various phenotypic modifications, involving morphological modifications, chromatin modifications, metabolic pathway alternation and induction of factors that causes inflammation [34]. Recently it is estimated by cytokines, proteases, growth factors, and extracellular matrix proteins (ECM) that aren't soluble [33]. All of these characteristics are essentially restricted the proliferation of cells that are both aged and weak relate to a normal cell cycle under physiological condition [35]. Senescence has been correlated with incremental telomere shortening, the normal tissue function that happens any time the cell splits and impairs the genomic integrity and stabilization associated with the activation of particular molecular senescence pathways [36, 37].

P53 plays a crucial role and can be triggered in a DNA damage response (DDR) through DDR-dependent or DDR independent way in the form of senescence [38,39]. First and foremost, telomere denudation, DNA damage, as well as hyper activation of oncogenes and inactivation of onco-suppressors resulting from replicative stress activate the DNA damage repair cascade [40]. DDR stimulates the ataxia telangiectasia-muted (ATM) or ataxia telangiectasia Rad3-related kinases of the tension sensors (ATR). In exchange, ATM/ATR stimulates the p53/p21 axis by phosphorylation of both p53 and its ubiquitin ligase Mdm2, which results stabilization [41].

Several internal or external stress factors activate DDR passageway, The p53 and/or p16 pathways are then activated. P16 permanently disables Cdk4/6 which leads to the aggregation of pRb, prevents transcription factors from being modulated of E2F and causes senescence (cell cycle arrest) [42, 43]. So the severity and duration of the stress stimulation seem to be a major factor in the induction of senescence; senescence appears to involve a constant stimuli, whereas temporary stimulus only cause temporary stop development, encouraging the cell that will try to restore the damage. Most serious stimuli contribute to program cell death respectively [44].

Role of p53 in progressing of Cancer

P53 is one of the tumor suppressor proteins most investigated, with mutations that contribute to loss of wild type p53 function often detected in several various forms of tumor [45]. When tumor suppressor genes like, p53 are mutated, the cells are unable to respond to cell-cycle checkpoints normally and DNA damage is severe unable to trigger programmed cell death. This could contribute to a more increase in abnormalities and the inability of the infected cell to escape the cell cycle as it may become umorigenic [46].

The mutations of the p53 include frame shift, missense and deletion missense is estimated about 74% which a single substitute of the original amino acid with other substitute one and mostly happen in the DNA-binding domain. On this domain many hotspot mutations like as Arg-175, Arg-249, Arg-273, Arg-282, Gly-245, Tyr-220 and Arg-248 is identified [47]. The frequency of TP53 mutation in hematopoietic malignancies, the prevalence of TP53 mutations ranges from ten (~10%) to fifteen-seventeen (50-70%) in vaginal, colonorectal, head and neck malignancies [48]. Li-Fraumeni syndrome, is a family cancer syndrome like breast cancer, soft tissue sarcoma, and several other forms of cancer induced germline mutation of *P53* [49]. Several p53 mutations are found in the DNA-binding domain, thereby avoiding p53 from transcription it's a goal genes. Therefore, mutant p53 has a result of which normal function was lost and also enhanced tumor potential [48]. Defects in TP53 causes impart cancer vulnerability can

be hereditary or somatic. P53 germline defects lead to Li-Fraumeni syndrome that cause number of early-stage cancers to be predisposed [50]. In several tumors, mutant p53 proteins are significant degree of expression which lead to progress tumor growth and resistancy to drugs through inhibiting wild type p53 member [51]. A majority of mutant p53 function originates from ability of mutant p53 to manipulate gene transcription. The fact has been established that mutant p53 transcriptional effects contribute to increased cellular, apoptosis resistance that can be induced by mutant p53 association with Ets-2, increased of migration, invasion, tumor inflammation, and increased metastasis [52].

Conclusion

P53 protein activate and transcripted of an important number of direct target genes as a result of cellular damage such as DNA damage. This responses depend on intensity of the stress, include in cell cycle arrest in G1 or G2, DNA repair, program cell death (intrinsic and extrinsic pathway), Senescence (DDR-dependent or DDR-independent). In addition, p53 mutations has been correlated with as an oncogene expression in many cancer types.

Acknowledgment

I would like to thanks and appreciates the Professor Dr. Alaa Hani Raziq- pathologist in College of duhok Medical University for his kind help for this review.

Conflicts of Interest

We declare that we have no conflict of interest.

Funding statement

No particular grant was given to this review by funding organizations in the public, private, or not-for-profit sectors.

Contribution of authors

The study was developed and designed by BS, and it was written up by GS.

References

1. May, P and May, E. Twenty years of p53 research: structural and functional aspects of the p53 protein. *Oncogene*., **18**(53), 7621–7636 (1999).
2. Dippold, W, Dippold, W. G. and Old, L. J. P53 transformation-related protein: Detection by monoclonal antibody in mouse and human cells. *Proceedings of the National Academy of Sciences*., **78**(3), 1695–1699 (1991).
3. Hupp, T. R., Lane, D. P and Ball, K. L. Strategies for manipulating the p53 pathway in the treatment of human cancer. *Biochemical Journal*, **352**(1), 1–17 (2000)
4. Christophorou, M. A., Ringshausen, I., Finch, A. J. and Evan, G. I. The pathological response to DNA damage does not contribute to p53-mediated tumour suppression. *Nature*, **443**(7108), 214–217 (2000)
5. Zhang, Y. The development of p53 tumor diagnosis and drug design strategy in its disordered region. *E3S Web of Conferences*, **78**, 2018–2020 (2019).
6. Joerger, A. C and Fersht, A. R. Structural Biology of the Tumor Suppressor p53 and Cancer-Associated Mutants. *Adv. Cancer Res.,* **97**, 1–23 (2007).
7. Toledo, F and Wahl, G. M. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. *Nature Reviews Cancer*. **6**(12), 909–923 (2007).
8. Toledo, F and Bardot, B. Three birds with one stone.*Nature*, **460**(7254), 466–467 (2009).
9. Chen, J. The Roles of MDM2 and MDMX Phosphorylation in Stress Signaling to p53. *Genes and Cancer*, **3**(3- 4), 274–282 (2012).
10. Bai, L and Zhu, W. G. p53: structure, function and therapeutic applications. *J. Cancer Mol*., **2**(4), 141–153 (2006).
11. Roxburgh, P. Manipulating the p53 pathway for cancer treatment. University of Glasgow.(2013).
12. Sundaram, G. Unit-11 Cell Cycle. in. Indira Gandhi National Open University, New Delhi, (2020).
13. Asghar, U., Witiewicz, K. A., Turner, C. N. and Knudsen, E. S. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nature Reviews Drug Discover,* **14**(2),130–146 (2015).
14. Singh, A. T. K and Wezel, E. S. Cell-cycle Checkpoints and Aneuploidy on the Path to Cancer. *In Vivo,* **32**(1),1-5 (2018).
15. El-Deiry, W. S. p21(WAF1) Mediates Cell-Cycle Inhibition, Relevant to Cancer Suppression and Therapy. *Cancer Research*, **76**(18), 5189–5191 (2016).

16. Slebos, R., Lee, M. H., Plunkett, B.S., Kessis, T. D., Williams, B. O., Jacks, T., Hendrick, L., Kastan, M. B. and Cho, K. R. p53-dependent G1 arrest involves pRB-related proteins and is disrupted by the human papillomavirus 16 E7 oncoprotein. *Proceedings of the National Academy of Sciences,* **91**(12), 5320–5324 (1994).

17. Toufektchan, E. and Toledo, F. The guardian of the genome revisited: P53 downregulates genes required for telomere maintenance, DNA repair, and centromere structure.*Cancers,* **10** (5),135 (2018).

18. Overton, K., Spencer, L. S.,Noderer, W. L., Meyer, T. and Wand, C. L. Basal p21 controls population heterogeneity in cycling and quiescent cell cycle states. *Proceedings of the National Academy of Science,* **111**(41), E4386–E4393 (2014).

19. Parveen, A., Akash, M. S. H., Rehman, K. and Kyunn, N. N. Dual Role of p21 in the Progression of Cancer and Its Treatment. *Critical Reviews in Eukaryotic Gene Expression,* **26**(1), 49–62(2016).

20. Taylor, W. R. and Stark, G. R. Regulation of the G2/M transition by p53. *Oncogene,* **20** (15), 1803–1815(2001).

21. Clair, S. S., Giono, L., Varmeh-Ziaie, S., Silverman, L. R., Liu, W. J., Padi, A., Dastidar, J., DaCosta, A., Mattia, M. and Manfredi, J. J . DNA Damage-Induced Downregulation of Cdc25C Is Mediated by p53 via Two Independent Mechanisms. *Molecular Cell,* **16**(5), 725–736 (2004).

22. Baguley, B. C and Kerr, D. J. Anticancer drug development. Elsevier(2001).

23. Giono, L. E and Manfredi, J. J. The p53 tumor suppressor participates in multiple cell cycle checkpoints. *Journal of Cellular Physiology,* **209**(1), 13–20 (2006).

24. Zhou, J. A. role for p53 in base excision repair. *The EMBO Journal,* **20**(4), 914–923 (2001).

25. Koniaras, K. A R Cuddihy, A. R., Christopoulos, H., Hogg, A. and O'Connell, M. J. Inhibition of Chk1-dependent G2 DNA damage checkpoint radiosensitizes p53 mutant human cells. *Oncogene,* 20(51), 7453–7463 (2001).

26. Riley, T., Sontag, E. and Levine, A. Transcriptional control of human p53-regulated genes. *Nature Reviews Molecular Cell Biology*, **9**(5), 402–412(2008).

27. Tabas, I. and Ron, D. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nature Cell Biology*, **13**(3), 184–190(2011).

28. Van Baarle, P., Van Belkum, A., Summerbell, R. C., Crous, P. W. Bart P.H. and Thomma, J. Molecular mechanisms of pathogenicity: how do pathogenic microorganisms develop cross-kingdom host jumps?. FEMS Microbiology Reviews, 31(3), 239–277 (2007).

29. Igney, F. H and Krammer, P. Death and anti-death: tumour resistance to apoptosis. *Nature Reviews Cancer*, **2**(4), 277–288 (2002).

30. Vaseva, A. V. Marchenko, D. N., Ji, K. Tsirka , S. E. , Sonja Holzmann, S. and Moll, U. M. p53 Opens the Mitochondrial Permeability Transition Pore to Trigger Necrosis. *Cell,* **149**(7),1536–1548 (2012).

31. Chen, J. The cell-cycle arrest and apoptotic and progression. Cold Spring Harbor Perspectives in Biology. 1- 16 (2016).

32. Mihara, M., Erster, S., Zaika, A., Petrenko, O., Chittenden, T. Pancoska, P. and Moll, U. M. p53 Has a Direct Apoptogenic Role at the Mitochondria. *Molecular Cell*, **11**(3), 577–590(2003).

33. Tait, S. and Green, D. Mitochondria and cell death: outer membrane permeabilization and beyond. *Nature Reviews Molecular Cell Biology*, **11**(9), 621–632 (2010).

34. Gorgoulis, V., Adams , P. D., Alimonti, A., Bennett , D. C., Bischof, O., Bishop 6, Judith Campisi , C., Collado, M., Evangelou, K., Ferbeyre, G., Gil, J., Hara, E., Krizhanovsky, V., Jurk, D., Maier, A. B., Narita, M., Niedernhofer, L., Passos , J. F., Robbins , P. D. Schmitt, C. A., Sedivy, J., Vougas , K., Von Zglinicki, T., Zhou , D., Serrano, M. and Demaria, M. Cellular Senescence: Defining a Path Forward. *Cell,* **179**(4), 813–827(2019).

35. Herranz, N. and Gil, J. Mechanisms and functions of cellular senescence. *Journal of Clinical Investigation*, **128**(4), 1238–1246(2018).

36. Victorelli, S. and Passos, J. Telomeres and Cell Senescence - Size Matters Not. *E. BioMedicine*, **21**, 14–20 (2017).

37. Bernadotte, A., Mikhelson, V. and Spivak, I. Markers of cellular senescence. Telomere shortening as a marker of cellular senescenc. *Aging,* **8**(1), 3- 11(2016).

38. Lujambio, A. To clear, or not to clear (senescent cells)? That is the question. *BioEssays,* **38,** S56–S64. (2016).

39. Valentine, J., Kumar, S. and Moumen, A. A p53-independent role for the MDM2 antagonist Nutlin-3 in DNA damage response initiation. *BMC Cancer*, **11** (1), Article no. 79 (2011).

40. Talens, F., and Van Vugt, M. A. Inflammatory signaling in genomically instable cancers. *Cell Cycle,* **18**(16), 1830–1848 (2019).

41. Hu, W., Feng, Z. and Levine, A. J. The Regulation of Multiple p53 Stress Responses is Mediated through MDM2. *Genes & Cancer,* **3**(3- 4),199–208 (2012).

42. Hobson, S., Arefin, S., Kublickiene, K., Shiels, P. G. and Stenvinkel, P. Senescent Cells in Early Vascular Ageing and Bone Disease of Chronic Kidney Disease-A Novel Target for Treatment. *Toxins,* **11**(2),82 (2019). doi: 10.3390/toxins11020082

43. Min, E , Kim In-Hye , Lee J., Kim E., Choi Y., Nam T. The effects of fucodian on senescence are controlled by the p16INK4a-pRb and p14Arf-p53 pathways in hepatocellular carcinoma and hepatic cell lines. *International Journal of Oncology*, **45**(1), 47–56(2014).

44. Spallarossa , P., Altieri, P., Aloi, C., Garibaldi, S., Barisione, C., Ghigliotti, G., Fugazza, G., Barsotti, A. and Brunelli, C. Doxorubicin induces senescence or apoptosis in rat neonatal cardiomyocytes by regulating the expression levels of the telomere binding factors 1 and 2. *American Journal of Physiology. Heart and Circulatory Physiology*, **297**(6), H2169-181 (2009).

45. Muller, P. and Vousden, K. Mutant p53 in Cancer: New Functions and Therapeutic Opportunities. *Cancer Cell,* **25**(3), 304–317 (2014).

46. Viatour, P. and Sage, J. Newly identified aspects of tumor suppression by RB. *Disease Models & Mechanisms*, **4**(5), 581-585 (2011).

47. Zhou, X., Hao, Q. and Lu, H. Mutant p53 in cancer therapy-the barrier or the path. *Journal of Molecular Cell Biology*, **11**(4), 293–305(2019).

48. Brosh, R. and Rotter, V. When mutants gain new powers: news from the mutant p53 field. *Nature Reviews Cancer*, **9**(10), 701–713 (2009).

49. Malkin, D., Li, F. P., Strong, L. C., Fraumeni, J. F., Nelson, C. E., Kim, D. H., Kassel, J., Gryka, M. A., Bischoff, F. Z., Tainsky, M. A. and Friend S. H. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science*, **250**(4985), 1233–1238(1990).

50. Petitjean, A., Mathe, E., Kato , S., Ishioka, C., Tavtigian, S. V., Hainaut, P. and Olivier, O. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. *Human Mutation*, **28**(6), 622–629 (2007).

51. Goh, A. M., Coffill, C. R. and Lane, D. P. The role of mutant p53 in human cancer. *Journal of Pathology*, **223**(2), 116–126 (2011).

52. Pfister, N. and Prives, C. Transcriptional regulation by wild-type and cancer-related mutant forms of p53. *Cold Spring Harbor Perspectives in Medicine*, **7**(2), a026054 (2017).

ألية عمل بروتين P53

غربت صالح علي[1] و باسم سالم احمد[2]
[1] كلية العلوم – جامعة دهوك - دهوك - إقليم كردستان - العراق.
[2] كلية العلوم - جامعة زاخو- دهوك - إقليم كردستان - العراق.

P53 في الانسان عبارة عن 393 من البروتينات المتبقية مع خمسة مجالات محتملة التي يرتبط بها سلسلة الحمض النووي مع-100 300تسلسل مهم جدًا للربط المباشر لـ p53 في محفزات الجينات المستهدفة بعناصر الاستجابة المحددة. P53 هو جين مثبط للأورام مع إلاجهاد الخلوي مثل نقص الأوكسجين والإجهاد التأكسدي والاشعاعات والمواد المسرطنة، وتحفيزها لها أدوار رئيسية في التنظيم الانتقالي وعمليات التغذية الراجعة ،هناك مجموعة واسعة من إلاشارات المنبه التي تتعلق بالاستقرار. التعديل اللاحق للترجمة وتوظيف p53 في مواقع الربط بالكروماتين التي تنشط مسار p53. كتنشيط لاستنساخ ، يتوسط p53 التغييرات النسخية التي تسهل موت الخلية أو الشيخوخة أوعكسها والتوقف الوقائي لدورة الخلية.P53 هو بروتين يخضع لفحص مكثف لأنه ضروري لمنع ظهورالاورام، وقد وجد أن الأورام البشرية تؤدي إلى إللغاء تنظيم نشاط p53. تركز الدراسة هذه على آلية التأثيرات القمعية لـ p53 في الاستجابة لأي إجهاد وارتباط طفرة p53 مع ورم مختلف.