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Mutual Antagonism of NF-KB and P53 - Major Phenomenon for Targeted Drug Therapies

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ABSTRACT

Targeted drug delivery has always been a safer approach for the treatment of cancer than the conventional chemotherapy. P53 and NF-κB pathways are the most influential metabolic pathways when it comes to chronic diseases and cancer. Mutations in any of the signaling cascades of these pathways eventually lead to chronic inflammation and cancer. Thus, most of the recent targeted therapies involves drugs which inhibit either of the pathways. It is known that p53 and NF-κB pathways have cross links with each other, and they even tend to mutually antagonize each other in various immune-regulated pathways of our body. This review shows the cross links between these pathways, the importance of this phenomenon in modern drug therapies, and various drugs that target both the pathways simultaneously.

Keywords: Cancer, mutual antagonism, NF-κB, p53, targeted therapy.

INTRODUCTION

Cancer or 'uncontrolled cell growth' is one of the deadliest disease mankind has ever witnessed. Despite recent medical advancements, cancer is still one of the leading causes of total worldwide deaths. In 2020 total worldwide cancer deaths rose to around 10 million according to WHO. Judging by its complexity, with over 200 individual diseases falling under Cancer according to the American Association for Cancer Research, scientists believe that it is difficult to make a common drug that works for all type of cancers.

Different Cancer treatment methods include chemotherapies, surgery, nuclear medicine, targeted drug therapies, etc. In Targeted therapy, anti-cancer drugs are manufactured to target specific binding sites or receptors to specifically inhibit or activate proteins thereby contributing in tumor response [1]. Unlike chemotherapies targeted drug therapiesmostly targets specific tumor cells and leaves the healthy cells alone, hence this is a lot safer approach.

P53 and NF-κB pathways play a crucial role in inflammatory regulation, cell proliferation, tumor suppression, cell apoptosis, synaptic plasticity, memory of cells, etc. These pathways often get crippled by mutation thereby leading to tumor formation and eventually cancer. P53 is a transcription factor which is often termed as the 'guardian of genome' since it regulates cell cycle. When the Tp53 gene gets mutated the whole cell cycle is crippled leading to oncogenesis.NF-κB is a heterodimer (RelA/p65 + p50) transcription factor which regulates cell proliferation and plays a crucial role in inflammation. Any mutations in the metabolic pathway leads to chronic inflammation which in turn promotes cancer growth.

These two signaling pathways are one of the most talked about research areas for cancer prevention in recent years. Although there have been many medical advancements in framing anticancer drugs that selectively inhibit NF-κB or activates p53 signaling pathways, there are very few research undergone on simultaneous inhibition of NF-κB and activation on p53 which could turn out to be one of the major aspects of targeted drug therapy. Cancer studies have shown cross links between these two metabolic pathways. Still much is unknown about how these two pathways co-regulate each other. Many Anti-Cancer Drugs have been framed in these recent years which tend to regulate both these pathways. Some of them include Nutlin-3, R-Roscovitine, 9-Aminoacridine derived compounds, Anti-malarial drug Quinacrine, Curaxins, etc.

NF-κB Pathway and Its Role in Oncogenesis

The NF-κB (Nuclear Factor-kappa light chain enhancer of activated B-cells) transcription factor was first discovered by Dr. Ranjan Sen and David Baltimore in the year 1986 [2]. The NF-κB protein transcription factor is a heterodimer comprising of RelA/p65 and p50 subunit, which is usually inactivated by IxB inhibitor until cell stress. The NF-κB protein is present in the cytosol and is found in almost all cell types, mostly leucocytes and macrophages.

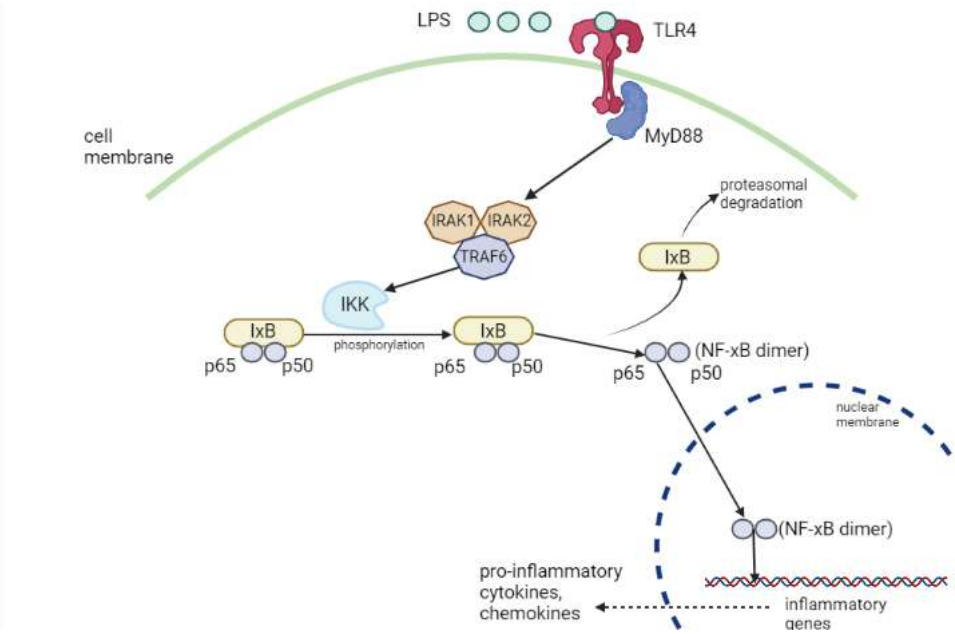

Figure 1. Schematic representation of NF-xB pathway showing major signaling molecules and their role in innate immunity. This diagram shows how signaling starts from LPS-TLR4 binding and leads to the formation of pro-inflammatory cytokines.

This serves asthe very first signaling pathway against any foreign pathogens. The NF-κB family is comprised of five known members namely, NF-κB1, NF-κB2, RelA, RelB and c-Rel [3]. The major roles of the NF-κB pathway include production of pro-inflammatory proteins (cytokines, chemokines, etc.) which regulate immunogenic response, cell proliferation, inflammation, cell apoptosis, etc. Due to its multiple roles pertaining to major immunological responses, this pathway is a major drug target for scientists.

Responses begin when phagocytic macrophages get triggered due to any foreign pathogenic invasion. Macrophages have single-pass membrane receptors known as Toll-like Receptors that recognize foreign microbial antigens. The microbial antigen binding to TLR receptor triggers MyD88 complex which in turn triggers the IRAK1/IRAK4 complex (Fig. 1). After a series of processes, TAK1 protein kinase is activated. This protein plays a significant role in activating two distinct signal transduction pathways – NF-κB dependent and MAPK dependent pathways. The TAK1 protein phosphorylates IKK complex; IKK in turn phosphorylates IxB, which is the potent inhibitor of the NF-κB complex, thereby releasing the RelA/p65+p50 complex into the cytoplasm. The NF-κB complex is now active and reaches the nucleus where it serves as the transcriptional activator for pro-inflammatory genes. Released protein recruits neutrophils and monocytes which further helps in the inflammation process.Thus, this pathway serves as a major inflammatory pathway; any malfunction in the pathway can lead to chronic inflammatory diseases like Cancer. There have been many theories on how exactly NF-κB pathway is responsible for oncogenesis, but still much is unknown. It is postulated that canonical NF-κB pathway actively participates in tumor progression by upregulating VEGF (vascular endothelial growth factor) and its receptors [4]. Also, NF-κB is known to contribute to oncogenesis by controlling epithelial to mesenchymal transition and metastasis [5,6]. Moreover, direct mutations of p65 genes were also observed which tend to contribute to lymphoid malignancies like B-cell and T-cell lymphoma [7,8]. It is also observed that NF-κB participates in cancer progression by acting as nodes of cross talks between reactive oxygen species and miRNAs. It is also believed that the reactive oxygen released by neutrophils to kill pathogens, participates in DNA damage thereby causing genetic mutations and cell cycle malfunctioning leading to oncogenesis [5]. Further studies highlighted that during cell stress, transglutaminase (TG2)/NF-κB mediated Interleukin (IL-6) signaling coordinates survival of mantle cell lymphoma cells [9]. NF-κB-mediated autophagy and programmed cell death is thus known to actively participate in tumor formation and oncogenesis [10]. Finally, upregulated NF-κB pathway leads to the increased formation of pro-inflammatory genes which thereby leads to the progression of chronic inflammation like tumors and hence leads to metastasis. Thus, many proteins in the pathway serve as a major drug target and downregulation of them can lead to inhibition of chronic inflammation. Identifying the major targets involved in oncogenesis are the utmost criterion for developing anti-cancer drugs. There have been major drug discoveries over recent years which involve inhibition of DNA binding activity of RelA, inhibition of IKK, proteasome inhibitors [3]. It is believed that NF-κB inhibition can treat cancer but also with serious side effects because NF-κB plays a vital role in innate immune response of the body.

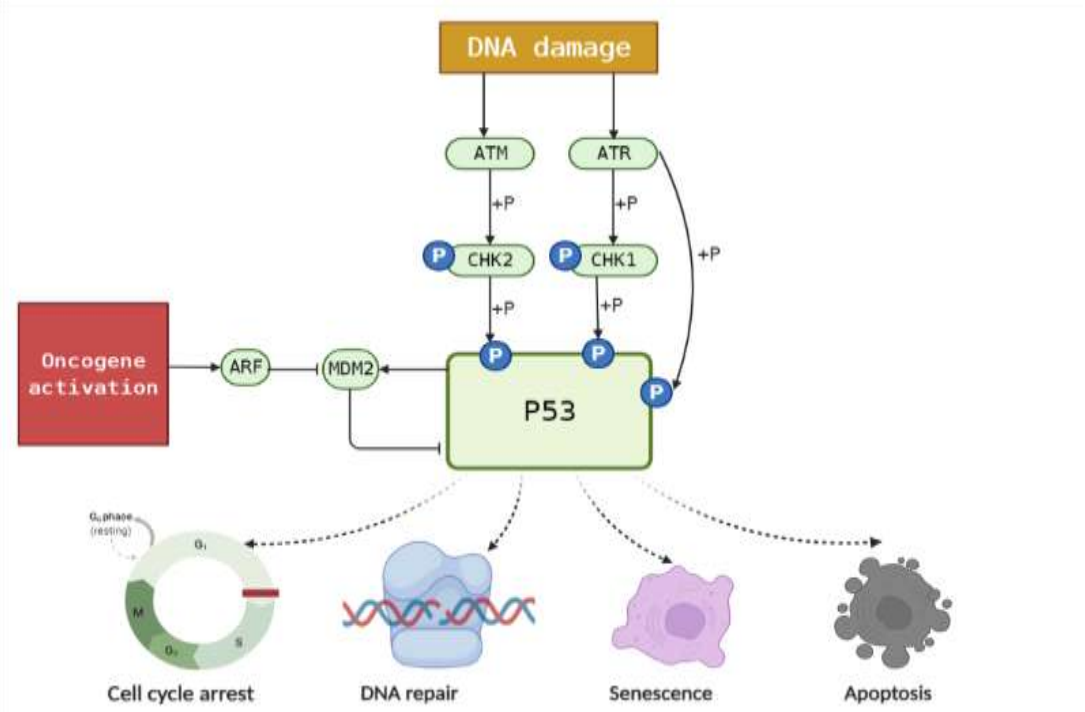

Figure 2. Schematic representation of p53 pathway showing major signaling pathways that gets activated during mutation or DNA damage. This diagram also shows major functions of p53 factor in cell cycle and DNA repair.

P53 Pathway and Its Role In Oncogenesis

Tumor protein p53, or simply p53 is a transcription factor protein encoded by the TP53 gene that helps in tumor suppression. It is often termed as "The Guardian o Genome" since it plays a significant role in preventing genomic mutation. It was first discovered by Lionel Crawford, David P. Lane, Arnold Levine, and Lloyd Old in the year 1979 [11, 12]. The p53 protein is present in the nucleus of cells throughout the body. The human genome contains 1copy (2 alleles) of TP53 gene and both the alleles need to be functioning for tumor prevention. The p53 family comprises of 3 known members – p53, p63 and p73 [13].

The p53 signaling pathway is activated during any DNA damage due to UV radiation or gamma irradiation, or by genotoxic drugs. Production of p53 goes up when there is DNA damage which thereby induces cell apoptosis, cell cycle arrest or DNA repair. During normal cell conditions p53 is usually unstable and has a very short half-life, about 6-20 minutes [14]. During cell stress, the production of CHK1 and CHK2 protein kinase is upregulated and thereby p53 production is altered with increased half-life. P53 upregulation activates 4 major pathways leading to - growth arrest, cell apoptosis, inhibition of angiogenesis, and DNA repair [14].P53 sits in the promoter region of the mRNA containing WAF1 gene. The WAF1 gene is responsible for the production of the p21 protein molecule. This p21 protein molecule plays a vital role in cell cycle arrest and hence cell apoptosis. The p21 protein binds with CDK-2 in the G1-S checkpoint and blocks the functioning of the CDK-2 complex thereby leading to growth arrest in G2-M phase of the cell cycle. CDKs (Cyclin-Dependent Kinase) are enzymes that are present in the check point of cell cycle which regulates cell cycle and thereby cell proliferation. P21 is the potent inhibitor of the CDK-2 complex and thereby plays a key role in tumor prevention by arresting the growth of abnormal cells. Thus, this pathway plays a crucial role in suppressing cancer growth [15]. A protein complex named MDM-2 (Murine Double Minute) which is the product of p53-activated gene is used to regulate the expression of p53. The overexpression of p53 results in the upregulation of MDM-2. MDM-2 protein acts as E3 ubiquitin ligase and is responsible for the degradation of p53. MDM-2 and p53 both regulate each other's expression and thereby form an interconnecting autoregulatory loop [16]. MDM-2 expression is regulated by another protein named MDMX which has a similar composition but does not have E3 ubiquitin ligase activity. Studies suggest that in normal cells MDMX and MDM-2 are essential for the negative regulation of p53[17]. Normal functioning of MDM-2 and MDMX is particularly important for the regulation of p53, which would otherwise lead to chronic inflammatory diseases.

The TP53 gene may be mutated by carcinogens (cancer causing substances) such as tobacco, drugs, etc. It is believed that 50% of all cancer types contains the mutated TP53 gene [18]. Research has shown that TP53 mutated gene is the leading causal agent in Brain cancer, Liver cancer, Osteosarcoma, Ovarian cancer, etc [19]. Mutated TP53 gene escapes the MDM-2 mediated inactivation and actively participates in cancer development. Many variant forms of p53 were

found to be directly participating in cancer growth. Some of them include- Δ133p53, Δ40p53, Δ133p53γ, Δ133p53β, etc. It is believed Δ133p53 acts as a negative inhibitor toward p53 and is responsible for 80% of primary Breast cancers [19].It is also believed that Mutant p53 also regulates the expression of MicroRNA 27a, which activates ERK1/2, facilitating uncontrolled growth and oncogenesis. Moreover, Mutp53 targets Methyltransferases MLL1 and MLL2 which facilitates histone modifications leading to cell proliferation and oncogenesis [20]. Autophagy, a catabolic process, plays a crucial role in tumor progression. During Cancer, mutant p53 interferes with autophagy and helps in oncogenesis [21]. Finally, Overexpression of MDM-2 complex leads to inactivity of p53, which will in turn lead to oncogenesis. MDM-2 mutations were most observed in osteosarcomas and soft tissue tumors [22]. The MDM-2-p53 complex is thus an attractive drug target for scientists all over the world. Recent studies have shown that inhibition of MDM2 is enhanced by the PD-1/PD-2 pathway which further upregulated the activity of p53 towards tumor regression [23]. Still much is unknown about the MDM-2-p53 interaction and a lot of medical research is going on in this area. Many small molecules have been developed so far to target mutp53, but only a few drugs have desired pharmacodynamic properties and toxicity results.

Can Simultaneous Inhibition Of Nf-Kb Pathway And Activation Of P53 Pathway Really Cure Cancer?

After all the research and studies undergone on NF-κB and p53 pathways, it is now clear that these two pathways individually play a pivotal role in the natural defense mechanisms of our body. These two pathways are the foremost regulators of innate immunity, cell proliferation, phagocytosis, cell apoptosis, cancer progression, etc. Studies have shown that almost all cancer types have mutations in both NF-κB and p53, making it the prime cause of cancer development. Although many targeted drug therapies involving selective regulation of p53 or NF-κB pathways have been developed over the recent years, very few drugs have been developed that target both the pathways. Based on the studies and research over the years we can hypothesize that simultaneous inhibition of NF-κB pathway and activation of p53 pathway may be beneficial in cancer treatment. To understand this concept in depth, first we need to know about how these two pathways co-regulate each other.

Cross-links between NF-κB and p53 pathways

NF-κB and p53 pathways simultaneously participate in the natural immune response of the body and play a critical role in determining oncogenesis. Research has shown that there are cross links between these pathways and they tend to mediate each other. Studies have shown that NF-κB and p53 co-mediate different metabolic pathways, protein expression, and several types of cancer progression. It is believed that the alternate NF-κB pathway is responsible for the regulation of p53 protein. The NF-κB2 pathway regulates the production of CDK6 and CDK4, and stabilizes the p21WAF1 and TP53 [24]. Research has also shown that ARF protein that activates p53 pathway actively participates in the inhibition of NF-κB functioning independent of MDM2-p53 interaction [25]. Moreover, it is believed that loss of novel p53 damaged the NF-κB transcription, which thereby implies that p53 is a key mediator of NF-κB molecule. Further research shows that over expression of p53 increases the binding affinity of IxB to p50+p65 and thereby downregulates NF-κB expression. This phenomenon is actively used to treat human colon cancer [26]. Though p53 and NF-κB have completely different effects in cancer, they tend to co-regulate pro-inflammatory gene expression in monocytes and macrophages. Research has shown NF-κB and p53 actively participate in IL-6 induction by binding to its promoter [27]. Further research has shown transcriptional interaction between RelA and p53 during induction of replication stress. It is believed that RelA and p53 are both required for the proper functioning of the NF-κB during S-phase checkpoint activation. Also, NF-κB gene expression induced by TNF (tumor necrosis factor) is regulated by p53 [28]. Hence it is observed that p53 plays a vital role in the NF-κB-mediated transcriptional pathway. Results have shown that a decrease in the level of NF-κB hindered p53-induced cell apoptosis, thereby indicating NF-κB correlates with p53 activity and is an active promoter of cell apoptosis.

RelA is known to promote p53-dependent/independent glycose metabolism through overexpression of GLUT3 (glucose transporters). It is also observed that NF-κB and p53 mediated glycolysis tend to protect the normal cells against chemotherapy treatment [29]. Research has also shown that NF-κB and p53 both play a crucial role in mitochondrial energy production. During mitochondrial DNA mutations, there is a high accumulation of calcium which in turn leads to upregulation of NF-κB. The NF-κB up regulation reduces the expression of p53 which thereby leads to oncogenesis [30]. NF-κB is responsible for the activation of p53-mediated pro-apoptotic signaling in response to doxycycline (antibiotic Drug). Thereafter, NF-κB downregulates MDM2 activity which facilitates phosphorylation of p53 at Ser-20 leading to pro-apoptotic gene expression such as p21 and Puma [31]. The NF-κB pathway actively promotes EMT (epithelial to mesenchymal transition), but p53 tends to suppress it. Research has also shown that in HNSCC (head and neck squamous cell carcinoma) p53 plays a crucial role in NF-κB mediated EMT signaling by p65 silencing [32]. A study showed that inhibition of NF-κB protein upregulates the p53 factor, which in turn upregulates the expression of DRAM (DNA-damage regulated autophagy modulator protein). This study confirms cross talks between p53 and NF-κB in regulation of pro-autophagic protein expression. Some research also shows that RelA and p53 inhibit each other's functioning as a transcription factor [33]. Extensive research showed that the p53 protein might inhibit the expression of

NF-κB complex by inducing p21; also, TNF-activated NF-κB might inhibit p53 functioning thereby exhibiting contradictory mediating responses [34].

Thus, it is now clear that co-regulation of p53 and NF-κB pathways plays a pivotal role in determining cancer progression and is thus considered one of the major cancer research areas. In most of the signaling pathways these two factors tend to oppose each other, while in a few cases these two pathways work simultaneously. Extensive studies are going on in this research field and many new drugs are being formulated based on the cross links between these two pathways. Although very few drugs have been developed that target both these pathways, the scope of this research area in the future is very promising.

Targeted drug therapies involving mutual antagonism of p53 and NF-κB

Scientific studies all over the world led to the discovery of major drug therapies targeting both the signaling pathways. Studies have shown that inhibition of TNF-induced NF-κB signaling is responsible for the activation of p53 pathway. R-Roscovitine, Flavopiridol, and Nutlin-3 are some of the major drug discoveries that inhibit TNF-dependent NF-κB pathway in a dose dependent manner [35,36,37]. Nutlin-3 and R-Roscovitine are known to inhibit NF-κB target genes like Intercellular Adhesion Molecule-1 (ICAM-1) and Monocyte Chemoattractant Protein (MCP-1) in a p53 dependent manner [35,37]. It is well known now that IKK plays a crucial role in the activation of NF-κB factor by phosphorylating IxB protein. R-Roscovitine and Flavopiridol are known to inhibit IKK activity thereby blocking NF-κB activation. This facilitates p53 activation and thereby prevents oncogenesis [35,36]. Further research led to the discovery of another major class of drug namely Curaxins which simultaneously inhibit NF-κB and activates p53 signaling. Curaxins activate p53 by phosphorylating Ser^{392} complex, which is achieved when Casein kinase 2 (CK2) binds with a protein complex namely FACT. FACT is further involved in Curaxin-mediated inhibition of NF-κB pathway [38]. 9-Aminoacridine (9AA) and its derivative Quinacrine are known to have anti-cancer effects. 9AA inhibits AKT/mTOR pathway thereby downregulating p110γ. This in turn downregulates NF-κB and activates p53 [39]. Quinacrine downregulates p62 which promotes p21 upregulation via Skp2. This in turn inhibits the NF-κB pathway and upregulates p53 [40].

CONCLUSION

It is now well understood that both p53 and NF-κB play a significant role in major metabolic pathways, and any abnormality will ultimately lead to oncogenesis. Overexpression of NF-κB and downregulation of p53 was found to be the foremost oncogenic cause. Hence mutual antagonism of p53 and NF-κB pathways plays a crucial role in modern anti-cancer drug discovery. Several drugs are being developed that is involved in (a)TNF-induced NF-κB activation, inhibition of IxB phosphorylation as seen in R-ROSCOVITIN and FLAVOPIRIDOL; (b) suppression of cell viability in A549 cells, inhibition of ICAM-1 and MCP-1 as seen in NUTLIN-3; (c) targeting FACT (histone complex) as seen in CURAXINS; (d) inhibition of AKT/mTOR pathway as seen in 9-AMINOACRIDINE; (e) Downregulation of p62 which promotes p21 upregulation via Skp2 as seen in QUINACRINE, etc. In this review I tried to hypothesize the fact that during cancer, simultaneous activation of p53 and inhibition of NF-κB is required for the normal functioning of basic cellular mechanisms like cell cycle and cell apoptosis. Although many small compounds have been developed, there lies the major question of the balance between efficacy and safety, since these two pathways serve as the backbone of vital cellular mechanisms. Thus, better understanding of these pathways, should be of utmost importance for developing more effective drugs in the near future.

REFERENCES

[1]. American Cancer Society -https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/what-is.html.
[2]. Singh H, Sen R, Baltimore D, Sharp PA. A nuclear factor that binds to a conserved sequence motif in transcriptional control elements of immunoglobulin genes. Nature. 1986 Jan 9-15;319(6049):154-8. doi: 10.1038/319154a0. PMID: 3079885.
[3]. Liu, T., Zhang, L., Joo, D. *et al.* NF-κB signaling in inflammation. *Sig Transduct Target Ther***2,** 17023 (2017). https://doi.org/10.1038/sigtrans.2017.23.
[4]. Yu, H., Lin, L., Zhang, Z. *et al.* Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. *Sig Transduct Target Ther***5,** 209 (2020). https://doi.org/10.1038/s41392-020-00312-6.
[5]. Hoesel, B., Schmid, J.A. The complexity of NF-κB signaling in inflammation and cancer. *Mol Cancer***12,** 86 (2013). https://doi.org/10.1186/1476-4598-12-86.
[6]. Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H, Wirth T. NF-κB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. The Journal of clinical investigation. 2004 Aug 16;114(4):569-81.

[7]. Courtois, G., and T. D. Gilmore. "Mutations in the NF-κB signaling pathway: implications for human disease." *Oncogene* 25.51 (2006): 6831-6843.
[8]. Neri A, Chang CC, Lombardi L, Salina M, Corradini P, Maiolo AT, Chaganti RS, Dalla-Favera R. B cell lymphoma-associated chromosomal translocation involves candidate oncogene lyt-10, homologous to NF-κB p50. Cell. 1991 Dec 20;67(6):1075-87.
[9]. Zhang H, Chen Z, Miranda RN, Medeiros LJ, McCarty N. TG2 and NF-κB Signaling Coordinates the Survival of Mantle Cell Lymphoma Cells via IL6-Mediated Autophagy. Cancer Res. 2016 Nov 1;76(21):6410-6423. doi: 10.1158/0008-5472.CAN-16-0595. Epub 2016 Aug 3. PMID: 27488529; PMCID: PMC5093039.
[10]. Verzella D, Pescatore A, Capece D, Vecchiotti D, Ursini MV, Franzoso G, Alesse E, Zazzeroni F. Life, death, and autophagy in cancer: NF-κB turns up everywhere. Cell Death Dis. 2020 Mar 30;11(3):210. doi: 10.1038/s41419-020-2399-y. PMID: 32231206; PMCID: PMC7105474.
[11]. Lane DP, Crawford LV 1979. T antigen is bound to at host protein in SV40-transformed cells. Nature 278: 261–263.
[12]. Linzer DI, Levine AJ 1979. Characterization of a 54K Dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. Cell 17: 43–52.
[13]. Bourdon JC. p53 Family isoforms. Current pharmaceutical biotechnology. 2007 Dec 1;8(6):332-6.
[14]. Creative Diagnostics - https://www.creative-diagnostics.com/p53-signaling-pathway.htm.
[15]. Harris, S.L. and Levine, A.J., 2005. The p53 pathway: positive and negative feedback loops. *Oncogene*, *24*(17), pp.2899-2908.
[16]. Nag S, Qin J, Srivenugopal KS, Wang M, Zhang R. The MDM2-p53 pathway revisited. Journal of biomedical research. 2013 Jul;27(4):254.
[17]. Shadfan M, Lopez-Pajares V, Yuan ZM. MDM2 and MDMX: Alone and together in regulation of p53. Translational cancer research. 2012 Aug;1(2):88.
[18]. Ozaki T, Nakagawara A. Role of p53 in cell death and human cancers. Cancers. 2011 Mar;3(1):994-1013.
[19]. Very well health - https://www.verywellhealth.com/the-p53-gene-its-role-in-cancer-2249349.
[20]. Cen Zhang, Juan Liu, Dandan Xu, Tianliang Zhang, Wenwei Hu, Zhaohui Feng, Gain-of-function mutant p53 in cancer progression and therapy, *Journal of Molecular Cell Biology*, Volume 12, Issue 9, September 2020, Pages 674–687, https://doi.org/10.1093/jmcb/mjaa040.
[21]. Alvarado-Ortiz E, de la Cruz-López KG, Becerril-Rico J, Sarabia-Sánchez MA, Ortiz-Sánchez E, García-Carrancá A. Mutant p53 Gain-of-Function: Role in Cancer Development, Progression, and Therapeutic Approaches. Front Cell Dev Biol. 2021 Feb 11;8:607670. doi: 10.3389/fcell.2020.607670. PMID: 33644030; PMCID: PMC7905058.
[22]. Nilbert, Mef, Felix Mitelman, Nils Mandahl, Anders Rydholm, and Helena Willén. "MDM2 gene amplification correlates with ring chromosomes in soft tissue tumors." *Genes, Chromosomes and Cancer* 9, no. 4 (1994): 261-265.
[23]. Wang HQ, Mulford IJ, Sharp F, Liang J, Kurtulus S, Trabucco G, Quinn DS, Longmire TA, Patel N, Patil R, Shirley MD, Chen Y, Wang H, Ruddy DA, Fabre C, Williams JA, Hammerman PS, Mataraza J, Platzer B, Halilovic E. Inhibition of MDM2 Promotes Antitumor Responses in p53 Wild-Type Cancer Cells through Their Interaction with the Immune and Stromal Microenvironment. Cancer Res. 2021 Jun 1;81(11):3079-3091. doi: 10.1158/0008-5472.CAN-20-0189. Epub 2021 Jan 27. PMID: 33504557.
[24]. Iannetti, A., Ledoux, A. C., Tudhope, S. J., Sellier, H., Zhao, B., Mowla, S., Moore, A., Hummerich, H., Gewurz, B. E., Cockell, S. J., Jat, P. S., Willmore, E., & Perkins, N. D. (2014). Regulation of p53 and Rb links the alternative NF-κB pathway to EZH2 expression and cell senescence. *PLoS genetics*, *10*(9), e1004642. https://doi.org/10.1371/journal.pgen.1004642.
[25]. Sonia Rocha, Kirsteen J. Campbell, Neil D. Perkins, p53- and Mdm2-Independent Repression of NF-κB Transactivation by the ARF Tumor Suppressor, Molecular Cell, Volume 12, Issue 1,2003, Pages 15-25, ISSN 1097-2765, https://doi.org/10.1016/S1097-2765(03)00223-5.
[26]. Shao J, Fujiwara T, Kadowaki Y, Fukazawa T, Waku T, Itoshima T, Yamatsuji T, Nishizaki M, Roth JA, Tanaka N. Overexpression of the wild-type p53 gene inhibits NF-kappaB activity and synergizes with aspirin to induce apoptosis in human colon cancer cells. Oncogene. 2000 Feb 10;19(6):726-36. doi: 10.1038/sj.onc.1203383. PMID: 10698490.
[27]. Lowe JM, Menendez D, Bushel PR, Shatz M, Kirk EL, Troester MA, Garantziotis S, Fessler MB, Resnick MA. p53 and NF-κBcoregulateproinflammatory gene responses in human macrophages. Cancer Res. 2014 Apr 15;74(8):2182-92. doi: 10.1158/0008-5472.CAN-13-1070. PMID: 24737129; PMCID: PMC3994464.
[28]. Schneider, G., Henrich, A., Greiner, G. *et al.* Cross talk between stimulated NF-κB and the tumor suppressor p53. *Oncogene***29,** 2795–2806 (2010). https://doi.org/10.1038/onc.2010.46.
[29]. Carrà, G., Lingua, M.F., Maffeo, B. *et al.* P53 vs NF-κB: the role of nuclear factor-kappa B in the regulation of p53 activity and vice versa. *Cell. Mol. Life Sci.***77,** 4449–4458 (2020). https://doi.org/10.1007/s00018-020-03524-9.

[30]. Lee, Y.-K.; Yi, E.-Y.; Park, S.-Y.; Jang, W.-J.; Han, Y.-S.; Jegal, M.-E.; Kim, Y.-J. Mitochondrial dysfunction suppresses p53 expression via calcium-mediated nuclear factor-kB signaling in HCT116 human colorectal carcinoma cells. BMB Rep 2018, 51, 296–301.

[31]. Fujioka, S.; Schmidt, C.; Sclabas, G.M.; Li, Z.; Pelicano, H.; Peng, B.; Yao, A.; Niu, J.; Zhang, W.; Evans, D.B.; et al. Stabilization of p53 is a novel mechanism for proapoptotic function of NF-kappaB. J. Biol. Chem. 2004, 279, 27549–27559.

[32]. Ferris, Robert & Grandis, Jennifer. (2007). NF- B Gene Signatures and p53 Mutations in Head and Neck Squamous Cell Carcinoma. Clinical cancer research: an official journal of the American Association for Cancer Research. 13. 5663-4. 10.1158/1078-0432.CCR-07-1544.

[33]. Zhu, B.-S.; Xing, C.-G.; Lin, F.; Fan, X.-Q.; Zhao, K.; Qin, Z.-H. Blocking NF-κB nuclear translocation leads to p53-related autophagy activation and cell apoptosis. World J. Gastroenterol. 2011, 17, 478–487.

[34]. Webster GA, Perkins ND. Transcriptional cross talk between NF-kappaB and p53. Mol Cell Biol. 1999 May;19(5):3485-95. doi: 10.1128/MCB.19.5.3485. PMID: 10207072; PMCID: PMC84141.

[35]. Dey, A., Wong, E., Cheok, C. *et al.* R-Roscovitine simultaneously targets both the p53 and NF-*κ*B pathways and causes potentiation of apoptosis: implications in cancer therapy. *Cell Death Differ***15,** 263–273 (2008). https://doi.org/10.1038/sj.cdd.4402257.

[36]. Takada Y, Aggarwal BB. Flavopiridol inhibits NF-kappaB activation induced by various carcinogens and inflammatory agents through inhibition of IkappaBalpha kinase and p65 phosphorylation: abrogation of cyclin D1, cyclooxygenase-2, and matrix metalloprotease-9. J Biol Chem. 2004 Feb 6;279(6):4750-9. doi: 10.1074/jbc.M304546200. Epub 2003 Nov 20. PMID: 14630924.

[37]. Anwesha Dey, E.T. Wong, P. Bist, V. Tergaonkar& David Lane (2007) Nutlin-3 inhibits the NFκB Pathway in a p53 Dependent Manner: Implications in Lung Cancer Therapy, Cell Cycle, 6:17, 2178-2185, DOI: 10.4161/cc.6.17.4643.

[38]. Gasparian AV, Burkhart CA, Purmal AA, Brodsky L, Pal M, Saranadasa M, Bosykh DA, Commane M, Guryanova OA, Pal S, Safina A, Sviridov S, Koman IE, Veith J, Komar AA, Gudkov AV, Gurova KV. Curaxins: anticancer compounds that simultaneously suppress NF-κB and activate p53 by targeting FACT. SciTransl Med. 2011 Aug 10;3(95):95ra74. doi: 10.1126/scitranslmed.3002530. PMID: 21832239; PMCID: PMC6281439.

[39]. Guo, C &Gasparian, Alexander & Zhuang, Z &Bosykh, DA &Komar, Anton &Gudkov, Andrei &Gurova, Katerina. (2009). 9-Aminoacridine-based anticancer drugs target the PI3K/AKT/mTOR,NF-kappa B and p53 pathways. Oncogene. 28. 1151-61. 10.1038/onc.2008.460.

[40]. [Jung, D., Khurana, A., Roy, D. *et al.*Quinacrine upregulates p21/p27 independent of p53 through autophagy-mediated downregulation of p62-Skp2 axis in ovarian cancer. *Sci Rep***8,** 2487 (2018). https://doi.org/10.1038/s41598-018-20531-w.