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Review Article

NF-κB–p53 axis antagonism: A therapeutic opportunity in cancer treatment

Ranjeet Kumar[1]*, Deepika Biswas[1]

[1]Dept. of Biochemistry, Combined Institute of Medical Sciences & Research, Dehradun, Uttarakhand, India

Abstract

P53 and NF-xB pathways play a crucial role in inflammatory regulation, cell proliferation, tumour suppression, cell apoptosis, synaptic plasticity, memory of cells, etc. These pathways often get crippled by mutation thereby leading to tumour 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 Tp53gene gets mutated the whole cell cycle is crippled leading to oncogenesis.NF-xB is a heterodimer (RelA/p65 + p50) transcription factor which regulates cell proliferation and plays a crucial role in inflammation. This study confirms cross talks between p53 and NF-xB in regulation of pro-autophagic protein expression. Some research also shows that RelA and p53 inhibit each other's functioning as a transcription factor. Extensive research showed that the p53 protein might inhibit the expression of NF-xB complex by inducing p21; also, TNF-activated NF-xB might inhibit p53 functioning thereby exhibiting contradictory mediating responses. Hence this review showed that mutual antagonism of p53 and NF-xB pathways plays a crucial role in modern anti-cancer drug discovery.

Keywords: p53, NF-xB, Mutual antagonism, Cancer, Drug discovery.

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1. Introduction

Cancer, also referred to as "uncontrolled cell growth," is one of the most deadly diseases that mankind has ever encountered. 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 tumour response.[1] Unlike chemotherapies targeted drug therapies mostly targets specific tumour cells and leaves the healthy cells alone, hence this is a lot safer approach.

The P53 and NF-xB pathways are essential in regulating inflammation, cell division, tumour suppression, cell death, synaptic plasticity, cell memory, and other processes. Mutations frequently impair these mechanisms, which results in the development of tumours and ultimately cancer. The transcription factor P53 is frequently referred to as the "guardian of the genome" since it controls the cell cycle. Oncogenes is occurs from the whole cell cycle being disrupted by a mutation in the Tp53 gene. The transcription factor NF-xB, which is a heterodimer of RelA/p65 and p50, controls cell division and is essential for inflammation. Any changes to the metabolic pathway cause persistent inflammation, which encourages the formation of cancer. 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-xB or activates p53 signaling pathways, there are very few research undergone on simultaneous inhibition of NF-xB and activation on p53 which could turn out to be one of the major aspects of targeted drug therapy. Cancer studies have shown

*Corresponding author: Ranjeet Kumar
Email: ranjeetkumar0087@gmail.com

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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.

2. NF-Xbpathway and its Role in Oncogenesis

Nuclear Factor-kappa light chain enhancer of activated B-cells (NF-xb) transcription factor was first discovered by Dr. Ranjan Sen and David Baltimore in the year 1986.[2] A heterodimer of RelA/p65 and p50 subunits, the NF-xB protein transcription factor is typically inactivated by IxB inhibitors until cell stress occurs. Almost in all type of cell, primarily leucocytes and macrophages, contains the cytosolic NF-xB protein. The initial line of defence against any alien pathogens is this signalling pathway. NF-xB1, NF-xB2, RelA, RelB, and c-Rel are the five known members of the NF-xB family.[3] The creation of pro-inflammatory proteins (cytokines, chemokines, etc.) that control immunogenic response, cell proliferation, inflammation, cell death, etc. is one of the main functions of the NF-xB pathway. Scientists are interested in this pathway as a potential therapeutic target because of its several functions related to important immune responses.

Responses commence when phagocytic macrophages become triggered as a result of any foreign pathogen invasion. Toll-like receptors are single-pass membrane receptors found on macrophages that are capable of identifying foreign microbial antigens. The IRAK1/IRAK4 complex is stimulated by the MyD88 complex, which is prompted by the microbial antigen binding to the TLR receptor (**Figure 1**). The activation of TAK1 protein kinase follows a sequence of events. Both the MAPK-dependent and NF-xB-dependent signal transduction pathways are significantly triggered by this protein. The TAK1 protein phosphorylates the IKK complex, which phosphorylates IxB, a powerful inhibitor of the NF-xB complex, releasing the RelA/p65+p50 complex into the cytoplasm. The NF-xB 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-xB pathway is responsible for oncogenesis, but still much is unknown. It is postulated that canonical NF-xB pathway is actively participates in tumour progression by up regulating VEGF (vascular endothelial growth factor) and its receptors.[4] NF-xB 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-xB 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-xB mediated Interleukin (IL-6) signaling coordinates survival of mantle cell lymphoma cells.[9] NF-xB-mediated autophagy and programmed cell death is thus known to actively participate in tumour formation and oncogenesis.[10] Finally, upregulated NF-xB pathway leads to the increased formation of pro-inflammatory genes which thereby leads to the progression of chronic inflammation like tumours and hence leads to metastasis. Thus, many proteins in the pathway serve as a major drug target and down regulation 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-xB inhibition can treat cancer but also with serious side effects because NF-xB plays a vital role in innate immune response of the body.

3. P53 Pathway and its role in Oncogenesis

Tumour protein p53, or simply p53 is a transcription factor protein encoded by the TP53 gene that helps in tumour suppression. It is often termed as “The Guardian o Genome” since it playsa significant role in preventing genomic mutation.[11,12] The p53 protein is present in the nucleus of cells throughout the body. The human genome contains one copy (2 alleles) of TP53 gene and both the alleles need to be functioning for tumour prevention. The p53 family comprises of 3 known members – p53, p63and p73.[13]

The p53 signaling pathway is activated during any DNA damagedue 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 protein binds to a site in the promoter region of the mRNA containing WAF1 gene. The WAF1 gene is responsible for the increased level 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 in that way leading to the

growth arrest in phase G2-M 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 tumour prevention by arresting the growth of abnormal cells. Thus, this pathway plays a crucial role in suppressing cancer growth.[1514] 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. Overexpression of p53 causes MDM-2 to be upregulated. MDM-2 protein is an E3 ubiquitin ligase that degrades p53. MDM-2 and p53 regulate each other's expression, resulting in an interconnected autoregulatory loop.[16] MDM-2 expression is controlled by another protein called MDMX, which has a similar composition but lacks E3 ubiquitin ligase activity. According to research, MDMX and MDM-2 are required in normal cells to negatively regulate p53.[17] The normal operation of MDM-2 and MDMX is especially critical for p53 control, which would otherwise result in chronic inflammatory disorders.

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 contain the mutated TP53 gene.[18] Research has shown that TP53 mutated gene is the leading causal agent in Brain cancer, Liver cancer, Osteosarcomas, 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 tumour progression. During Cancer, mutant p53 interferes with autophagy and helps in oncogenesis.[21] Finally, over expression 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 tumours.[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 tumour 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.

4. Can Simultaneous Inhibition of NF-xB Pathway and Activation of p53 Pathway Really Cure Cancer

After extensive study and studies on the NF-xB and p53 pathways, it is now obvious that these two pathways each play an important part in our body's natural defence mechanisms. These two pathways are the primary regulators of innate immunity, cell proliferation, phagocytosis, cell death, and cancer progression. Studies have shown that almost all cancer types have mutations in both NF-xB and p53, making it the prime cause of cancer development. Although many targeted drug therapies involving selective regulation of p53 or NF-xB 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-xB 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.

4.1. Cross-links between NF-xB and p53 pathway

NF-xb and p53 pathways simultaneously participate in the natural immune response of the body and play a critical role in determining oncogenesis. According to research, these pathways cross-link and tend to mediate each other. According to research, NF-xB and p53 work together to regulate many metabolic pathways, protein expression, and cancer progression. It is thought that the alternative NF-xB pathway regulates the p53 protein. The NF-xB2 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-xB functioning independent of MDM2-p53 interaction.[25] Moreover, it is believed that loss of novel p53 damaged the NF-xB transcription, which thereby implies that p53 is a key mediator of NF-xB molecule. Further research shows that over expression of p53 increases the binding affinity of IxB to p50+p65 and thereby downregulates NF-xB expression. This phenomenon is actively used to treat human colon cancer.[26] Though p53 and NF-xB have completely different effects in cancer, they tend to co-regulate pro-inflammatory gene expression in monocytes and macrophages. Research has shown NF-xB 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-xB during S-phase checkpoint activation. Also, NF-xB gene expression induced by TNF (tumour necrosis factor) is regulated by p53.[28] Hence it is observed that p53 plays a vital role in the NF-xB-mediated transcriptional pathway. Results have shown that a decrease in the level of NF-xB hindered p53-induced cell apoptosis, thereby indicating NF-xB correlates withp53 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-xB and p53 mediated glycolysis tend to protect the normal cells against chemotherapy treatment.[29] Research has also shown that NF-xB and p53 both play a crucial role in mitochondrial energy production. During mitochondrial DNA alterations, calcium accumulates rapidly, which leads to increased NF-xB activity. Upregulating NF-xB lowers p53 expression, which can contribute to oncogenesis.[30] In response to doxycycline (an antibiotic drug), NF-xB activates p53-mediated pro-apoptotic signalling. NF-xB then inhibits MDM2 activity, allowing p53 to be phosphorylated at Ser-20, resulting in the activation of pro-apoptotic genes such as p21 and Puma.[31] The NF-xB pathway actively promotes EMT (epithelial to mesenchymal transition), whereas p53 suppresses it. Research has been shown that in HNSCC (head and neck squamous cell cancer), p53 plays an important role in NF-xB-mediated EMT signalling by suppressing p65.[32] The study confirms the interaction between p53 and NF-xB in the control of pro-autophagic protein production. Some studies have also found that RelA and p53 hinder each other's transcription factor activity.[33] Extensive research has shown that the p53 protein may restrict the production of the NF-xB complex by increasing p21; additionally, TNF-activated NF-xB may inhibit p53 activity, resulting in conflicting mediation responses.[34] Thus, it is now clear that co-regulation of p53 and NF-xB 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.

4.2. Targeted drug therapies involving mutual antagonism of p53 and NF-xB

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-xB 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-xB pathway in a dose dependent manner.[35-37] Nutlin-3 and R-Roscovitine are known to inhibit NF-xB 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-xB factor by phosphorylating IxB protein. R-Roscovitine and Flavopiridol are known to inhibit IKK activity thereby blocking NF-xB 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-xB 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-xB pathway.[38] 9-Aminoacridine (9AA) and its derivative Quinacrine are known to have anti-cancer effects. 9AA inhibits AKT/mTOR pathway thereby down regulating p110γ. This in turn down regulates NF-xB and activates p53.[39] Quinacrine down regulates p62 which promotes p21 upregulation via Skp2. This in turn inhibits the NF-xB pathway and upregulates p53.[40]

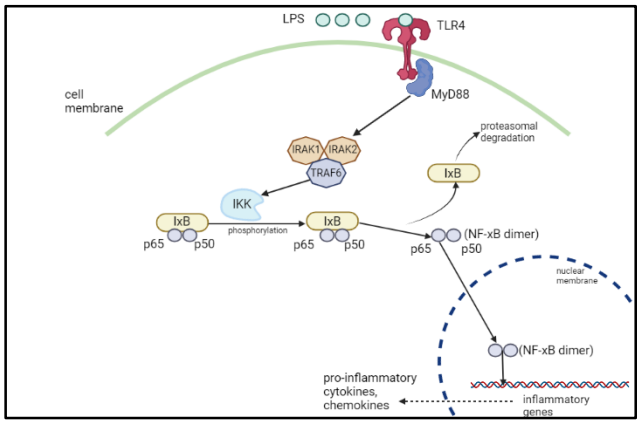

Figure 1: Schematic representation of NF-xB pathway

It shows a 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.

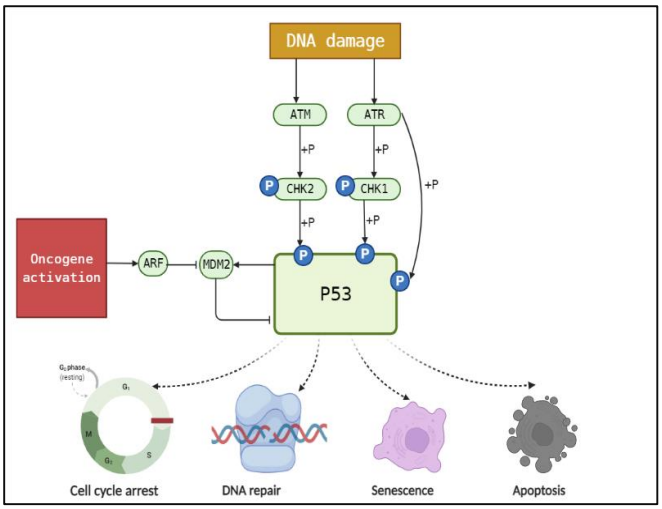

Figure 2: Schematic representation of p53 pathway

It shows a major signaling pathway that gets activated during mutation or DNA damage. This diagram also shows major functions of p53 factor in cell cycle and DNA repair.(**Figure 2**)

5. Conclusion

It is now well understood that both p53 and NF-xB play a significant role in major metabolic pathways, and any abnormality will ultimately lead to oncogenesis. Overexpression of NF-xB and down-regulation of p53 was found to be the foremost oncogenic cause. Hence mutual antagonism of p53 and NF-xB pathways plays a crucial role in modern anti-cancer drug discovery. Several drugs are being developed that is involved in (a)TNF-induced NF-xB 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) Down regulation of p62 which promotes p21 upregulation via Skp2 as seen in QUINACRINE, etc. In this review we tried to hypothesize the fact that during cancer, simultaneous activation of p53 and inhibition of NF-xB 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.

6. Source of Funding

None.

7. Conflicts of Interest

The authors declare that there is no conflict of interest.

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