P53 vs NF-κB: the role of nuclear factor-kappa B in the regulation of p53 activity and vice versa

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Keywords: NF-κB, P53, apoptosis, crosstalk

Keywords: p53, regulation, NF-kB, functional inhibition

Abstract

The onco-suppressor p53 is a transcription factor that regulates a wide spectrum of genes involved in various cellular functions including apoptosis, cell cycle arrest, senescence, autophagy, DNA repair and angiogenesis. p53 and NF-κB generally have opposing effects in cancer cells. While p53 activity is associated with apoptosis induction, the stimulation of NF-κB has been demonstrated to promote resistance to programmed cell death. Although the transcription factor NF-κB family is considered as the master regulator of cancer development and maintenance, it has been mainly studied in relation to its ability to regulate p53. This has revealed the importance of the crosstalk between NF-κB, p53 and other crucial cell signaling pathways. This review analyzes the various mechanisms by which NF-κB regulates the activity of p53 and the role of p53 on NF-κB activity.

Introduction

The transcription factor p53 is one of the most studied tumor suppressors in almost all cancer types [1,2]. p53 pathway is activated by DNA damage, hypoxia or other stressors and it mainly induces cell cycle arrest,apoptosis and cellular senescence in response to these stimuli.

In addition to these responses, the p53 pathway regulate also bioenergetic balancing, inflammation and epithelial-mesenchymal transition (EMT). Finally, p53 activation influences a set of proteins that can be directly involved in DNA damage repair process. For this reason, its activity is severely compromised in virtually every tumor for mutations in the p53 gene or by reversible inactivation [3]. The NF-κB family of transcription factors comprises five DNA-binding proteins with a central function in the regulator of immune response [4–6]. NF-κB proteins are frequently hyper-activated in cancer, where promote chronic inflammation, in turn favoring tumor development and chemo-resistance [7]. The crosstalk between p53 and NF-κB transcription factors has been extensively studied and it has been proved to have a key role in tumorigenesis [8–10].

Because the activation of NF-κB generally inhibits p53 function and vice versa, their relationship seems to be antagonistic [8,9]. However, their reciprocal regulation can have different outputs related to the context. For example, it has been shown that p53 regulation requires an intact NF-κB site in its promoter and that NF-κB induction by TNFα, or transient expression of the p65 subunit of NF-κB, activates p53 expression [11]. Moreover, in some cases p53 and NF-κB can cooperate in the regulation of apoptosis [12]. On the contrary, NF-κB can induce the expression of the E3 ubiquitin ligase Mdm2, thereby negatively regulating p53 stability and leading to p53 degradation through a ubiquitin-dependent mechanism [13]. The relationship between p53 and NF-κB can influence several important pathways in cancer cells: tumor cell metabolism, pro-inflammatory activity, DNA damage, mitochondrial function and ATP production [14,15]. Various mechanisms able to control NF-κB on p53 activity are indeed able to cooperate in different conditions. Here, we discuss some specific examples where NF-κB/p53 crosstalk can affect tumor cell properties.

NF-κB and p53 crosstalk regulates tumor metabolism

RelA a member of NF-κB transcription factor family has been demonstrated to be involved in cell metabolism. In particular, Mauro et al. showed that knock down of RelA in mouse embryonic fibroblasts (MEFs) recapitulates Warburg effect by enhancing glucose consumption and lactate production in normal culture conditions [16]. These effects are mediated in part by p53 activation, which in turn up-regulates several genes including glucose transporters (GLUT1, GLUT3, GLUT4) and SCO2, a subunit of the mitochondrial cytochrome C oxidase (COX) complex. These data identify NF-κB–p53 axis as a bioenergetic pathway [16]. However, NF-κB and more specifically RelA were also observed to have an opposite role, promoting glycolysis in a p53-null background through the up-regulation of GLUT3. This suggests the possible existence of antithetic mechanisms mediated by NF-κB in the regulation of glucose metabolism, in a p53-dependent or –independent way [17].

Interestingly, p53/NF-κB-mediated metabolic regulation can also have a role in normal tissue protection under chemotherapy treatment [18]. In particular, it has been observed that low doses of arsenic in non-transformed cells can induce the concomitant suppression of p53 and activation of NF-κB. This shift in turn induces glycolysis and provides cells an effective protection against cytotoxic chemotherapy (Figure 1).

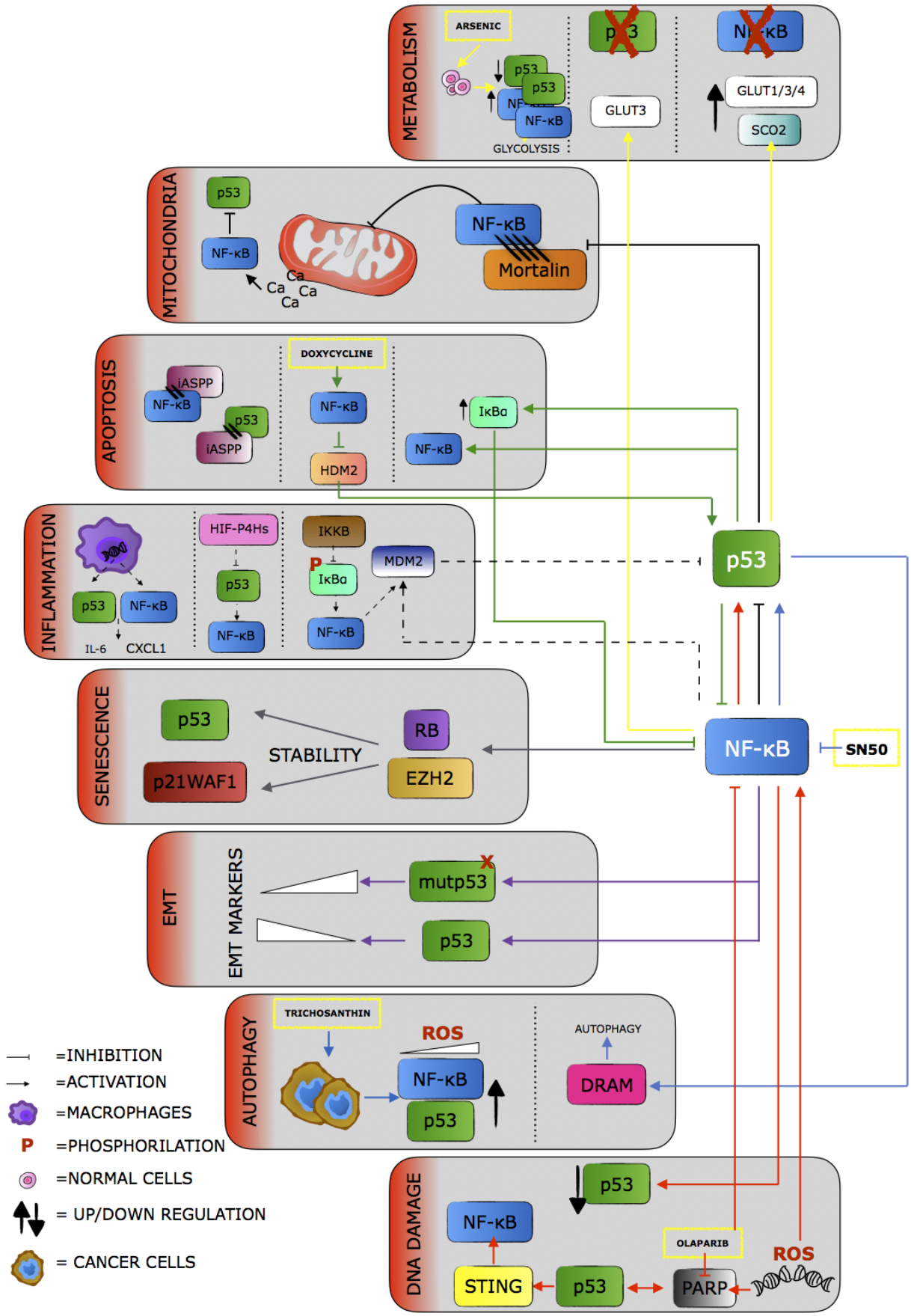
NF-κB and p53 crosstalk regulates mitochondria

In addition to the role of p53 and NF-κB in the control of aerobic glycolysis, a direct involvement of p53 in the regulation of NF-κB in mitochondrial activity has also been proposed. Indeed, together with other NF-κB subunits such as IκBα, RelA has been identified among mitochondrial proteins [19,20]. During tumor progression, p53 loss removes an important control on NF-κB/RelA regulation of mitochondrial function. In particular, in a p53-null context, NF-κB/RelA translocates into the mitochondria and is recruited to the mitochondrial genome where it represses mitochondrial gene expression and consequently oxygen consumption and cellular ATP production. p53 is able to prevent NF-κB/RelA mitochondrial localization by inhibiting its interaction with Mortalin, thereby increasing mitochondrial energy production [21]. On the contrary, in the case of mitochondrial dysfunction due to alterations in mitochondrial DNA, the accumulation of intracellular calcium leads to the up-regulation and activation of NF-κB [22]. In turn, NF-κB signaling reduces the expression of p53 and protects tumor cells from apoptosis. (Figure 1)

NF-κB and p53 crosstalk regulates apoptotic response

The p53 tumor suppressor is involved in multiple central cellular processes, but one of its most important roles is the induction of apoptosis in response to DNA damage or other stressors [23]. For this reason, most tumors are characterized by loss of function mutations within the p53 gene or regulatory defects in its induction. The re-activation or introduction of p53 induce apoptosis in many cellular tumor models and provide a potentially effective cancer therapy [24]. Another crucial

Figure 1: NF-κB and p53 crosstalk in regulating pathways



protein that can modulate apoptotic response is the NF-κB transcription factor family, that can both protect from, or in other situations contribute to, apoptosis [25]. These two pathways can be closely linked and in particular, one of the mechanisms promoting apoptosis in tumor cells can involve the downregulation of NF-κB by p53. For instance, p53 over-expression in human colon cancer cells suppresses NF-κB activity, presumably by enhancing cytoplasmic IκBα expression and activating the apoptotic program [26]. Similarly, p53 represses RelA/NF-κB activity by disrupting the complex or reducing RelA/ NF-κB binding to κB DNA sites. Also in this scenario, modulation of RelA/NF-κB activity by p53 results in induction of programmed cell death [27]. In contrast, induction of p53 in osteorsacoma Saos-2 cells increases NF-κB DNA-binding activity, demonstrating a clear correlation between the ability of p53 to activate apoptosis and the activation of NF-κB. Therefore, in this setting inhibition of NF-κB may reduce the therapeutic response [12]. Oppositely, NF-κB also plays an essential role in the activation of p53 allowing to promote the pro-apoptotic signaling in response to doxycycline. In this context, NF-κB reduces HDM2 activity and induces p53 phosphorylation at Ser-20. These results in the activation and stabilization of p53, which in turn promotes the expression of p53-regulated pro-apoptotic genes, such as Puma and p21waf1 [28]. Moreover, NF-κB was also observed to have a role in promoting apoptosis both in a $p53^{-/-}$ or $p53^{+/+}$ cells, after arsenic treatment [29]. Another mechanism by which p53 and RelA/p65 can regulate apoptotic response is through the intervention of other partners. This is the case of protein iASPP. After some apoptotic stimuli, iASPP can be cleaved in two fragments able to interact with p53 and p65 proteins. Binding with iASPP reduces the transcriptional activity both of p53 and p65, suggesting a novel negative or positive regulator mechanism of the apoptotic process [30]. Therefore, the evaluation of NF-κB/p53 interconnection in apoptosis regulation, could provide a potential new direction for cancer treatment. (Figure 1).

NF-κB and p53 crosstalk regulates pro-inflammatory gene responses

The NF-κB pathway is well known as a central mediator of innate- and adaptive-immune responses and inflammation [31,32]. Pro-inflammatory stimuli activate the canonical pathway, typically characterized by hyper-phosphorylation of IκBα proteins and their proteasome-mediated degradation. As a consequence, NF-κB subunits are released and translocate into the nucleus, leading to the activation of hundreds of genes involved in proliferation, migration, survival or antagonizing cell regulators, including the tumor suppressor p53 [32,33]. This chain of events, and in particular the mutual antagonism between NF-κB and p53 pathways, induces a chronic inflammatory status, frequently involved in the progression of several types of cancer [33]. More in detail, NF-κB can interfere with p53 activity by different mechanisms. For example, NF-κB can up-regulate the p53 inhibitor MDM2 [34]. Alternatively, IKKB while activating NF-κB through phosphorylation of IκB, also alters p53 stability through its post-translational modification [35]. p53 acts also as a regulator of NF-κB repression by the glucocorticoid receptor, suggesting that nonfunctional p53 may correlate to the impaired glucocorticoid repression of inflammation [36]. Finally, IKKα mediates phosphorylation of the coactivator p300/CBP, rendering it a preferential partner of NF-κB instead of p53, inhibiting p53 functions [13]. All these mechanisms mediated by NF-κB activation, interfere with p53 protective functions, thereby favoring an inflammatory condition and promoting cellular transformation processes. On the other hand, can act as a mediator of the glucocorticoid receptor repressive function. Moreover, it has been observed that inactivation of HIF-P4Hs, an hydroxylase regulating HIF1α stability, increases p53 stability and activity [37]. In turn, p53 negatively regulates NF-κB signaling, impairing the pro-inflammatory response. However, recent findings also suggest a possible agonistic role of NF-κB and p53 in the regulation of pro-inflammatory response. In particular, NF-κB and p53 were found to co-regulate the expression of pro-inflammatory genes, including cytokines and chemokines, in healthy and tumor-associated (TAM) macrophages [15]. Mechanistically, in normal or tumor microenvironment, stressors (such as DNA-damaging agents or Nutlin-3) activate NF-κB and p53 pathways in macrophages, stimulating the activation of both transcription factors in the promoter of target genes,

like IL-6 and CXCL1, inducing their expression and consequently a pro-inflammatory and potentially pro-tumorigenic effect. Therefore, despite tightly interconnected in the inflammatory response, NF-κB and p53 pathways can behave in a mutual antagonistic or agonistic way, dependently on the stimulus and cellular context, whose full vision is far to be complete (Figure 1).

NF-κB and p53 crosstalk regulates senescence

The transcription factor NF-κB family consists of five transcription factors including RELA (p65), RELB (RelB), REL (c-Rel), NFKB1 (NF-κB1) and NFKB2 (NF-κB2) [38,39]. In addition to the well-known function of NF-κB/RelA with respect to p53, also the NF-κB2/RelB pathway can interact with the activity of p53. Indeed, it has been demonstrated that NF-κB2/RelB, the component of the alternative NF-κB pathway, suppresses senescence through inhibition of p53 activity. Specifically, Iannetti and colleagues using primary human fibroblasts, demonstrated that NF-κB2/RelB regulates Rb activity and consequently EZH2 expression, which in turn controls the stability of p21WAF1 and p53 in primary human fibroblasts [40] (Figure 1).

NF-κB and p53 crosstalk regulates epithelial-to-mesenchymal transition

The process of epithelial-to-mesenchymal transition (EMT) plays a critical role in tumor invasion and metastatization [41,42]. While NF-κB pathway plays a pivotal role in promoting EMT, on the contrary, p53 has been demonstrated to suppress it [43,44]. Indeed, NF-κB and p53 cooperate antagonistically in the modulation of this process. In particular, Yuan Lin and colleagues demonstrated that p53 mutational status modulates the NF-κB-mediated EMT. More in detail, in head and neck squamous cell carcinoma (HNSCC), p65 over-expression promotes EMT only in the case of a functional wild type p53. Conversely, in HNSCC with a p53 loss of function, the re-introduction of p65 not significantly alters the expression of EMT markers, whereas they are induced by p65 silencing. Thereby, these findings showed the critical role of p53 in mediating the outcome of NF-κB signaling on EMT [45] (Figure 1).

NF-κB and p53 crosstalk regulates autophagy

The NF-κB activity has also been associated with p53-mediated activation of autophagy. It has been described in gastric cancer cells MKN-45, that treatment with Trichosanthin induces autophagy in concomitance with the up-regulation of NF-κB and p53, through a mechanism dependent on the generation of ROS [46]. On the contrary, another study showed that the inhibition of NF-κB with SN50 is capable of inducing autophagy, through p53 induction. In particular, inhibition of the translocation into the nucleus of NF-κB induces an increase in p53 level, which in turn promotes the expression of the pro-autophagic protein DRAM [47]. Thereby, further investigations of the relationship between autophagy and NF-κB/ p53 crosstalk are required and they could unveil new therapies for cancer treatment. (Figure 1).

NF-κB and p53 crosstalk regulates DNA Damage Response

p53 is well known to play a fundamental role in mediating DNA Damage Response (DDR), promoting DNA repair or eventually cell cycle arrest, senescence and apoptosis [48]. However, recent evidences suggest a strong interconnection between p53 and NF-κB pathways in mediating the response to DNA breaks. For example, reactive oxygen species (ROS)-mediated DDR induces NF-κB p65/RelA nuclear translocation in lung cancer cells [49]. In turn, NF-κB signaling controls p53 levels after ROS induction, indeed NF-κB inhibition induces an up-regulation of p53 and exacerbates H2O2-induced apoptosis [49]. Furthermore, Poly (ADP-ribose) polymerase (PARP), a key player in the DDR, is able to induce NF-κB signaling in head and neck cancer cells with low p53 expression [50]. Consequently, treatment with the PARP inhibitor Olaparib decreases NF-κB levels, through a mechanism dependent on p53 up-regulation [50]. Another important mediator of DDR is the DNA sensing adaptor STING [51]. In detail, DNA damage-induced PARP-1 and ATM signaling results in the assembly of an alternative STING complex involving an active p53. In turn this complex is able to induce the activation of NF-κB and a specific transcriptional program, promoting the innate immune response following DNA damage [51]. Moreover, bioinformatics analyses suggested the existence of a strong and dynamic transcriptional network involving ATM, p53, NF-κB and Wip1 phosphatase, implied in the regulation of DDR [52,53]. On the other hand,

DNA damage in myeloid leukemia cells can promote NF-κB activation in a p53-independent manner, stimulating the expression of the tumor suppressor p21 and inducing terminal differentiation. (Figure 1) [54].

Crosstalk between NF-κB and mutant p53

p53 mutations are very common in cancer. Some of these mutations induce a p53 down-regulation or decreasing its activity. Instead, others mutations can induce oncogenic properties of p53 and favor the promotion of cancer [55]. It has been demonstrated that mutant p53 is associated with a NF-κB-increasing activity. For example, p53-R175H, -R273H, the two of the most common p53 mutants, and p53-D281G found in human lung cancer cells regulate NF-κB2 expression. Unfortunately, the mechanism by which p53 induces NF-κB2 and the exact function of NF-κB2 are still unclear. Probably, as suggest by authors, the activation of NF-κB2 is involved in cellular survival and in the response to chemotherapy [56]. Similarly, mutant p53 activated anti-apoptotic NF-κB, together with the activation of the ERK pathway, in human melanoma cell lines [57]. In addition, it has also been proposed that mutant p53 can enhances nuclear accumulation of NF-κB activation in response to TNFα stimulation. Conversely, down-regulation of mutant p53 sensitizes cells to TNFα-induced apoptosis [58]. Finally, the increase in NF-κB activation following the presence of mutated p53 was also demonstrated by Cooks and colleagues, which also attribute it a possible role in the pathogenesis of colorectal cancer. Specifically, mutated p53 perpetuates NF-κB activation through its prolonged stabilization on κB sites. Furthermore, NF-κB activation induces inflammatory cytokine and a general chronic inflammatory state, which in turn is associated with DNA damage and genome instability. These effects could augments the capacity of cancer cells to enforce the invasiveness of colon carcinoma and to evade apoptosis [59].

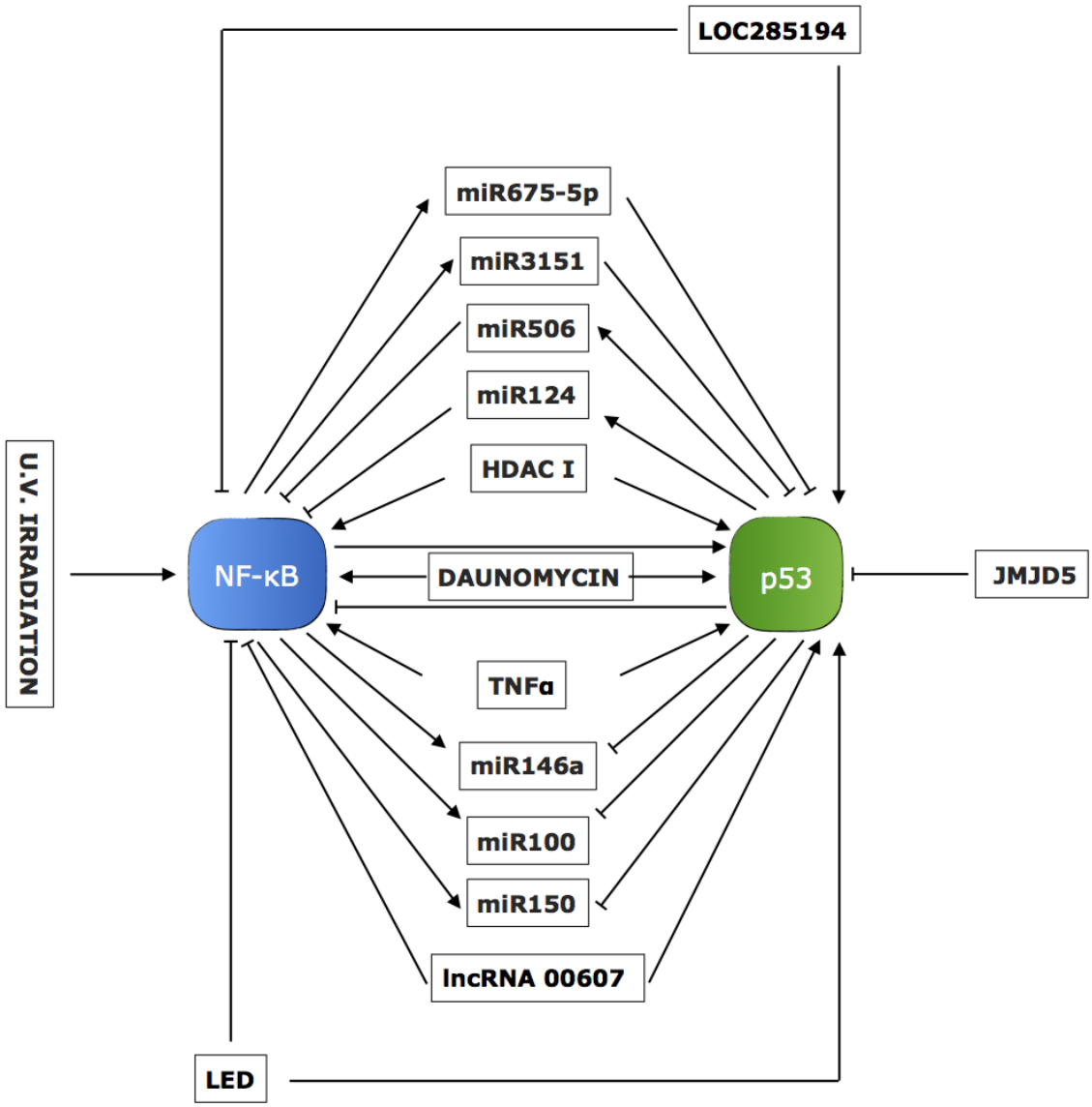
Transcriptional crosstalk between NF-κB and p53

The transcriptional regulation of p53 occurs at many levels and involves both the promoters of target genes and some intron sequences [60]. Moreover, it has been shown that p53 promoter

sequence is responsive to p53 itself, however in this sequence a predicted NF-κB-binding site has also been observed [11,61]. This direct evidence suggests that NF-κB can be considered a transcriptional inductor of p53. Indeed, NF-κB was found to recognize the κB sites in the p53 promoter and to activate its expression. Accordingly, under certain stimuli NF-κB activation occurs simultaneously with the induction of p53. For example, treatment with daunomycin induces the expression of both p53 and NF-κB. In particular, the activation of p53 in response to daunomycin is evident both in terms of p53 mRNA and protein levels and it is induced by the binding of p50/p65 heterodimers to the κB site of p53 promoter [62]. A common inducer of both NF-κB and p53 is the tumor necrosis factor alpha (TNF-α), a cytokine involved in inflammatory and immune responses. TNFα induces phosphorylation and dissociation of IκBα from the NF-κB complex and consequently its translocation into the nucleus [63]. Moreover, TNFα is able to induce a p65-mediated activation of the p53 promoter in HeLa cells [11]. Finally, stressors such as U.V. irradiation can induce the activation of NF-κB and in turn NF-κB is able to activate p53 transcriptionally.

The transcriptional crosstalk between NF-κB and p53 can involve also specific epigenetic modulators. Specifically, different chemotherapeutic agents are able to promote a Class I Histone Deacetylase (HDAC I) -dependent co-induction of both p53 and NF-κB [64]. Accordingly, Class I HDAC inhibitors attenuate p53 and NF-κB signaling, interfering with their crosstalk [64]. Furthermore, the H3K36me2 demethylase JMJD5 is an epigenetic remodeler promoting cancer cell proliferation and migration [65]. It was recently observed in oral squamous cell carcinoma that JMJD5 knockdown up-regulates p53 and interferes with NF-κB expression, impairing tumor migration and invasion [66]. Conversely, JMJD5 over-expression decreases p53 and increases NF-κB levels, promoting malignant progression and metastatization. (Figure 2) [66].

Figure 2: Transcriptional and post transcriptional crosstalk between NF-κB and p53



Post-transcriptional crosstalk between NF-κB and p53

MicroRNAs (miRNAs) are an abundant and conserved class of non-coding RNAs that modulate gene function by binding the 3′ untranslated region (3′UTR) of target mRNAs [67]. In B cell lymphoma miR-124 directly targets nuclear factor-κB (NF-κB) p65 and this repression results in the down-modulation of two important oncogenes: MYC and BCL-2. Interestingly, the miR-124 promoter includes a functional p53 binding site. Thus, the wild type p53 but not its mutant counterpart, directly modulates miR-124 expression that in turn, post-transcriptionally suppresses p65 and consequently MYC and BCL2 [68]. A pivotal antagonist role of p53 and NF-κB on miRNA function has been showed in cervical carcinoma. In this tumor type, the two TFs directly modulate the following miRNAs: miR-100, miR-146a and miR-150. However, while NF-κB p65/RelA induces these miRNAs, p53 represses all of them, providing additional support of the opposite functional crosstalk of both TFs in cancer pathogenesis [69]. Similarly, in lung cancer, p53 modulates miR-506 levels that in turn directly represses NF-κB p65, a down-modulation that in this context results in ROS accumulation and in the consequent reduction of cell viability [70]. A different post-transcriptional interplay has been proposed in malignant melanoma and in papillary thyroid cancer. In both tumor types mutant BRAF acts in association with the SP1/NF-κB complex to promote the aberrant expression of the oncomiR miR-3151, that directly targets p53 and other members of the pathway [71]. More recently, in colorectal cancer a novel crosstalk has been showed. In this tumor Prostaglandin E2 induces miR-675-5p expression with the contribution of NF-κB and other oncogenic pathways. Again, upon induction, miR-675-5p exerts its oncogenic potential by suppressing p53 by binding its 3'UTR [72]. Overall, all these finding reveals a complex interplay among microRNAs, the NF-κB pathway and p53 function in tumorigenesis. (Figure 2)

Long non-coding RNA modulates NF-κB/p53 crosstalk

Many evidence suggests a roles of long non-coding RNA (lncRNA) in cancer [73]. Among the annotate cancer-associated lncRNAs, lncRNA 00607 has an important role in regulating the

p53/NF-κB network. Functionally, lncRNA 00607 is downmodulated in hepatocellular carcinoma (HCC). Furthermore, over-expression of lncRNA 00607 inhibits proliferation and enhances apoptosis in HCC both *in vitro* and *in vivo.* Mechanistically, lncRNA 00607 is able to bind p65 promoter and to reduce its transcription, while promotes p53 expression at protein and mRNA levels [74].

Deciphering the role of lncRNAs in cancer, it has been demonstrated that lncRNA activator of enhanced domain (LED) and LOC285194 are involved in p53 regulation. To this end, after treatment with 1-hydroxy-1-norresistomycin, both LED and LOC285194 induce p53 expression, suppress proliferation and promote apoptosis in hepatocellular carcinoma. Concomitantly, LED and LOC285194 inhibit the expression of NF-κB. (Figure 2) [75].

Room for direct interactions between NF-κB and p53 protein

All the interactions described above are mostly consequences of the transcriptional events favored by NF-κB and/or p53 [76]. It is however worth to note that p53 protein may physically interact with NF-κB family members. In particular, p53 was shown to binds to IκBα, the NF-κB inhibitor, [77–81] as we have reviewed [82], suggesting a sort of regulator mechanism of NF-κB pathway on p53. Similarly, NF-κB, and specifically RelA/p65, can interact with p53 family member. Indeed, it has been that MDM2, a major negative regulator of p53, can act as a direct negative regulator also of NF-κB by binding and inhibiting RelA/p65 [83]. It is demonstrated that probably, mutated p53 directly interacts with NF-κB [84]. The interactome of NF-κB family members is substantially expanding overtime [85], and may eventually identify novel mechanisms able to modulate p53 activities at protein level.

Concluding remarks

The crosstalk between p53 and NF-κB has a key role in the pathogenesis of most tumors. The relationship between these two transcription factors is fundamental in the regulation of important mechanisms during all stages of tumorigenesis and is involved in the regulation of many cancer cell properties, including altered metabolism, apoptosis deregulation, chronic inflammation and metastatization. This interconnection appears to be opposite in some circumstances, while in other cases can converge in the same signaling pathway. This contraposition of agonistic and antagonistic mechanisms is often related to the different context or system in which the crosstalk between p53 and NF-κB acts. Also, the final results of the NF-κB/p53 interplay may also depend on the complexity of transcriptional mechanisms and protein-protein interactions. Indeed, the contradictions proposed by the different studies can be difficult to take in full considerations. The purpose of this review has been to summarize the principal molecular mechanisms regulating the cross-signaling between p53 and NF-κB and how this can reciprocally influence the activation of their own pathways. Finally, the study and the comprehension of the complex signal network between p53 and NF-κB could contribute to the development of new therapeutic approaches, based on their reciprocal regulation.

Acknowledgments: we thank the Dept. of Clinical and Biological Science for funding our research (Ex-60 grant).

Author Contributions

G.C. and M.F.L. wrote the manuscript and generated the figures. B.M. helped in the preparation of the manuscript. R.T. and A. reviewed the manuscript.

Conflicts of Interest

Authors have no conflict to declare.

FIGURE LEGENDS:

Figure 1: NF-κB and p53 crosstalk in regulating pathways

The scheme depicts the multiple mechanisms of p53/NF-κB control the activity several pathway; See text for details and references.

Figure 2: Transcriptional and post transcriptional crosstalk between NF-κB and p53

Principal transcriptional and post-transcriptional mechanisms responsible for NF-κB/p53 regulation. See text for details and references.

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