Biochimica et Biophysica Acta 1815 (2011) 90–103

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

NFκB/p53 crosstalk—a promising new therapeutic target

Günter Schneider [a,1], Oliver H. Krämer [b,*]

[a] Technische Universität München, Klinikum rechts der Isar, II. Medizinische Klinik, Ismaninger Str. 22, D-81675 München, Germany
[b] Friedrich-Schiller-University Jena, Center for Molecular Biomedicine, Institute of Biochemistry and Biophysics, Hans-Knöll-Str. 2, D-07745 Jena, Germany

ARTICLE INFO

Article history:
Received 1 September 2010
Received in revised form 2 October 2010
Accepted 7 October 2010
Available online 15 October 2010

Keywords:
RelA/p65
NFκB
p53
Signaling
Therapy
Cancer

ABSTRACT

The transcription factors p53 and NFκB determine cellular fate and are involved in the pathogenesis of most–if not all–cancers. The crosstalk between these transcription factors becomes increasingly appreciated as an important mechanism operative during all stages of tumorigenesis, metastasis, and immunological surveillance. In this review, we summarize molecular mechanisms regulating cross-signaling between p53 and NFκB proteins and how dysregulated interactions between p53 and NFκB family members contribute to oncogenesis. We furthermore analyze how such signaling modules represent targets for the design of novel intervention strategies using established compounds and powerful combination therapies.

Contents

Abbreviations: AD, activation domain; AKT, cellular homolog of murine thymoma virus akt8 oncogene, serine/threonine kinase B; AML, acute myeloid leukemia; AP-1, JUN/FOS transcription factor; ATM, ataxia telangiectasia mutated; ATR, ATM- and RAD3-related; ARD, ankyrin repeat domain; ARF, alternate reading frame of the INK4a/ARF locus; α5/β1, integrin α5/β1; BAFF, B-cell-activating factor; BAX, BCL-2-associated X protein; BCL, B cell lymphoma; BH3, BCL-2 homology domain 3; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CHUK, conserved helix-loop-helix ubiquitous kinase; CK2, casein kinase 2; COP1, caspase recruitment domain family, member 16; CTD, C-terminal domain; DBD, DNA-binding domain; DDR, DNA damage response; dsB, double strand breaks; EGCG, epigallocatechin-3-gallate poly-phenol; EGF, EGFR ligand; EGFR, epidermal growth factor receptor; EGR1, early growth response 1; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated kinase; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugase; E3, ubiquitin-ligase; FAK, non-receptor focal adhesion kinase; FAS, TNF-receptor superfamily, member 6 (CD95, APO-1); FASL, FAS-ligand; GLUT, glucose transporter; HAT, histone acetyltransferase; HB-EGF, Heparin-binding EGF-like growth factor; HCC, hepatocellular carcinoma; HDACI, histone deacetylase inhibitor; HDAC, histone deacetylase; HDM2, human double minute ubiquitin ligase; HNSCC, head and neck squamous cell carcinoma; HU, hydroxyurea; ICAM, intracellular adhesion molecule; IκB, NFκB inhibitory proteins; IKK, IκB kinase; IL-1, interleukin-1; JAK, Janus kinase; KAI1/CD82, cluster of differentiation 82; LTβ, lymphotoxin-β; LPA, lysophosphatidic acid; MCP, monocyte chemoattractant protein; MDM2, murine double minute (ubiquitin ligase); MEK, Mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; MnSOD, superoxide dismutase 2, mitochondrial; NEMO, NFκB essential modulator; NLS, nuclear localization signal; NFκB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NIK, NFκB inducing kinase; p53-AIP1, p53-regulated Apoptosis-Inducing Protein 1; PAT, protein acetyltransferase; PDAC, protein deacetylase; PC, prostate carcinoma; PI3K, phosphatidylinositol 3-kinase inhibitor; PPase, phosphatase; PAI1, senescence regulator; PAMPs, pathogen associated molecular patterns; PARP, poly(ADP-ribose)-polymerase; PDGF-A, platelet-derived growth factor; PIASy, protein inhibitor y of activated STAT; PIDD, p53-induced protein with death domain; PIRH2, p53-induced ubiquitin-protein ligase; PRD, proline rich domain; PUMA, p53 upregulated modulator of apoptosis; p21, cyclin-dependent kinase inhibitor 21 kDa; p53, tumor suppressor protein 53 kDa; p63, p53 homologue 63 kDa; p73, p53 homologue 73 kDa; RCP, RAB-coupling protein; RSK, ribosomal serine/threonine kinase; RIP, receptor interacting protein; Rel v-rel, reticuloendotheliosis viral oncogene homolog (A, avian); RHD, Rel-homology domain; ROS, reactive oxygen species; SCF, ubiquitin ligase complex of Skp1/Cul1/Rbx1/F-box proteinβ-TrCP1; SHP, SH2 domain containing phosphatase; SUMO, small ubiquitin-like modifier; ssB, single strand breaks; SIRT, silencing information regulator; SNAIL, C2H2-type zinc finger transcription factor; STAT, signal transducer and activator of transcription; TAD, transcriptional activation domain; TGFβ, transforming growth factor β; TIGAR, TP53-induced glycolysis and apoptosis regulator; TNFα, tumor necrosis factor-α; TRAF, TNF receptor associated factor; TRIM24, Tripartite motif-containing 24 (TRIM24), transcriptional intermediary factor 1α; ZEB1/ZEB2, zinc finger E-box binding transcription factors

* Corresponding author. Tel.: +49 3641949362; fax: +49 3641949352.
E-mail addresses: guenter.schneider@lrz.tum.de (G. Schneider), Oliver.Kraemer@uni-jena.de (O.H. Krämer).
[1] Tel.: +49 8941406395; fax: +49 8941404910.

0304-419X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbcan.2010.10.003

1. Introduction

Members of the nuclear factor-κB (NFκB) and p53 protein families are pivotal for the maintenance of homeostasis and are frequently dysregulated in cancer. Intense investigations have demonstrated that both factors are linked to oncogenesis and all steps of tumorigenesis. Crosstalk of p53 and NFκB occurs at multiple levels and has to be considered as a highly context-specific event. Generalizing this process as simply synergistic or antagonistic is hence misleading. Here, we focus on the crosstalk between the NFκB family member p65 and p53 and we summarize possibilities to influence their interactions. Ongoing research will further clarify how p53 and NFκB interact in specific cellular contexts and under specific stimuli. This knowledge will help to identify and develop strategies for tailored therapies.

2. Characteristics and activation of NFκB proteins

2.1. NFκB family members

The NFκB transcription factor family crucially controls diverse biological processes, such as immune responses, development, cell survival, and growth. Therefore, it is not surprising that NFκB signaling contributes to the development and progression of human diseases including cancer and aberrant immunological functions [1]. In mammals, five different NFκB members have been identified: RelA (p65), RelB, c-Rel, p50/p105 (NFκB1), and p52/p100 (NFκB2). These proteins form hetero- or homodimers [2]. All NFκB family members share an N-terminal stretch of approximately 300 amino acids. This Rel-homology domain (RHD) is responsible for DNA-binding, dimerization, and nuclear translocation. In resting cells, the majority of NFκB dimers are associated with a family of ankyrin repeat domain (ARD) containing NFκB inhibitory proteins. These inhibitors of κB (IκBs), e.g. IκBα or IκBβ, mask the nuclear localization signal (NLS) present in the RHD and sequester NFκB in the cytoplasm. Only RelA, RelB, and c-Rel possess the C-terminal transcriptional activation domain (TAD).

2.2. Classical and alternative pathways

Three major pathways regulate NFκB proteins. These are the canonical, the alternative, and the atypical pathways. The canonical pathway is engaged in response to various inflammatory stimuli like the cytokines tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and pathogen associated molecular patterns (PAMPs). Central for the canonical pathway is the IκB kinase (IKK) complex. The IKK signalosome consists of at least three core subunits, the two kinases IKKα (IKK1/CHUK) and IKKβ (IKK2) and the regulatory subunit IKKγ/NEMO [3,4]. Upon activation, the IKK complex phosphorylates IκBs which allows their ubiquitin-dependent proteasomal degradation. This proteolysis permits nuclear translocation of classical NFκB (RelA/p50) (Fig. 1A). Proteasomal degradation of IκB involves the E3-ubiquitin ligase SCF (Skp1/Cul1/Rbx1), which uses the F-box proteins β-TrCP1 or β-TrCP2 as a serine $S^{32/36}$-phosphorylated IκBα recognition subunit [5–7]. Classical NFκB mediates survival under pro-inflammatory conditions.

The second, more recently described non-canonical or alternative pathway is for example triggered by B-cell-activating factor (BAFF), CD40 ligand, and lymphotoxin-β (LTβ). Such signals promote processing of the p52 precursor p100 [2]. This pathway is characterized by delayed kinetics with a dependency on *de novo* protein synthesis. Activation of non-canonical NFκB signaling involves the NFκB inducing kinase (NIK), which phosphorylates the T-loop serines of IKKα [8,9]. Independent of IKKβ and IKKγ, IKKα phosphorylates S^{872} of p100 with subsequent ubiquitinylation of p100 at lysine K^{855}. Proteasomal processing of the p100 C-terminal domain liberates p52 [10,11]. Afterwards, p52/RelB translocate to the nucleus and activate a subset of NFκB target genes harboring κB elements with high affinity for such dimers [12]. Under physiological conditions, the alternative pathway controls the development of secondary lymphoid organs, T- and B-cells.

2.3. Atypical pathways

Atypical NFκB signaling refers to all pathways that do not fall in the two categories mentioned above [13,14]. This heterogeneous group of pathways is evoked by replicational or genotoxic stress (e.g. UV-light, γ-irradiation or chemotherapeutically active drugs inhibiting topoisomerases or the replication machinery) (Fig. 1B). Central to NFκB activation by genotoxic stress is the regulatory IKK subunit IKKγ/NEMO [14,15]. Upon induction by genotoxic stress, NEMO accumulates in the nucleus and forms a complex with PIDD (p53-induced protein with death domain) and RIP1 (receptor interacting protein 1) [16,17]. In the presence of PIDD, the E3 SUMO-ligase PIASy (protein inhibitor y of activated STAT) catalyzes covalent modification of NEMO with a small ubiquitin-like modifier (SUMO) [18]. Subsequently, NEMO is phosphorylated by the ataxia telangiectasia mutated (ATM) kinase at serine S^{85}, which leads to desumoylation and K^{63}-linked ubiquitinylation (Ub^{K63}) of NEMO [17,19,20]. As a consequence, NEMO/ATM complexes locate to the cytoplasm and activate the IKK complex. Besides DNA-damage and cell cycle disturbances, other cellular stressors, like oxidative stress or heat shock, activate this NFκB signaling pathway [21]. Interestingly, the ATM-related kinase ATR (ATM- and RAD3-related) blocks NEMO phosphorylation and NFκB-dependent anti-apoptotic gene expression patterns [22].

Recent data demonstrate that the DNA-damage sensor poly(ADP-ribose)-polymerase-1 (PARP1) also contributes to NFκB activation by genotoxic stress [23]. PARP1 generates poly(ADP-ribose) (PAR) chains that are transferred to glutamic acid residues of target proteins. After sensing single-strand DNA damage, PARP catalyzes its auto-PARylation. After dissociation from DNA-damage foci, PARylated PARP1 builds a scaffold to recruit NEMO, PIASy, and ATM, needed for subsequent NEMO sumoylation and NFκB-dependent survival signaling [23]. In addition to

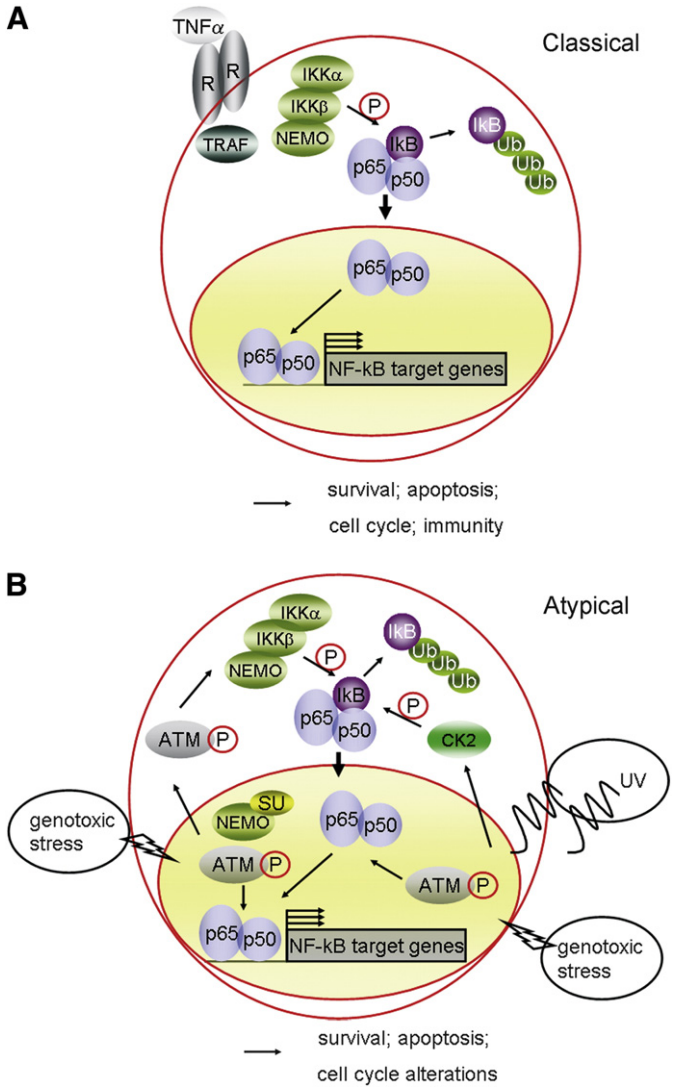

Fig. 1. NFκB signaling pathways. (A) Activating mechanisms for NFκB are well characterized. The classical (or canonical) pathway of NFκB activation involves the I-κB kinase (IKK) complex consisting of catalytic kinase subunits (IKKα and/or IKKβ) and the regulatory non-enzymatic scaffold protein NEMO (also known as IKKγ). Adaptors (such as TRAFs) recruit IKKs, which catalyze phosphorylation of IκBs. This posttranslational modification permits their proteasomal degradation and nuclear translocation of active NFκB transcription factors for induction of their target genes, e.g. for innate immune responses and cellular survival. TNFα is the prototypical inducer of the classical pathway activating NFκB dimers comprising p65 (RelA) and p50. (B) Stimuli evoking atypical NFκB activation are diverse. They can for example comprise DNA damage by genotoxic drugs and radiation, mitochondrial dysfunctions, endoplasmic stress, aging, and replicational arrest. Atypical NFκB activation is initiated from the nucleus, e.g. when genotoxic drugs set DNA dsBs and ssBs. These cause auto-phosphorylation of ATM essential for stress-dependent NFκB activation. Sumoylated NEMO associates with activated ATM. ATM-dependent phosphorylation of NEMO allows its nuclear export which might be associated with activation of the canonical IKK complex. UV light can induce NFκB via casein kinase 2 (CK2) phosphorylating IκB. NFκB activation by atypical inducers can promote anti-apoptotic gene expression antagonizing the success of chemotherapy. P, phosphorylation; Su, sumoylation; UV, ultraviolet light.

the nuclear to cytoplasmic mode of DNA-damage-dependent NFκB activation, a novel nuclear pathway regulated by the IKK-related kinase IKKε was lately demonstrated to contribute to NFκB-mediated survival. Upon treatment of cells with the topoisomerase II inhibitor etoposide, IKKε translocates into promyelocytic leukemia protein-nuclear bodies [24]. These nuclear signaling platforms coordinate DNA-damage responses and posttranslational modifications of various proteins including the tumor suppressor p53. The E3 ligase TOPORS sumoylates IKKε and this ensures its retention in nuclear bodies. Active IKKε executes survival functions by phosphorylating nuclear p65 at S^{468} permitting anti-apoptotic gene expression [24].

Given that chemotherapeutics and radiotherapy activate NFκB-dependent gene expression conferring tumor cell resistance, inhibition of this transcription factor appears as an attractive goal in cancer research [25,26]. Understanding NFκB within the context of other factors, like p53, is necessary to integrate and optimize therapeutic approaches.

3. Characteristics and activation of p53

The p53 protein has been in the focus of research for more than 30 years. It is considered as a first line tumor suppressor regulating cell proliferation, senescence, (re-) differentiation, apoptosis, and metabolism [27,28]. Sophisticated regulatory circuits negatively regulate p53 in non-stressed cells and allow its rapid induction upon exposure to stressors (Fig. 2A).

p53 regulates cell cycle progression and cell death by transcription-dependent and -independent mechanisms. Low levels of stress induce p53 activating genes linked to cell cycle arrest, DNA repair, and senescence. Thus, p53 can promote repair and survival signaling, e.g. via transcriptional induction of the cyclin-dependent kinase inhibitor $p21^{Cip1}$. More intense stress stimuli enhance accumulation of p53 and activation of pro-apoptotic genes like *PUMA, NOXA* and *BAX*. These unleash caspases, which dismantle critical cellular proteins including those previously induced to permit repair and arrest. Consequently, damaged and potentially harmful cells can be eliminated [29–33] (Fig. 2B). Inactivation of anti-apoptotic mitochondrial BCL proteins by p53, control of autophagocytosis, regulation of miRNAs and the control of metabolic activity and kinase-dependent signaling are additional routes by which p53 affects cell fate decisions [34–37].

The p53 protein harbors seven functional domains and a fairly large set of enzymes catalyzes its posttranslational modifications [38,39]. These are phosphorylation, acetylation, methylation, glycosylation and the transfer of ubiquitin, SUMO, and NEDD (Fig. 2C). Each of these modifications can determine the stability and activity of p53 and the number of p53 regulators identified increases constantly. For example, dependent on the cell type and condition, several ubiquitin-ligases, COP1, PIRH2, TRIM24, β-TrCP, and HDM2/MDM2, target p53 for proteasomal degradation. These enzymes are functionally interconnected with each other and occur within ubiquitinylating complexes receiving input from numerous signaling pathways [40–44]. Likewise, a large set of serine/threonine kinases and lysine acetyltransferases, which are regulated by cell cycle progression, growth hormones and cytokines, direct phosphorylation and acetylation of p53 at different sites [45,46]. In addition, the *p53* gene has several promoters and codes for different isoforms created by alternative splicing and translation initiation sites [47]. The p53 homologues p63 and p73 share this configuration at the gene and protein level. Nonetheless, this protein family exerts a multitude of agonistic and antagonistic functions creating multifaceted regulatory modules and networks [48–51].

Abolishing p53 functions accelerates oncogenic cascades at several levels. Genetic or structural inactivation of this protein occurs in over half of all human cancers [52]. Common p53 mutants carry “hot spot mutations.” These are e.g. the conformational mutants $p53^{R172H}$ (*Mus musculus*)/$p53^{R175H}$ (*Homo sapiens*) ($p53^{R175H}$ is the Li–Fraumeni syndrome mutation of p53) and the DNA-contact mutants $p53^{R270H}$/$p53^{R273H}$. Either of these mutations is located within the DBD. Tumor-associated mutations in the TAD ($p53^{SA}$/$p53^{LWQS}$), PRD ($p53^{TA}$/$p53^{\Delta P}$), and CTD ($p53^{KR}$/$p53^{SA}$) are also found frequently [38]. As a result, p53 mutants often lack the ability to bind DNA sequences recognized by the wild type protein or have lost transcriptional activation capacity. Nevertheless, they functionally and physically interact with cancer-relevant transcription factors, including wild type p53 and NFκB [53–56]. Such p53 mutants are hence able to affect signaling and chromatin modifications relevant for tumor maintenance, genetic instability, metastasis, immunological control, and chemotherapy

resistance [57–59]. Compared to a loss of p53, mutant p53 even correlates with more aggressive tumor phenotypes and worse prognosis [28,60,61]. It should though be noted that biochemically different p53 mutants can be distinct functional units [54]. Biological outcomes of p53 mutation(s) may furthermore be dictated by the combination of mutant molecules and the levels of wild type p53. For example, co-expression of $p53^{V274F}$/$p53^{P223L}$ alters p53 activity and promotes prostate cancer cell proliferation and resistance against FAS [62]. Another mutant, $p53^{R175H}$, is structurally defective and confers pro-survival NFκB activation in several cancer cell types [55,56]. These data prove that interactions of p53 with other (transcription) factors form additional layers controlling p53-dependent processes. Disturbances in such pathways might be a reason why mutations of p53 sometimes aggravate oncogenesis more than the loss of p53, e.g. from the perspective of stress responses (Fig. 2B). Below, we summarize examples of the functional interplay between p53 and NFκB in particular contexts.

4. Crosstalk scenarios

Nuclear crosstalk between two transcription factors can occur at several levels. We would like to summarize and propose a matrix for models concerning transcriptional crosstalk phenomena. Therefore, transcription factor 1 and transcription factor 2 in Fig. 3 represent examples, e.g. NFκB and p53. An indirect model explains crosstalk between transcription factors by induction of gene products. These could be receptors, cytosolic factors, or further DNA binding proteins (Fig. 3A). The exclusion model relies on one factor preventing binding of the other to target DNA. Transcription factor 2 could for example replace transcription factor 1 and shut down transcription (e.g. via recruitment of negative regulators) (Fig. 3B). Transcription factors can compete not only for space on chromatin, but also for cofactors. Depending on the levels, stability, localization, and posttranslational modifications these can recruit activators, and potentially also repressors from the other factor (Fig. 3C).

Activation *in trans* could be exerted by co-recruitment of positive transcriptional regulators by two transcription factors. Accordingly, *trans*-repression can be carried out via recruitment of repressors. *Cis*-activation relies on positive signals recruited by a transcription factor on chromatin. These can affect the other transcription factor directly or by altering the conformation of chromatin. Accordingly, suppressive effects in *cis* involve recruitment of transcriptional repressors creating an overall negative effect (Fig. 3D).

The model termed clearance builds on the removal of deposited, inactive forms of a transcription factor. This complex re-set model e.g. suggests that a receptor activates two transcription factors and that induction of one of them removes inactive forms of the other from chromatin. Upon cognate stimulation, e.g. by a ligand-bound receptor, active transcription factors proceed to DNA and promote gene expression. This may involve posttranslational modifications, which can also be generated from within the cell. For productive transcriptional induction by both proteins, this model requires a delay in the activation of transcription factor 1 versus transcription factor 2. This could for example be achieved with receptor-mediated activation of one protein and time-delayed induction of the other in the nucleus. Chromatin cleared can then set for re-activation or can be target for further transcription factors entering from the cytosol. Such processes might create persistent target gene expression (Fig. 3E).

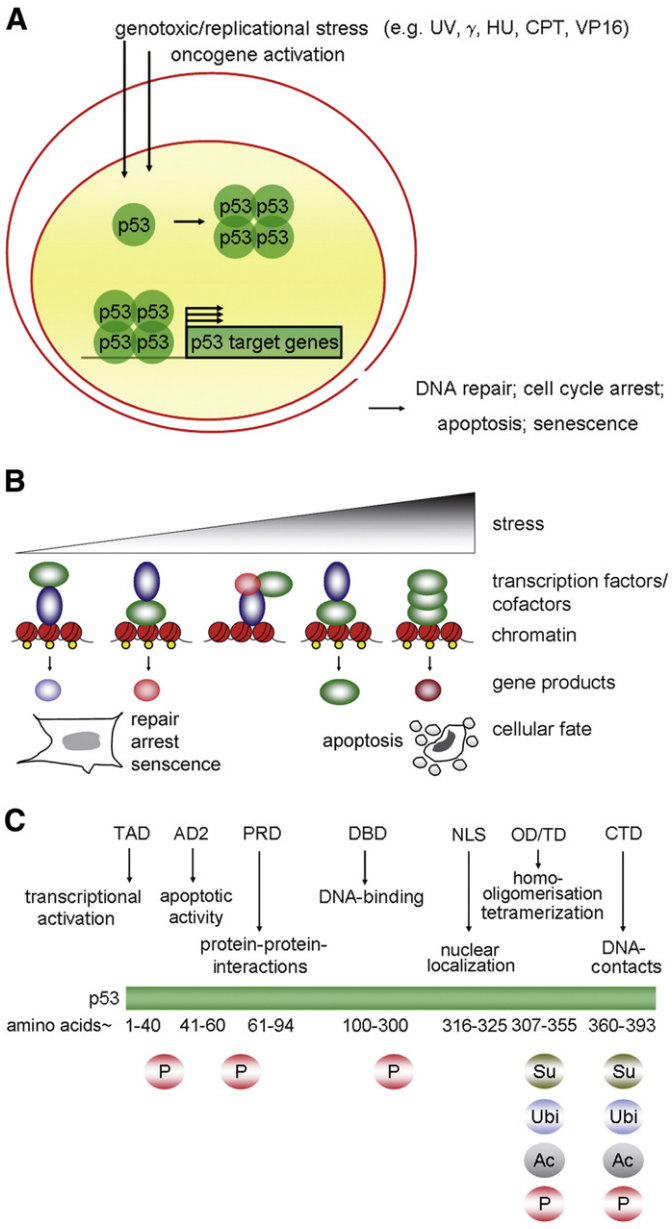

Fig. 2. p53 signaling pathways and p53 structure. (A) The tumor suppressor p53 is activated by stimuli endangering the integrity of the genome and by oncogenes. Thus, p53 serves as a first line barrier against tumorigenesis. Tetramers of p53 bind target gene DNA. While low levels of p53 promote gene expression for survival and repair, higher levels induce pro-apoptotic genes. The efficacy of a lot of chemotherapies relies on p53 induction. UV, ultraviolet light; γ, gamma-irradiation; HU, hydroxyurea; CPT, camptothecin; VP16, etoposide. (B) As p53 is a central modulator of cellular life/dead decisions, it is not surprising that a very complex network controls and fine-tunes its functions tightly. The amplitude and persistence of stress stimuli determine accumulation of p53, with more intense stressors switching from arrest, repair, and survival signaling to pro-apoptotic gene expression patterns. The dose-dependent phenomenon characterized by low dose-induced prevention and regeneration on the one hand and damage caused by high doses on the other hand has been termed "hormesis." Changes of chromatin mediate such processes and crosstalk phenomena also dictate ON/OFF states ruling cellular survival or death. Active chromatin is marked with yellow dots representing positive transcriptional marks. Green, red, blue ovals are transcription factors or cofactors, which can be gene products of the stress response, e.g. the reduction oval. See text for details. (**C**) Human p53 is 393 amino acids long and falls into seven domains: The N-terminal transcription-activation domain (TAD), also known as activation domain 1 (AD1), which activates transcription; activation domain 2 (AD2) and proline rich domain (PRD) are important for apoptotic activities of p53. PRD furthermore is the surface for p53 interactions with other proteins. The DNA-binding domain (DBD) spans a large part of p53, which contains numerous arginine residues and binds one zinc atom. Several oncogenic hot-spot mutations, e.g. $p53^{R175H}$, locate within this domain. A nuclear localization signal (NLS) precedes the homo-oligomerization/-tetramerization domain (OD/TD), which is crucial for the activity of p53 in vivo. The C-terminal domain (CTD) attenuates DNA binding of the central domain to target gene DNA. Murine p53 has 390 amino acids and shares the structural and functional organization with human p53. Posttranslational modifications critically regulate the functions of p53. Phosphorylation (P) of p53 occurs at several serine and threonine residues. Acetylation (Ac), ubiquitinylation (Ubi), and sumoylation (Su) of lysines are mainly found in the C-terminal part of this protein. For example, acetylation of several C-terminal lysine moieties in the CTD is catalyzed by p300/CBP/PCAF. These are recruited through phosphorylation of distant serine residues in the NTD.

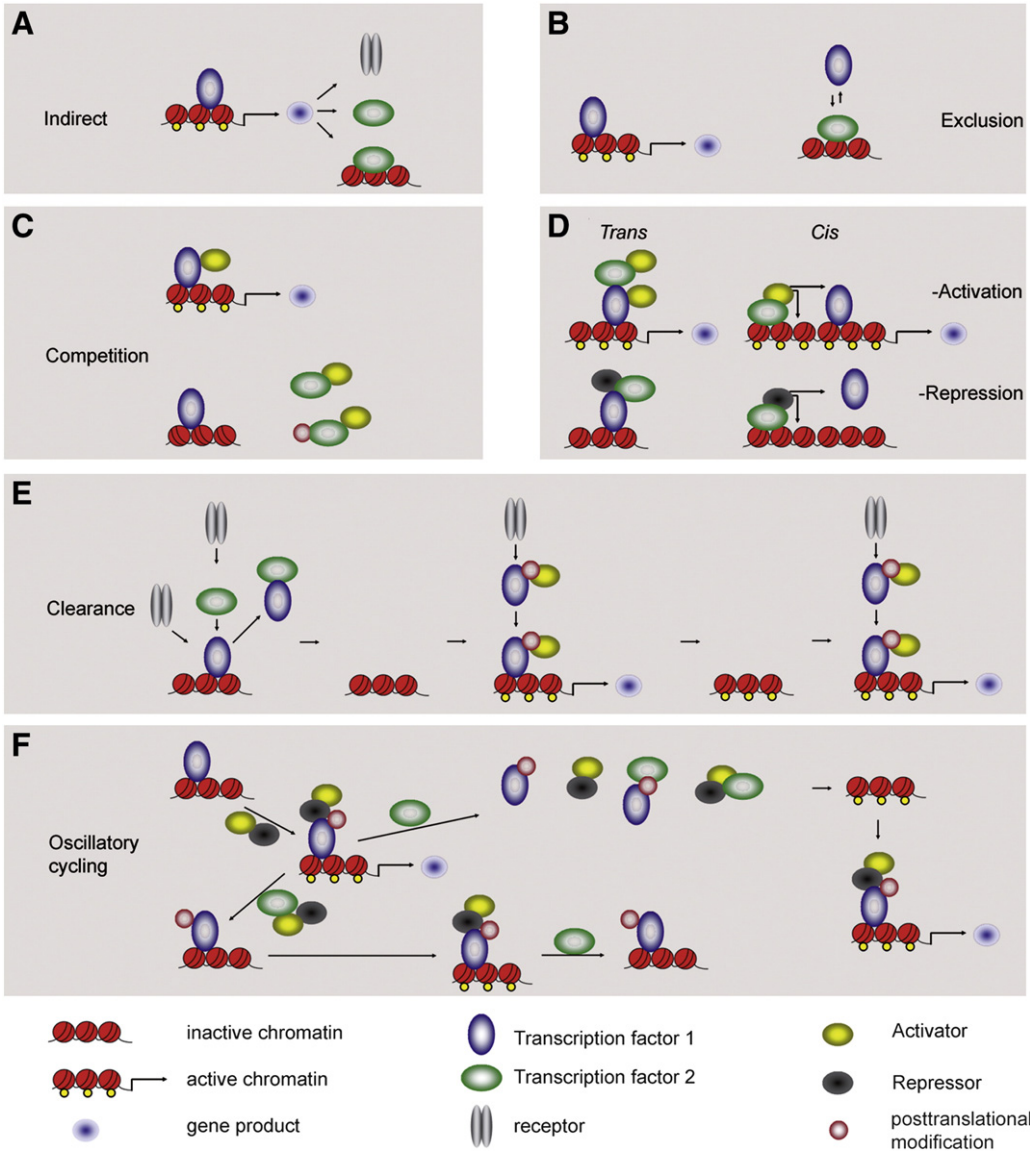

Fig. 3. Proposed models for nuclear NFκB/p53 crosstalk. Active chromatin is marked with yellow dots representing positive transcriptional marks. See text for details. (A) Indirect model (B) Exclusion model (C) Competition model (D) Activation *in trans* or *cis* and *cis* or *trans*-repression (E) Clearance model and (F) Oscillatory model.

The oscillatory model argues further for permanent but transitory states. This model involves dynamic changes which require timed antagonistic activities, e.g. of HATs and HDACs, kinases and phosphatases. A second transcription factor could promote such exchanges leading to a continuous clearing and loading of chromatin. The upper row shows a rather complete reset of transcriptional complexes. The lower one considers that e.g. the activated transcription factor might persist. In both scenarios cofactors cycle constantly and antagonistic enzymatic activities maintain fully processive rounds of oscillatory cycling (Fig. 3F). Such rather complex networks have already been found for signaling via the estrogen receptor and STAT proteins. In addition to alterations at the chromatin level, non-histone protein modifications are involved in these processes [46,63–69].

5. Processes regulated by the crosstalk between NFκB and p53

5.1. Cell cycle progression and apoptosis

The intricate regulation of cell survival or death is critical for normal and transformed cells. One cannot simply place p53 and NFκB family members into pro- or anti-survival categories. Instead, the molecular mechanisms of their interactions are complex and still to be elucidated fully. Identifying critical points where NFκB and p53 form functional units, up- and down-stream of each other, can be a critical step broadening our understanding of cancer biology.

A very surprising initial report on the interplay between p53 and NFκB reveals that, despite of its role as a tumor suppressor, NFκB becomes activated upon (re-)activation of p53. Even more so, p53-induced apoptosis requires NFκB. This mechanism of NFκB activation does not resemble TNFα-induced NFκB signaling, but is linked to activated MEK1 and RSK p90 serine/threonine kinases [70]. Agents causing double-strand DNA breaks also induce RSK-dependent phosphorylation of nuclear p65, which lowers its affinity for IκBα. Consequently, the binding of NFκB to its cognate enhancers and NFκB activity increase [71]. Similar data are found with a dominant-positive p53 variant in glioma cells [72]. Thus, NFκB activation can be associated with apoptosis in cells with (hyper)active p53.

These findings argue that NFκB signaling linked to p53 can be a nuclear process and independent of cytosolic IκB degradation. Nevertheless, nuclear IκB can also be ubiquitinylated and processed, with p53 catalyzing this process [73]. In addition, replicational stress and DNA damage signaling evoke nuclear translocation of NFκB

subunits [56,74], and functionally relevant degradation of IκBα upon DNA damage signaling has been reported [22,75].

Possible explanations for anti-survival NFκB signaling might be that NFκB is necessary to induce accumulation of the pro-apoptotic BH3-only proteins PUMA (p53 upregulated modulator of apoptosis), NOXA, and p53-AIP1 [76,77]. For example, TNFα-mediated upregulation of the p53 target gene *PUMA* at mRNA and protein levels depends on NFκB p65. Apoptosis of small intestinal epithelial cells, hepatocytes, and thymocytes, was consequently attenuated in *PUMA*-deficient mice treated with this cytokine [77]. TNFα stimulation of colon cancer cell lines carrying $p53^{R273H}$ (HT-29) also enhanced nuclear p53 levels and increased *PUMA* mRNA levels [78]. As this DNA-binding defective p53 mutant is recruited to this promoter via p65, it has retained or acquired an indirect ability to bind the *PUMA* promoter. Curiously, IL1β and IFNγ induce PUMA in pancreatic β-cells via NFκB but independent of p53 [79]. Also surprising is the finding that p53-dependent induction of the NOXA protein is blocked by a super-inhibitor of IκBα although the mechanism responsible is independent of *NOXA* transcription. This finding suggests involvement of so far unknown pathways [76]. Such data argue that our view on p53 and NFκB target genes requires a novel definition.

Independent of the exact mechanisms, loss of NFκB p65 can confer resistance against stimuli that signal death through p53 activation. In contrast to a lack of p53, loss of p65 still cannot induce anchorage-independent growth or oncogene-induced tumorigenesis. Hence, p53 restricts tumor development by p65-dependent and -independent mechanisms [80]. Mouse embryonic fibroblasts (MEFs) from different p65 knockouts are morphologically heterogeneous with transformation linked to alterations in the p53 pathway. The fact that v-RAS^{+}/$p65^{-}$ cells formed fewer colonies than control MEFs and kept high sensitivity to TNFα-induced apoptosis hints that p65 suppresses or restrains tumorigenesis depending on individual circumstances [81].

Albeit these findings argue for certain anti-tumor properties of NFκB, one has to keep in mind that p53 suppresses anti-apoptotic oncogenic NFκB in resting cells [56,82,83]. Dysregulation of this control mechanism can well be linked to cellular survival, e.g. as resistance towards chemotherapeutics or as adaptation to stresses. In particular, the $p53^{R172H}$ (corresponding to human $p53^{R175H}$) mutant evokes strong NFκB signaling and protects murine pancreatic cells from apoptosis. [56]. These data are in agreement with a recent publication demonstrating that mutant p53 augments TNFα-induced NFκB activity and protects tumor cells from TNFα -induced apoptosis [55]. Therefore, p53 mutation rather than its loss can provide NFκB-dependent survival advantages to tumor cells of various origins.

Interestingly, a common feature of mutant p53-dependent gene signatures is an enrichment of genes associated with proliferation [53]. Since NFκB is linked to the regulation of cell cycle genes, it is interesting to investigate whether mutant p53 drives proliferation via p53/p65 complexes. In fact, mutant p53/NFκB cross signaling drives cell cycle progression indirectly, via activation of the mitogen-activated protein kinase-kinase 3 (MAP2K3, upstream activator of the p38 MAPK). Here, it was demonstrated that mutant p53 binds together with NFκB and NF-Y to the *MAP2K3* promoter and activates transcription of the gene. Furthermore, the *MAP2K3* gene was shown to mediate proliferative functions of mutant p53 [84]. It has furthermore been found that p53 null lung cancer cells acquire a growth-advantage by producing soluble factors suppressing p53 in adjacent stromal cells [85].

Replicational stress, e.g. G1/S-phase arrest induced by dNTP depletion, also activates NFκB p65 and triggers its interaction with nuclear p53 [56]. Whereas ATM and CHK1 signaling and cytosolic activation of NFκB p65/p50 are intact in p53 null cells, formation of a transcriptionally active complex requires nuclear p65 as well as p53. These findings, which were collected in diverse solid tumor cell lines and MEFs, argue for p53 being a licensing factor for NFκB target gene activation in cells arrested in S-phase. Since functionally important interactions of p53 and p65 also occurs after stimulation with the pro-inflammatory cytokine TNFα, the p53 licensing function equally operates upon canonical NFκB activation (Fig. 4). We speculate that this represents a cancer-protective mechanism facilitating elimination of p53 null cells. In agreement with this idea, a recent *in vivo* study assessing K-RAS driven lung tumorigenesis disclosed that NFκB suppression results in apoptosis of p53 null cancers [86]. It is moreover possible that p53/NFκB interactions operate during normal S-phase and meiosis. Furthermore, structurally mutant p53 reverts checking functions of wild type p53 on NFκB as it promotes anti-apoptotic gene expression patterns [55,56].

5.2. Metastasis

Metastasis is a fatal late-stage condition of cancer. This highly organ-specific process requires multiple steps and interactions between cancer cells and the host [87,88]. One mechanism of metastasis formation is the change from highly differentiated epithelial cell morphology to a mesenchymal phenotype. Epithelial-mesenchymal transition (EMT) involves alterations in gene expression patterns, e.g. a loss of E-cadherin and cytokeratins and an induction of N-cadherin, Vimentin, Fibronectin, metalloproteases, and SNAIL [89]. During EMT, cancer cells acquire migratory capacity and invasiveness [90]. Identifying signaling pathways and the origin of pathologically transformed mesenchymal cells can give insights into valuable therapeutic interventions potentially targeting metastasis formation at early stages. Since wild type and mutant p53 as well as

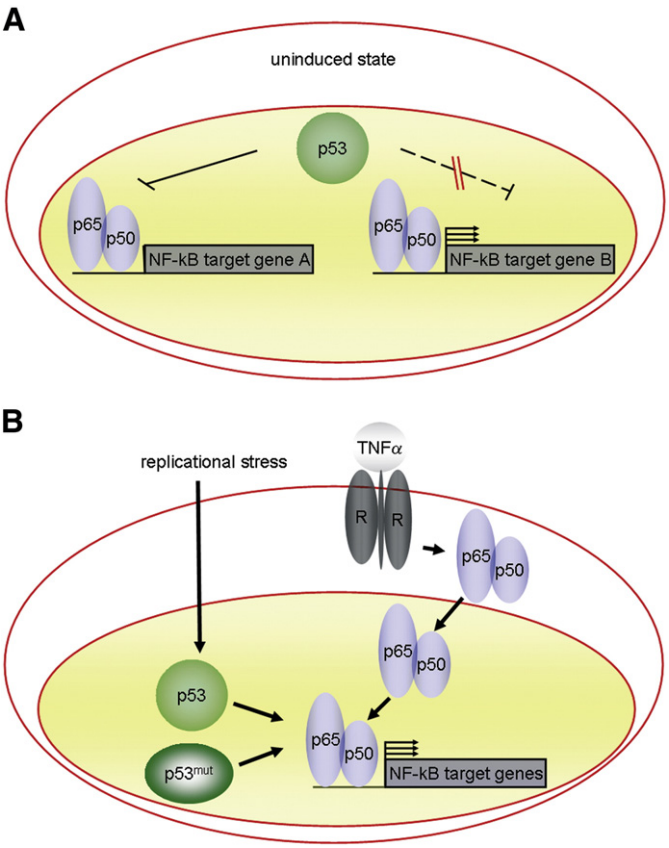

Fig. 4. Interactions between NFκB, wild type p53 and oncogenic p53. (A) In resting cells, p53 can repress NFκB target gene transcription. Certain NFκB target genes are though regulated independent of p53. (B) Fresh evidence suggests that p53 is necessary for the expression of NFκB targets upon replicational stress or cytokine stimulation. Mutant p53 variants, potent oncogenes, activate NFκB independent of external stimuli. This promotes anti-apoptotic gene expression. R, TNFα receptor; $p53^{mut}$, oncogenic mutant p53.

NFκB orchestrate gene expression associated with metastasis, they could be critical targets for such strategies [91,92].

Crosstalk between p53 and NFκB is associated with EMT [59]. For example, expression of wild type p53 in human soft tissue sarcoma cells and xenografts bearing mutant p53 decreased matrix metalloproteinase-9 (MMP-9) levels required for invasiveness. Of note, this cancer is highly lethal with metastasis determining survival. Interestingly, the effect of p53 on MMP-9 expression strictly depended on a κB binding site in the MMP-9 promoter, which indicates effects of p53 on transcriptionally active NFκB [93]. Additional metastasis regulators are regulated by p53 and NFκB. The tumor suppressor KAI1/CD82 is a target gene of p53 and NFκB. Mutant $p53^{R248Q}$ though cannot impair TNFα-mediated activation of KAI1/CD82 in lung cancer cells [94,95]. In contrast, $p53^{R273H}$ expression promotes cellular invasion and migration of endometrial cancer cells via dominant-negative effects on p53. This mutant p53 represses expression of the metastasis suppressors KAI1 and maspin, and the senescence regulator PAI1 [96].

Critical functions of mutant p53 also occur at the level of signaling initiated by a membrane-bound receptor tyrosine kinase involved in oncogenesis. Mutant p53 stimulates metastatic patterns via constitutive activation of epidermal growth factor receptor (EGFR) and integrin α5/β1-signaling in various cell lines, mice, and primary tumors [60]. Mechanistically this relies on enhanced RAB-coupling protein (RCP)-dependent trafficking and recycling of these factors, with mutant p53 promoting interaction of α5/β1 and RAB indirectly. Activation of the serine/threonine kinase AKT by mutated p53 in cultured cells and human colorectal cancers proves EGFR (hyper) activation. Moreover, TGF-β-independent binding of $p53^{R175H}$ and $p53^{R273H}$ to p63 inactivates this transcription factor and promotes invasive migratory phenotypes [60].

Of note, certain breast cancers overexpressing EGFR demonstrate highly active NFκB. As both factors contribute to transformation of ER-negative human mammary epithelial cells [97], it will be interesting to determine how p53 is tied into this sequela. Other studies likewise report that $p53^{R175H}$ expression correlates with cell migration, invasive capacities, and EGFR/AKT activation, for example in endometrial cancer cells [98]. In prostate adenocarcinoma cells carrying intact wild type p53, p53 mutants (V143A; R175H; R249S; R273H) enhance expression of EGR1 (early growth response 1) at the mRNA and protein levels. EGR1 increases the expression of stimulatory EGFR ligands (HB-EGF), cytokines promoting angiogenesis (PDGF-A), TGFβ, and EGFR levels [99]. Secretion of such factors might hence impose p53 mutant properties to p53 positive cells *in vivo*. Senescence due to EGFR overexpression is equally suppressed by $p53^{R175H}$ and by temperature-induced inactivation of $p53^{V143A}$. This finding, which was collected in telomerase-immortalized human esophageal cells, suggests that a loss of p53 functionality, but not EGFR signaling *per se*, expands a subpopulation of aberrantly regulated cells. A critical role for p53 in this system is further stressed by the finding that p53 controls *p21* and the zinc finger E-box binding transcription factors *ZEB1*/*ZEB2*. These proteins belong to a senescence checkpoint counteracting EMT [100].

5.3. Immune surveillance

NFκB proteins regulate the differentiation, survival, and proliferation of immune cells. Accordingly, inflammatory cytokines and mediators, toxins, viruses, bacteria, and irradiation trigger beneficial NFκB during acute host responses. However, persistent NFκB signaling causes detrimental chronic inflammation, which is linked to genetic instability and carcinogenesis. Other key transcription factors for inflammation are e.g. STAT1 and STAT3. As for NFκB, a plethora of reports links their pro- and anti-apoptotic properties to p53 at multiple stages of immune responses [101–104].

Another aspect to be considered is that NFκB p53-dependently induces the FAS/FAS-ligand (FASL) system for immunological tumor surveillance [22,56]. Expression of this molecule can induce apoptosis of immune cells [105]. On the other hand, a lack of FASL expression in p53-negative cells could promote their elimination via immunologic surveillance. Neighboring p53-proficient cells could promote this by secreting the NFκB induced Interleukin-8 [56], a chemokine attracting immune cells. These examples show that p53 suppresses cancer via cell-autonomous as well as non-cell-autonomous activities.

Cells expressing p53 not only protect themselves by FASL secretion. Upon exposure to TNFα or stress, they induce the NFκB target gene MnSOD, an enzyme balancing ROS signaling [56,106]. Such complex interactions between p53 and NFκB likely are relevant for tumorigenesis associated with chronic inflammation and tissue damage [107–109]. The situation though seems complicated, as p65- and p53-dependent transcriptional activation of the *MnSOD* gene depends on the intensity of stress encountered. Tansfection of low concentrations of p53 into p53 null prostate carcinoma cells increases, whereas high amounts suppress MnSOD levels. At the level of the *MnSOD* promoter, p53 binding does not affect its activity. Instead, the presence of an intronic-enhancer element harboring NFκB binding sites is necessary for positive effects of p53 on MnSOD expression [110]. The presence of NFκB at different genomic sites can therefore rule p53-NFκB crosstalks. Whether or not p53 and p65 interact and/or compete at such sites remains to be proven formally.

Above we summarized that DNA single (ssBs) and double (dsBs) strand breaks signal to p53 and NFκB. Similar lesions occur during T- and B-cell receptor recombination, normal S-phase and meiosis. Proper maturation of immunocompetent cells may hence be subject to control by p53/NFκB modules. Furthermore, the immune system serves as a barrier for neoplastic transformation and p53 contributes to the communication between cancer and immune cells [111]. Tumors carrying mutant p53 isoforms can e.g. protect themselves from attacks by the immune system via anti-apoptotic NFκB target gene induction [55,56,110]. Moreover, paracrine and autocrine stimuli secreted by cells with activated NFκB influence immunological reactions associated with inflammatory conditions ultimately leading to tumorigenesis. Cancer cells furthermore activate and signal reciprocally with infiltrating white blood cells, adjacent fibroblasts, the endothelial cell wall, and the extracellular matrix [112,113]. Therefore, targeting p53-NFκB modules might be a valuable strategy for therapies aiming at the tumor stroma and its dialog with the cellular environment.

5.4. Metabolic control

Tumor cells often prefer glycolysis and therefore generate ATP by metabolizing glucose to lactate. In contrast, oxidative phosphorylation occurs in normal tissues under conditions of sufficient oxygen supply. This observation was first described by Otto Warburg in the last century [114]. Recent work demonstrates that both, p53 and NFκB regulate metabolism in opposite manners, with p53 favoring oxidative phosphorylation and NFκB enhancing aerobic glycolysis [115]. p53 slows uptake of glucose by repressing the glucose transporters *GLUT1* and *GLUT4* [116], inhibits glycolysis by induction of the *TIGAR* (TP53-induced glycolysis and apoptosis regulator) gene [117], and favors oxidative phosphorylation by the *synthesis of cytochrome c oxidase 2* gene encoding an important regulator of the cytochrome c oxidase complex [118]. Furthermore, loss of p53 promotes glycolysis dependent on p65, as p65 transcriptionally activates the *GLUT3* gene [119]. High cellular glucose shunts through the hexosamine biosynthetic pathway to produce uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), the active substrate for *O*-GlcNAcylation (O-linked-N-acetylglucosamine, O-GlcNAc). Mechanistically, p53 deficiency permits *O*-GlcNAcylation of IKKβ on the inhibitory phosphorylation site S^{733} and increased activity of the enzyme [120].

Although these data provide functional insights into the crosstalk of p53 with NFκB at the level of metabolism, we may learn more about the therapeutic potential. For example, what are the roles of p53 and

p65 upon the treatment of cells with inhibitors of glycolysis? Is deletion of p65 in tumor cells reversing the Warburg effect? Furthermore, is the enzyme mediating *O*-GlcNAcylation, the O-GlcNAc transferase (OGT), therapeutically relevant and what are functions of p53 and p65 upon OGT inhibition?

Considering that p53 is more often mutated than deleted in tumors we also have to carefully consider mutual interactions of $p53^{mut}$ and p65 with respect to metabolism. Interestingly, $p53^{R175H}$ synergizes with oncogenic RAS to accelerate glycolysis and to induce GLUT3 p65-dependently [119]. Bearing in mind complex formation of $p53^{R172H}$ with p65 in solution and on DNA [56], it is essential to investigate effects of this complex for metabolism. Deciphering the signaling pathways needed to build the complex should define novel targets for intervention with $p53^{mut}$/p65 cross signaling.

6. Modulators of NFκB/p53 cross-signaling

6.1. Proteins regulating the p53/NFκB crosstalk

Collaborations between NFκB and p53 govern stress- and inflammation-induced cancer and therapeutic resistance [55,56,70,71,82,110]. Which factors regulate their interactions?

A protein regulating both p53 and p65 is e.g. the tumor suppressor ARF. The *ARF* gene (alternate reading frame INK4a) encodes p14 (*Homo sapiens*) or p19 (*Mus musculus*). These proteins inhibit HDM2/MDM2, which augments p53 stability and suppress cell proliferation driven by the transcription factor E2F1 [43]. The p53 protein suppresses *ARF* transcription to maintain low levels of p53 in unstressed cells. Oncogene activation triggers anti-apoptotic NFκB p65 activity and ARF, which induces the checkpoint kinases ATR and CHK1. CHK1 phosphorylates p65 at threonine T^{505} and this modification inactivates its TAD. Since ATR induces and activates p53, ARF integrates p65 and p53 functions [121]. Furthermore, this kinase causes partial suppression of NFκB induced by DNA breaks. ATR interacts with NEMO and disrupts its phosphorylation by ATM in cells with intact p53 signaling. Curiously, the established chemotherapeutic drug etoposide causes overall anti-apoptotic NFκB-dependent gene expression, whereas another clinically relevant anti-cancer agent, hydroxyurea (HU), evokes pro-apoptotic gene expression [22]. Solving this issue further could explain why ATM-specific inhibition accentuates cytotoxicity evoked by chemotherapeutics inducing atypical NFκB signals [122]. Experiments carried out with myeloblasts from myelodysplastic syndrome or acute myeloid leukemia (AML) patients already propose that pharmacological inhibition of ATM causally inhibits p65 and induces apoptosis [123]. The interesting question remains whether blocking ATM abrogates NFκB signaling dependent or independent of p53.

A murine model of spontaneous melanoma, driven by $H\text{-}RAS^{V12}$ and a lack of ARF revealed that IKKβ also integrates p53 and NFκB. In this system, IKKβ impairs p53 expression and supports melanoma development. Genetic depletion accordingly unleashes p53 expression. Stabilized p53 carrying p-S^{15} decreases BCL2 and Survivin evokes apoptosis as well as cell cycle arrest, and attenuates cyclin-dependent and aurora kinases. Apparently, IKKβ is central for NFκB activity and equally for keeping p53 low during oncogene-induced melanocyte transformation [83].

Regulatory processes can also operate at the level of transcription factors beyond NFκB and p53. For example, NFκB and STAT3 cooperatively regulate genes implicated in survival and proliferation, mostly via transcriptional cooperation or via induction of cytokines releasing the other transcription factor from latency. Accordingly, NFκB and STAT3 agonistically promote the development and progression of colon, gastric, and liver cancers [113]. The crosstalk between STAT3 and NFκB therefore represents an attractive chemotherapeutic target. Since p53 and STAT3 affect each other antagonistically [124–126], activating p53 might reach this goal. This strategy could as well complement approaches targeting pro-inflammatory IKK-dependent NFκB, for STAT3 delays NFκB nuclear export in tumors and associated immune cells [127].

Contrary to wild type p53, mutant $p53^{G199V}$ promotes expression of STAT3 in anaplastic thyroid cancer cells [128]. In head and neck squamous cell carcinomas (HNSCC), decreased p53 expression enhances cytokine-induced activation of NFκB, STAT3, and induces higher expression of their target gene *BCL-XL* and low levels of *BAX*. Such observations further support inhibition of NFκB and STAT3 together with restoration of p53 functions [126].

6.2. Pharmacological and physiological stimuli

Restoring wild type p53 leading to transcription-dependent and -independent control of tumor growth by this protein is clearly desired. Do we have drugs available that restore pro-apoptotic functions of p53 and NFκB and on the other hand inhibit their cancer cell-protective properties? We would like to summarize some agents that target both factors (Fig. 5A) and which are promising for clinical

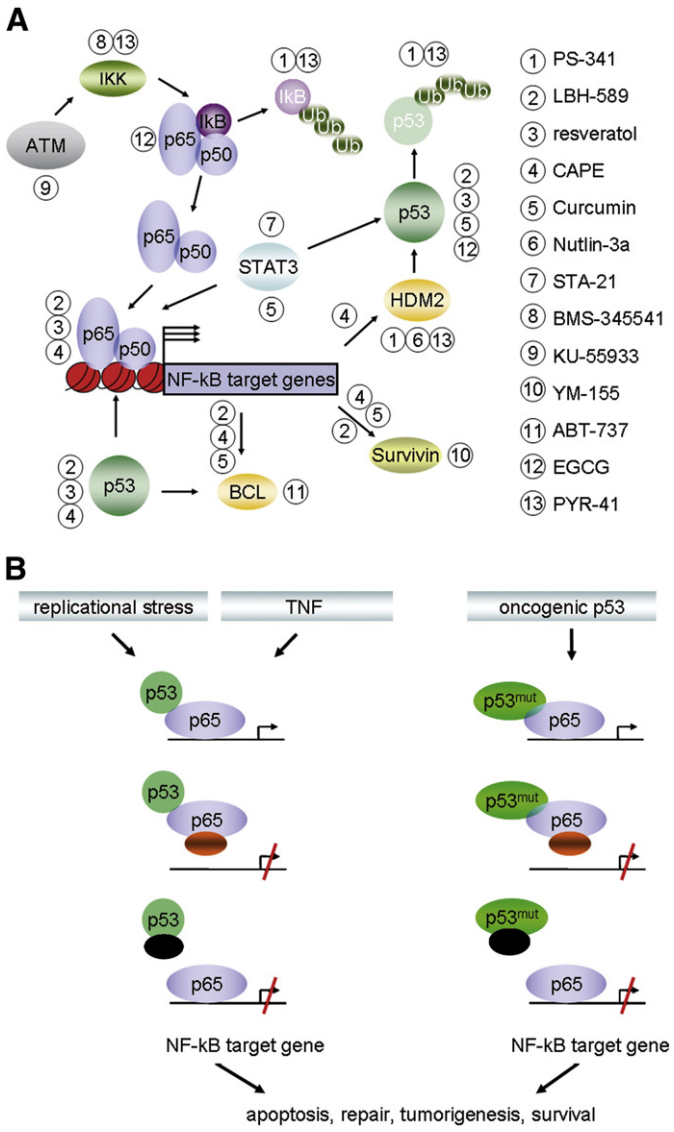

Fig. 5. (Bi)targeting aberrant NFκB and mutant p53 in cancer. (A) NFκB, p53, their target genes, and regulators are structures for anti-cancer drug development. Shown are examples for agents currently used or tested in the clinic. (B) The interaction between p53 and NFκB, especially with mutant p53 ($p53^{mut}$), is linked to anti-apoptotic NFκB target gene expression. Blocking this crosstalk could be a valid therapeutic option for tumors with aberrant NFκB signaling mediated by oncogenic p53 (red sphere: agent blocking p65 DBD; black sphere: agent blocking p65–p53 interaction surfaces).

use. Optimal characteristics of such compounds are inhibition of anti-apoptotic NFκB survival signaling and (re-)activation of p53. Both can eliminate transformed and malignant cells [52,129].

The NFκB and p53 signaling pathways are regulated in a different manner by the proteasome. Whereas HDM2 and other E3 ubiquitin-ligases induce proteasomal degradation of p53, degradation of IκB proteins is a pre-requisite for NFκB activation. Nutlins specifically block interactions between HDM2/MDM2 and p53 allowing its accumulation inhibiting NFκB. Simultaneous suppression of basal and induced NFκB by this strategy promoted tumor cell death and suppressed metastasis-associated gene expression in lung and pancreatic cancers [130,131]. For example, Nutlin-3 attenuates NFκB-mediated *ICAM-1* and *MCP-1* expression linked to cancer cell invasion and metastasis [130]. Of note, derivatives and analogs of the HDM2 inhibitors MI-219 and Nutlin-3 have already entered clinical trials [132].

Anti-oxidative polyphenols such as theaflavins (TF) and derivatives thereof are formed during the enzymatic oxidation of tea leaves. In breast cancer cells, TF inhibit NFκB-mediated cell migration, putatively by attenuating expression of the metastatic proteins metalloproteinase (MMP)-2 and MMP-9. This inhibitory effect on NFκB requires p53-phosphorylation via p38 MAP-kinase and the formation of reactive oxygen species (ROS), i.e. inhibition of NFκB via a p38–p53–ROS crosstalk is a pre-requisite for theaflavins to accomplish the anti-migratory effect in breast cancer cells [133].

Other small molecule compounds, CP-31398, PRIMA-1, the cytotoxic plant alkaloid ellipticine, and its derivative NSC-176327 correct certain mutants of p53 towards the p53 wild type conformation. Ellipticine can for example restore activation of p53-responsive genes by nine different p53 mutants (e.g. $p53^{R175H}$) in cultured tumor cells and xenografts. Such properties permit selective elimination of tumors expressing mutant p53 [134,135]. Reconstituting p53 function is hence feasible for certain mutants [136]. The fact that cancers with mutant p53 might be targeted with therapies directed against EGFR and integrin signaling [60] furthermore opens a new avenue for (co-) targeting approaches.

Several agents correcting proteasomal dysfunctions are currently tested in clinical trials [40–44,137,138]. Bortezomib (PS-341) is the first proteasome inhibitor approved for the therapy of multiple myeloma [139]. These agents and other proteasomal inhibitors, e.g. S-2209, lactacystin, and MG-132, suppress NFκB DNA binding and target gene expression by stabilizing IκBs [73,140]. In addition, such compounds enhance p53 levels, alter the corepressor/coactivator balance in the cell, and disturb cell cycle regulation [141,142]. Interestingly, proteasomal inhibitors were also found to kill tumor cells devoid of p53 [143]. This observation is promising regarding the insufficient p53 pathways in most tumors and the unleashed NFκB activation in p53-negative cells [56,82]. An inhibitor acting at the most apical step of ubiquitinylation targets ubiquitin-activating enzyme (E1), which transfers activated ubiquitin to E2 ubiquitin-conjugases. PYR-41 is the first such agent identified. This compound blocks ubiquitinylation and cytokine-induced NFκB, probably via impaired ubiquitinylation of IκBα due to inhibition of the TRAF6-IKK module. Remarkably, induction of p53 and its target genes by PYR-41 correlates with the successful elimination of tumor-derived cells [144].

NFκB protects cells from lethal effects of TNFα, which limit usage of this cytokine in clinical settings. Optimized chemotherapy might rely on preservation of pro- and inhibition of anti-apoptotic NFκB functions. Inhibitors of histone deacetylases (HDACI; e.g. LBH-589; SAHA; VPA) can activate genes by loosening tight chromatin structures formed by hypoacetylated histones and DNA. However, certain genes are repressed by hyperacetylation. The induction of non-histone protein acetylation together with secondary effects can likewise antagonize cellular signaling. Indeed, HDACI turned out to be inhibitors of NFκB-activated pathways [145–147]. At the molecular level, HDACI e.g. induce IκBs, loss of TNFR, and acetylation of STAT1. These alterations, which counteract NFκB and facilitate apoptosis induction, likely are the reason for enhanced killing when cells undergo treatment with HDACI and TNFα [141,142]. So far, wild type p53 could not be linked to cellular sensitivity towards HDACI. Induction of *p21* in HDACI-treated cells rather is due to an unspecific permissiveness of chromatin [141,142]. Even reduced levels of p53 were found in HDACI-sensitive AML cells [148]. Remarkably, HDACI also attenuate mutant p53 and they kill cells with mutant p53 more efficiently than p53 null cells. Whether non-specific restoration of p53-like functions [149], the inhibition of NFκB [53–56], or other effects caused by HDACI explain their preferential cytotoxicity to cells with mutant p53 needs to be resolved. Reduced survival signaling due to different effects on these transcription factors may be a reason for potent anti-tumor activities of HDACI and genotoxic drugs when given combined to patients suffering from breast or lung cancers [150–152].

Like other phytochemicals, e.g. resveratrol (*Vitis vinifera*), silibinin (*Silybum marianum*), catechins (*Camellia sinensis*; *Theobroma cacao*), derivatives of diferuloylmethane (curcumin, the primary bioactive compound of *Curcuma longa*) suppress NFκB activation associated with the expression of genes implicated in cellular growth, transformation, angiogenesis, metastasis, and inflammation [153]. At the molecular level, curcumin was found to attenuate the expression of NFκB target genes, such as *cyclin D1* and *HDM2*, to induce wild type p53 and its target gene *p21*, and to inhibit STAT3 [154]. The safety and efficacy of this poly-phenol in cell culture and animal models prompted phase I clinical trials for its use as an anti-cancer agent [155]. Resveratrol is an antioxidant counteracting inflammation, metastasis, and angiogenesis by inhibition of NFκB and AP-1 (JUN/FOS). This agent furthermore activates pro-apoptotic p53 sparing normal cells [156]. Since p53 and NFκB are regulated by the class III HDAC SIRT1 (silencing information regulator 1), a potential mechanism by which resveratol mediates its cellular effects is the inhibition of such enzymes [46]. Low bioavailability of this compound in humans though represents a challenging problem.

A synthetic derivative of the *Dracaena* benzofuran lignan (benfur) also shows anti-tumor activities. It represses MDM2, inhibits NFκB, and provokes apoptosis of p53-positive and -negative leukemic cells [157]. The sesquiterpene α-bisabolol promotes accumulation of nuclear wild type p53 and NFκB subunits. Nevertheless, this substance equally attenuates NFκB-mediated transcription and causes apoptosis of cell lines derived from solid tumors [158]. Another poly-phenol, epigallocatechin-3-gallate (EGCG) from green tea (*Camellia sinensis*), and the EGFR tyrosine kinase inhibitor erlotinib synergistically inhibit the growth of head and neck squamous cell carcinomas (HNSCC) *in vitro* and in murine xenograft models. Treatment with EGCG and erlotinib strongly inhibits erlotinib-induced expression of the CDK inhibitors p21 and p27 [159], which restrict apoptosis in other systems and upon other stimuli [33,160,161]. Moreover, EGFR inhibition and EGCG lowers p65 protein levels and promotes expression of p53, which was found required for growth inhibition by these agents [159]. It seems that natural products and derivatives thereof might serve as drugs complementing the arsenal of chemicals and biologicals for the fight against cancer and unbalanced inflammation.

7. Novel models and considerations for therapies

7.1. Possible chemotherapeutic caveats

Although p53 is induced by most chemotherapeutics, it should be kept in mind that p53 mutation occurs in over half of all human tumors. Thus, any p53-based strategy may trigger mutant p53 worsening disease [52]. Moreover, tumors harboring p53 may have lost cell-cycle arrest and apoptosis sensitivity by further mutations. While depletion of mutant p53 represents an extremely attractive target, one may consider that even wild type p53 is able to promote

undesired survival of cancer cells exposed to chemotherapeutics [28,56,162]. Up to ten p53 variants and various mutants furthermore make it difficult to judge whether a unique p53-based optimal cancer therapy might arise [27,47,49]. Crosstalk of p53 with other cellular signaling molecules and transcription factors might equally be subject to the ratio of its isoforms and the abundance of its interaction partners.

IKKs are at the heart of inducible NFκB activities [3,163]. Targeting these kinases, e.g. with BMS-345541, therefore appears as very attractive targets for pharmacological interference strategies. However, NFκB is able to suppress liver carcinogenesis *in vivo*. The mechanism underlying is IKKβ-dependent inhibition of hepatocyte death associated with compensatory proliferation and hepatocellular carcinoma (HCC). At the molecular level, IKKβ-deficiency leads to increased ROS levels, inhibition of phosphatases, and STAT3 phosphorylation. Hepatocyte-specific STAT3 ablation prevented cancer development and progression [164], which supports the intense search for inhibitors of STAT3, e.g. STA-21 [165] (Fig. 5A).

Targeted approaches could also aim for target genes of NFκB. Examples are the *Survivin* gene, which can be repressed with YM-155 [166], or the inactivation of BCL proteins by BH3 mimetics such as ABT-737 [167] (Fig. 5A). Similar as IKK blockage, inhibition of BCL family members has recently been called into question as a therapeutically valid approach. Independent labs noted that γ-irradiation evoked PUMA-driven apoptotic leukocyte death followed by lymphomagenesis [168,169]. *Bim* which is not a target gene of p53 or p65 is still not linked to tumorigenesis [168,169]. Therefore, agents supporting induction of this BH3-only protein might circumvent undesired effects of puma induction. As in the HCC model [164], reduced proliferation as well as less replication stress-associated DNA damage in the puma null hematopoietic stem/progenitor cells protects mice from irradiation-induced tumorigenesis [168,169]. The high risk of translocations upon T- and B-cell receptor recombination may accelerate lymphomagenesis in this model. Nonetheless, the fact that IL1β and IFNγ induce PUMA in pancreatic β-cells illustrates that similar processes operate in non-hematopoietic cells [79].

Co-activation of p53 with NFκB in tumors treated with drugs targeting replication or DNA stability might be the reason for therapeutic failures due to pro-survival NFκB signaling [55,56,70,71,82,110]. On the other hand, the above mentioned results attest that NFκB can prevent excessive repopulation via mutants from the stem cell niche. Perhaps, a life/death balance evolved during centuries of evolution and this Yin/Yang is far more delicate and intertwined than previously assumed. At present, we are also unable to answer if adaptive responses tie into this complicated scenario. Whether sole induction of p53 or mere suppression of NFκB is sufficient for therapy correspondingly requires cautious reflection. Furthermore, p53 activation allows DNA repair responses as well as apoptosis. Even more, p53 and NFκB target genes can play unexpected pro- or anti-tumorigenic roles and examining p53 and NFκB target genes without considering possible crosstalks and interactions seems insufficient. Tumors treated with p53 inductors furthermore represent heterogeneous mixtures of cells. Stochastic distribution of p53 regulation might allow oscillatory responses [32] and error-prone repair can promote oncogenesis [170]. Therefore, precise targeting of cancers is required, also to avoid secondary tumor formation. Whereas depletion of p53 or p65 might have unforeseeable tumor-promoting effects, depletion of oncogenic p53 mutants clearly represents an attractive pharmacological target. Such agents could interfere with the DNA binding capacity of NFκB or disrupt the surface connecting p65 and p53 (Fig. 5B).

7.2. New model systems

Many of the ideas concerning the molecular crosstalk between p53 and p65 come from valid cell-based *in vitro* models. However, the rapid progress of genetic engineering in the mouse and the development of defined mouse models for most relevant cancers [171], now allows investigating the impact of p53/p65 interactions for the initiation and progression of tumors *in vivo*. Furthermore, many mouse lines to manipulate expression and function of p53 (see http://www.p53.free.fr/p53_info/Mouse_model/p53_mouse_models.html) [172] or p65 [173,174] are available. They offer the opportunity to generate simple (e.g. murine low-passage genetically engineered tumor cell lines [56]) or complex cell-based *ex vivo* models (e.g. tumor cells where floxed alleles can be manipulated by tamoxifen in a Cre^{ERT2}-dependent manner [86]). The magnitude of this experimental approach was recently demonstrated in a mouse model of lung adenocarcinoma. In MEFs the conditional expression of the $K\text{-}RAS^{G12D}$ oncogene from the endogenous promoter (lox-stop-lox (LSL)-$K\text{-}RAS^{G12D}$) induces nuclear translocation of p65 only in the case of the simultaneous deletion of p53. The molecular mechanism by which p53 loss activates p65 upon expression of $K\text{-}RAS^{G12D}$ is though still unclear. However, critical functions of p53/p65 cross signaling are demonstrated elegantly with this experiment and the impact of NFκB signaling towards tumor initiation was revealed with a dominant-negative IκBα "super-inhibitor" [86]. Consistently, adeno-CRE-dependent activation of $K\text{-}RAS^{G12D}$ in the lung induces NFκB and conditional deletion of p65 reduces tumor formation [175]. Although this work shows that deletion of p65 affects tumor formation irrespectively of p53 proficiency or deficiency, the observed effects were less dramatic than with dominant-negative IκBα, arguing that other NFκB family members, like c-Rel [86], may (co-)contribute to lung tumor formation. More importantly, inhibiting NFκB signaling by targeting IκBα in established lung tumors, leads to a profound tumor regression *in vivo*, arguing that blocking NFκB is a therapeutic approach for K-RAS mutant tumors. Interestingly, only lung cancer cells with the $K\text{-}RAS^{G12D}$/p53-negative phenotype are addicted to p65 *ex vivo* and respond with an apoptotic program upon inhibition of canonical NFκB signaling [86]. Whether NFκB is indeed the therapeutic "Achilles heel" of K-RAS and p53 mutated lung tumor *in vivo*, compared to K-RAS mutated wild type p53 tumors, awaits further clarification. Nevertheless, the model described demonstrates ways to tailor therapies.

A novel murine K-RAS-induced melanocyte transformation model reveals that IKKβ attenuates p53 and allows transformation. Hence, melanoma patients with highly active NFκB and wild type p53 could benefit from inhibition of the IKKβ integrator [83]. The observation that NFκB inhibition though sufficed to eliminate p53 negative lung cancers [86] contrasts the need for p53 in melanoma development [83]. However, this discrepancy may reflect differences between lung and skin cancers or technical variations - suppression of IKKβ versus blocking NFκB nuclear import. The latter can alter the NFκB/p53 complex ratio, as direct interaction between the p65 N-terminal protion (1–285) and p53 is possible [55,176]. Moreover, DNA damage caused by adriamycin enhances formation of p65–p53–IKKα and p53–IKKβ complexes [176]. Thus, given that p65 and p53 can associate, retention of one factor in a cellular compartment might affect the other (e.g. the cytosolic functions of p53 or the duration of nuclear retention of p65), and altered posttranslational modifications and quenching effects will possibly take place. Whether p53–NFκB interactions are the reason for an unexpected activation of their target genes or a lack thereof [177,178] is equally possible though remains to be proven formally.

8. Concluding remarks

Inventive new therapeutics could rely on the knowledge about the hallmarks of cancer. Up to now we perceive them as independence from external growth signals, the ability to override growth inhibitors, reduced response to hormones and chemotherapeutic agents, evasion of apoptosis, unlimited replication, tissue invasion, metastasis, sustained angiogenesis, manipulation of the tumor microenvironment, subversion of adaptive immunity, cancer-related inflammation, genetic instability, and accumulation of random genetic alterations

[35,103,112,179]. Aberrant NFκB and p53 regulation has been observed in many cancers, including both solid and hematopoietic malignancies, and both factors impinge on all hallmarks of cancer [35,103,112,179].

Cellular functions of p53 and NFκB in health and disease depend on their quantity and qualitative factors. Either is governed by posttranslational modifications. These structural alterations create novel interaction surfaces with other proteins, rule intracellular localization, and affect DNA-binding and gene expression. Thus, the activation state of regulators, PAT/PDAC, kinase/PPase, transferase/deconjugase, etc., is able to determine the outcome of crosstalk between transcription factors in a cell-type- and stimulus-dependent manner. A multiplicity of dose-dependent or time-related responses of biological systems to stressors has already been described, but the molecular understanding of these phenomena often awaits detailed clarification. Perhaps, NFκB-p53 crosstalks affect the decision when p53 ceases repair functions and activates pro-apoptotic gene expression patterns. It is plausible that dynamic alterations ruling these transcriptional regulators direct chromatin accessibility and cell fate decisions.

The fact that replicational stops, genotoxic noxes and other potentially harmful stressors activate cytoprotective NFκB and p53 at repair genes argues for initial cellular decisions towards repair. At present, we are not aware in how far these mechanisms can prime cells for adaption or elimination. Future research will explore the signaling topology of stress responses and how NFκB and p53 reactions control ambivalent reaction patterns of cells and organisms to stress time- and dose-dependently. An improved understanding of the molecular signatures of stress responses may also promote ongoing efforts for the effective use of the organism's preventive and regenerative potentials. Preconditioning effects of stressors are of extraordinary medical relevance and interest, since organisms can develop marked robustness towards noxious stimuli below a specific threshold. Protective gene expression patterns can hence protect cells from stimuli that would normally eliminate potentially harmful (pre) transformed cells and such effects could also be the reason for undesired pro-tumorigenic properties of NFκB and p53.

All regulatory steps concerning p53 and NFκB principally represent targets for therapeutical interventions, i.e. chemotherapy to correct biological systems out of balance. However, p53 and NFκB cannot be divided into simply “good” or “bad” and are not solitary entities—out of context and on our lab shelves. The question remains why these signaling molecules are simultaneously activated by a lot of agents and why certain therapeutic regimens might fail or are inhibited by induction of these factors. An explanation might be that biology takes three conditions in account: (1) prevention of excessive cell death by repair or arrest, when stress stimuli are too low to justify elimination of cells; (2) induction of senescence as biological aging; and (3) gate-keepers to allow the removal of potentially dangerous cells. In these scenarios NFκB and p53 set up oscillatory rhythms of vital decisions for the maintenance of homeostasis.

Acknowledgments

We thank Prof. T. Heinzel for critical reading of the manuscript and invaluable comments. We are also grateful for advice and comments from C. Schäfer, A. Brandl and T. Wagner. We would like to apologize for not citing any relevant reports due to lack of space, the need to selectively choose examples, or an oversight on our part. This work was supported by a grant form the Deutsche Krebshilfe (grant number 109265).

References

[1] M. Karin, Nuclear factor-kappaB in cancer development and progression, Nature 441 (2006) 431–436.
[2] M.S. Hayden, S. Ghosh, Shared principles in NF-kappaB signaling, Cell 132 (2008) 344–362.
[3] C. Scheidereit, IkappaB kinase complexes: gateways to NF-kappaB activation and transcription, Oncogene 25 (2006) 6685–6705.
[4] N.D. Perkins, Integrating cell-signalling pathways with NF-kappaB and IKK function, Nat. Rev. Mol. Cell Biol. 8 (2007) 49–62.
[5] S.Y. Fuchs, A. Chen, Y. Xiong, Z.Q. Pan, Z. Ronai, HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin, Oncogene 18 (1999) 2039–2046.
[6] D. Krappmann, C. Scheidereit, A pervasive role of ubiquitin conjugation in activation and termination of IkappaB kinase pathways, EMBO Rep. 6 (2005) 321–326.
[7] S.Y. Fuchs, V.S. Spiegelman, K.G. Kumar, The many faces of beta-TrCP E3 ubiquitin ligases: reflections in the magic mirror of cancer, Oncogene 23 (2004) 2028–2036.
[8] U. Senftleben, Y. Cao, G. Xiao, F.R. Greten, G. Krahn, G. Bonizzi, Y. Chen, Y. Hu, A. Fong, S.C. Sun, M. Karin, Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway, Science 293 (2001) 1495–1499.
[9] G. Xiao, E.W. Harhaj, S.C. Sun, NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100, Mol. Cell 7 (2001) 401–409.
[10] R.E. Amir, H. Haecker, M. Karin, A. Ciechanover, Mechanism of processing of the NF-kappa B2 p100 precursor: identification of the specific polyubiquitin chain-anchoring lysine residue and analysis of the role of NEDD8-modification on the SCF(beta-TrCP) ubiquitin ligase, Oncogene 23 (2004) 2540–2547.
[11] S. Beinke, S.C. Ley, Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology, Biochem. J. 382 (2004) 393–409.
[12] G. Bonizzi, M. Bebien, D.C. Otero, K.E. Johnson-Vroom, Y. Cao, D. Vu, A.G. Jegga, B.J. Aronow, G. Ghosh, R.C. Rickert, M. Karin, Activation of IKKalpha target genes depends on recognition of specific kappaB binding sites by RelB:p52 dimers, EMBO J. 23 (2004) 4202–4210.
[13] M. Neumann, M. Naumann, Beyond IkappaBs: alternative regulation of NF-kappaB activity, FASEB J. 21 (2007) 2642–2654.
[14] S. Janssens, J. Tschopp, Signals from within: the DNA-damage-induced NF-kappaB response, Cell Death Differ. 13 (2006) 773–784.
[15] H. Sebban, S. Yamaoka, G. Courtois, Posttranslational modifications of NEMO and its partners in NF-kappaB signaling, Trends Cell Biol. 16 (2006) 569–577.
[16] S. Janssens, A. Tinel, S. Lippens, J. Tschopp, PIDD mediates NF-kappaB activation in response to DNA damage, Cell 123 (2005) 1079–1092.
[17] Z.H. Wu, Y. Shi, R.S. Tibbetts, S. Miyamoto, Molecular linkage between the kinase ATM and NF-kappaB signaling in response to genotoxic stimuli, Science 311 (2006) 1141–1146.
[18] A.M. Mabb, S.M. Wuerzberger-Davis, S. Miyamoto, PIASy mediates NEMO sumoylation and NF-kappaB activation in response to genotoxic stress, Nat. Cell Biol. 8 (2006) 986–993.
[19] N. Li, S. Banin, H. Ouyang, G.C. Li, G. Courtois, Y. Shiloh, M. Karin, G. Rotman, ATM is required for IkappaB kinase (IKKk) activation in response to DNA double strand breaks, J. Biol. Chem. 276 (2001) 8898–8903.
[20] T.T. Huang, S.M. Wuerzberger-Davis, Z.H. Wu, S. Miyamoto, Sequential modification of NEMO/IKKgamma by SUMO-1 and ubiquitin mediates NF-kappaB activation by genotoxic stress, Cell 115 (2003) 565–576.
[21] S.M. Wuerzberger-Davis, Y. Nakamura, B.J. Seufzer, S. Miyamoto, NF-kappaB activation by combinations of NEMO SUMOylation and ATM activation stresses in the absence of DNA damage, Oncogene 26 (2007) 641–651.
[22] Z.H. Wu, S. Miyamoto, Induction of a pro-apoptotic ATM-NF-kappaB pathway and its repression by ATR in response to replication stress, EMBO J. 27 (2008) 1963–1973.
[23] M. Stilmann, M. Hinz, S.C. Arslan, A. Zimmer, V. Schreiber, C. Scheidereit, A nuclear poly(ADP-ribose)-dependent signalosome confers DNA damage-induced IkappaB kinase activation, Mol. Cell 36 (2009) 365–378.
[24] F. Renner, R. Moreno, M.L. Schmitz, SUMOylation-dependent localization of IKKepsilon in PML nuclear bodies is essential for protection against DNA-damage-triggered cell death, Mol. Cell 37 (2010) 503–515.
[25] F. Li, G. Sethi, Targeting transcription factor NF-kappaB to overcome chemoresistance and radioresistance in cancer therapy, Biochim. Biophys. Acta 1805 (2010) 167–180.
[26] H.M. Shen, V. Tergaonkar, NFkappaB signaling in carcinogenesis and as a potential molecular target for cancer therapy, Apoptosis 14 (2009) 348–363.
[27] M. Hollstein, P. Hainaut, Massively regulated genes: the example of TP53, J. Pathol. 220 (2010) 164–173.
[28] E. Kim, A. Giese, W. Deppert, Wild-type p53 in cancer cells: when a guardian turns into a blackguard, Biochem. Pharmacol. 77 (2009) 11–20.
[29] T. Abbas, A. Dutta, p21 in cancer: intricate networks and multiple activities, Nat. Rev. Cancer 9 (2009) 400–414.
[30] K.H. Vousden, C. Prives, Blinded by the light: the growing complexity of p53, Cell 137 (2009) 413–431.
[31] E.C. Pietsch, S.M. Sykes, S.B. McMahon, M.E. Murphy, The p53 family and programmed cell death, Oncogene 27 (2008) 6507–6521.
[32] K. Puszynski, B. Hat, T. Lipniacki, Oscillations and bistability in the stochastic model of p53 regulation, J. Theor. Biol. 254 (2008) 452–465.
[33] O.H. Krämer, S.K. Knauer, D. Zimmermann, R.H. Stauber, T. Heinzel, Histone deacetylase inhibitors and hydroxyurea modulate the cell cycle and cooperatively induce apoptosis, Oncogene 27 (2008) 732–740.
[34] D. Speidel, Transcription-independent p53 apoptosis: an alternative route to death, Trends Cell Biol. 20 (2010) 14–24.
[35] L. Galluzzi, E. Morselli, O. Kepp, M.C. Maiuri, G. Kroemer, Defective autophagy control by the p53 rheostat in cancer, Cell Cycle 9 (2010) 250–255.
[36] K.H. Vousden, K.M. Ryan, p53 and metabolism, Nat. Rev. Cancer 9 (2009) 691–700.

[37] M. Shi, D. Liu, B. Shen, N. Guo, Helpers of the cellular gatekeeper-miRNAs dance in P53 network, Biochim. Biophys. Acta 1805 (2010) 218–225.
[38] F. Toledo, G.M. Wahl, Regulating the p53 pathway: in vitro hypotheses, in vivo veritas, Nat. Rev. Cancer 6 (2006) 909–923.
[39] A.G. Uren, J. Kool, K. Matentzoglu, J. de Ridder, J. Mattison, M. van Uitert, W. Lagcher, D. Sie, E. Tanger, T. Cox, M. Reinders, T.J. Hubbard, J. Rogers, J. Jonkers, L. Wessels, D.J. Adams, M. van Lohuizen, A. Berns, Large-scale mutagenesis in p19 (ARF)- and p53-deficient mice identifies cancer genes and their collaborative networks, Cell 133 (2008) 727–741.
[40] A.K. Jain, M.C. Barton, Regulation of p53: TRIM24 enters the RING, Cell Cycle 8 (2009) 3668–3674.
[41] M. Wade, Y.V. Wang, G.M. Wahl, The p53 orchestra: Mdm2 and Mdmx set the tone, Trends Cell Biol. 20 (2010) 299–309.
[42] L. Wang, G. He, P. Zhang, X. Wang, M. Jiang, L. Yu, Interplay between MDM2, MDMX, Pirh2 and COP1: the negative regulators of p53, Mol. Biol. Rep. 38 (2010) 229–236.
[43] S.L. Harris, A.J. Levine, The p53 pathway: positive and negative feedback loops, Oncogene 24 (2005) 2899–2908.
[44] Y. Xia, R.C. Padre, T.H. De Mendoza, V. Bottero, V.B. Tergaonkar, I.M. Verma, Phosphorylation of p53 by IkappaB kinase 2 promotes its degradation by beta-TrCP, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 2629–2634.
[45] A. Olsson, C. Manzl, A. Strasser, A. Villunger, How important are post-translational modifications in p53 for selectivity in target-gene transcription and tumour suppression? Cell Death Differ. 14 (2007) 1561–1575.
[46] S. Spange, T. Wagner, T. Heinzel, O.H. Krämer, Acetylation of non-histone proteins modulates cellular signalling at multiple levels, Int. J. Biochem. Cell Biol. 41 (2009) 185–198.
[47] R.U. Janicke, V. Graupner, W. Budach, F. Essmann, The do's and don'ts of p53 isoforms, Biol. Chem. 390 (2009) 951–963.
[48] P. Lunghi, A. Costanzo, L. Mazzera, V. Rizzoli, M. Levrero, A. Bonati, The p53 family protein p73 provides new insights into cancer chemosensitivity and targeting, Clin. Cancer Res. 15 (2009) 6495–6502.
[49] L. Collavin, A. Lunardi, G. Del Sal, p53-family proteins and their regulators: hubs and spokes in tumor suppression, Cell Death Differ. 17 (2010) 901–911.
[50] T. Stiewe, The p53 family in differentiation and tumorigenesis, Nat. Rev. Cancer 7 (2007) 165–168.
[51] C. Oswald, T. Stiewe, In good times and bad: p73 in cancer, Cell Cycle 7 (2008) 1726–1731.
[52] C.J. Brown, S. Lain, C.S. Verma, A.R. Fersht, D.P. Lane, Awakening guardian angels: drugging the p53 pathway, Nat. Rev. Cancer 9 (2009) 862–873.
[53] R. Brosh, V. Rotter, When mutants gain new powers: news from the mutant p53 field, Nat. Rev. Cancer 9 (2009) 701–713.
[54] M. Oren, V. Rotter, Mutant p53 gain-of-function in cancer, Cold Spring Harbor Perspect. Biol. 2 (2010) a001107.
[55] L. Weisz, A. Damalas, M. Liontos, P. Karakaidos, G. Fontemaggi, R. Maor-Aloni, M. Kalis, M. Levrero, S. Strano, V.G. Gorgoulis, V. Rotter, G. Blandino, M. Oren, Mutant p53 enhances nuclear factor kappaB activation by tumor necrosis factor alpha in cancer cells, Cancer Res. 67 (2007) 2396–2401.
[56] G. Schneider, A. Henrich, G. Greiner, V. Wolf, A. Lovas, M. Wieczorek, T. Wagner, S. Reichardt, A. von Werder, R.M. Schmid, F. Weih, T. Heinzel, D. Saur, O.H. Krämer, Cross talk between stimulated NF-kappaB and the tumor suppressor p53, Oncogene 29 (2010) 2795–2806.
[57] S. Strano, S. Dell'Orso, S. Di Agostino, G. Fontemaggi, A. Sacchi, G. Blandino, Mutant p53: an oncogenic transcription factor, Oncogene 26 (2007) 2212–2219.
[58] L. Weisz, M. Oren, V. Rotter, Transcription regulation by mutant p53, Oncogene 26 (2007) 2202–2211.
[59] D.P. Liu, H. Song, Y. Xu, A common gain of function of p53 cancer mutants in inducing genetic instability, Oncogene 29 (2010) 949–956.
[60] P.A. Muller, P.T. Caswell, B. Doyle, M.P. Iwanicki, E.H. Tan, S. Karim, N. Lukashchuk, D.A. Gillespie, R.L. Ludwig, P. Gosselin, A. Cromer, J.S. Brugge, O.J. Sansom, J.C. Norman, K.H. Vousden, Mutant p53 drives invasion by promoting integrin recycling, Cell 139 (2009) 1327–1341.
[61] A. Petitjean, M.I. Achatz, A.L. Borresen-Dale, P. Hainaut, M. Olivier, TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes, Oncogene 26 (2007) 2157–2165.
[62] K.V. Gurova, O.W. Rokhlin, A.V. Budanov, L.G. Burdelya, P.M. Chumakov, M.B. Cohen, A.V. Gudkov, Cooperation of two mutant p53 alleles contributes to Fas resistance of prostate carcinoma cells, Cancer Res. 63 (2003) 2905–2912.
[63] O.H. Krämer, T. Heinzel, Phosphorylation-acetylation switch in the regulation of STAT1 signaling, Mol. Cell. Endocrinol. 315 (2010) 40–48.
[64] O.H. Krämer, S.K. Knauer, G. Greiner, E. Jandt, S. Reichardt, K.H. Guhrs, R.H. Stauber, F.D. Bohmer, T. Heinzel, A phosphorylation-acetylation switch regulates STAT1 signaling, Genes Dev. 23 (2009) 223–235.
[65] R. Metivier, G. Huet, R. Gallais, L. Finot, F. Petit, C. Tiffoche, Y. Merot, C. LePeron, G. Reid, G. Penot, F. Demay, F. Gannon, G. Flouriot, G. Salbert, Dynamics of estrogen receptor-mediated transcriptional activation of responsive genes in vivo: apprehending transcription in four dimensions, Adv. Exp. Med. Biol. 617 (2008) 129–138.
[66] S. Kangaspeska, B. Stride, R. Metivier, M. Polycarpou-Schwarz, D. Ibberson, R.P. Carmouche, V. Benes, F. Gannon, G. Reid, Transient cyclical methylation of promoter DNA, Nature 452 (2008) 112–115.
[67] G. Reid, R. Metivier, C.Y. Lin, S. Denger, D. Ibberson, T. Ivacevic, H. Brand, V. Benes, E.T. Liu, F. Gannon, Multiple mechanisms induce transcriptional silencing of a subset of genes, including oestrogen receptor alpha, in response to deacetylase inhibition by valproic acid and trichostatin A, Oncogene 24 (2005) 4894–4907.
[68] M. Xu, L. Nie, S.H. Kim, X.H. Sun, STAT5-induced Id-1 transcription involves recruitment of HDAC1 and deacetylation of C/EBPbeta, EMBO J. 22 (2003) 893–904.
[69] S.A. Johnsen, S. Kangaspeska, G. Reid, F. Gannon, Interfering with the dynamics of estrogen receptor-regulated transcription, Ernst Schering Found. Symp. Proc. (2006) 1–12.
[70] K.M. Ryan, M.K. Ernst, N.R. Rice, K.H. Vousden, Role of NF-kappaB in p53-mediated programmed cell death, Nature 404 (2000) 892–897.
[71] J. Bohuslav, L.F. Chen, H. Kwon, Y. Mu, W.C. Greene, p53 induces NF-kappaB activation by an IkappaB kinase-independent mechanism involving phosphorylation of p65 by ribosomal S6 kinase 1, J. Biol. Chem. 279 (2004) 26115–26125.
[72] J. Seznec, S. Weit, U. Naumann, Gene expression profile in a glioma cell line resistant to cell death induced by the chimeric tumor suppressor-1 (CTS-1), a dominant-positive variant of p53—the role of NFkappaB, Carcinogenesis 31 (2010) 411–418.
[73] B. Cvek, Z. Dvorak, The value of proteasome inhibition in cancer. Can the old drug, disulfiram, have a bright new future as a novel proteasome inhibitor? Drug Discov. Today 13 (2008) 716–722.
[74] S.A. Ansari, M. Safak, L. Del Valle, S. Enam, S. Amini, K. Khalili, Cell cycle regulation of NF-kappa b-binding activity in cells from human glioblastomas, Exp. Cell Res. 265 (2001) 221–233.
[75] Z.H. Wu, S. Miyamoto, Many faces of NF-kappaB signaling induced by genotoxic stress, J. Mol. Med. 85 (2007) 1187–1202.
[76] J. O'Prey, D. Crighton, A.G. Martin, K.H. Vousden, H.O. Fearnhead, K.M. Ryan, p53-mediated induction of Noxa and p53AIP1 requires NFkappaB, Cell Cycle 9 (2010) 947–952.
[77] P. Wang, W. Qiu, C. Dudgeon, H. Liu, C. Huang, G.P. Zambetti, J. Yu, L. Zhang, PUMA is directly activated by NF-kappaB and contributes to TNF-alpha-induced apoptosis, Cell Death Differ. 16 (2009) 1192–1202.
[78] D.M. Pastor, R.B. Irby, L.S. Poritz, Tumor necrosis factor alpha induces p53 up-regulated modulator of apoptosis expression in colorectal cancer cell lines, Dis. Colon Rectum 53 (2010) 257–263.
[79] E.N. Gurzov, C.M. Germano, D.A. Cunha, F. Ortis, J.M. Vanderwinden, P. Marchetti, L. Zhang, D.L. Eizirik, p53 up-regulated modulator of apoptosis (PUMA) activation contributes to pancreatic beta-cell apoptosis induced by proinflammatory cytokines and endoplasmic reticulum stress, J. Biol. Chem. 285 (2010) 19910–19920.
[80] K.M. Ryan, J. O'Prey, K.H. Vousden, Loss of nuclear factor-kappaB is tumor promoting but does not substitute for loss of p53, Cancer Res. 64 (2004) 4415–4418.
[81] M.E. Gapuzan, O. Schmah, A.D. Pollock, A. Hoffmann, T.D. Gilmore, Immortalized fibroblasts from NF-kappaB RelA knockout mice show phenotypic heterogeneity and maintain increased sensitivity to tumor necrosis factor alpha after transformation by v-Ras, Oncogene 24 (2005) 6574–6583.
[82] W.H. Hoffman, S. Biade, J.T. Zilfou, J. Chen, M. Murphy, Transcriptional repression of the anti-apoptotic survivin gene by wild type p53, J. Biol. Chem. 277 (2002) 3247–3257.
[83] J. Yang, R. Splittgerber, F.E. Yull, S. Kantrow, G.D. Ayers, M. Karin, A. Richmond, Conditional ablation of Ikkb inhibits melanoma tumor development in mice, J. Clin. Invest. 120 (2010) 2563–2574.
[84] A. Gurtner, G. Starace, G. Norelli, G. Piaggio, A. Sacchi, G. Bossi, Mutant p53-induced up-regulation of mitogen-activated protein kinase kinase 3 contributes to gain of function, J. Biol. Chem. 285 (2010) 14160–14169.
[85] J. Bar, R. Feniger-Barish, N. Lukashchuk, H. Shaham, N. Moskovits, N. Goldfinger, D. Simansky, M. Perlman, M. Papa, A. Yosepovich, G. Rechavi, V. Rotter, M. Oren, Cancer cells suppress p53 in adjacent fibroblasts, Oncogene 28 (2009) 933–936.
[86] E. Meylan, A.L. Dooley, D.M. Feldser, L. Shen, E. Turk, C. Ouyang, T. Jacks, Requirement for NF-kappaB signalling in a mouse model of lung adenocarcinoma, Nature 462 (2009) 104–107.
[87] G.P. Gupta, J. Massague, Cancer metastasis: building a framework, Cell 127 (2006) 679–695.
[88] R. Kalluri, R.A. Weinberg, The basics of epithelial-mesenchymal transition, J. Clin. Invest. 119 (2009) 1420–1428.
[89] J.F. Fries, C.A. Williams, D.A. Bloch, The relative toxicity of nonsteroidal antiinflammatory drugs, Arthritis Rheum. 34 (1991) 1353–1360.
[90] J.P. Thiery, H. Acloque, R.Y. Huang, M.A. Nieto, Epithelial–mesenchymal transitions in development and disease, Cell 139 (2009) 871–890.
[91] Y. Wu, B.P. Zhou, TNF-alpha/NF-kappaB/Snail pathway in cancer cell migration and invasion, Br. J. Cancer 102 (2010) 639–644.
[92] K. Wu, B. Bonavida, The activated NF-kappaB-Snail-RKIP circuitry in cancer regulates both the metastatic cascade and resistance to apoptosis by cytotoxic drugs, Crit. Rev. Immunol. 29 (2009) 241–254.
[93] J. Liu, M. Zhan, J.A. Hannay, P. Das, S.V. Bolshakov, D. Kotilingam, D. Yu, A.F. Lazar, R.E. Pollock, D. Lev, Wild-type p53 inhibits nuclear factor-kappaB-induced matrix metalloproteinase-9 promoter activation: implications for soft tissue sarcoma growth and metastasis, Mol. Cancer Res. 4 (2006) 803–810.
[94] T. Shinohara, T. Miki, N. Nishimura, H. Nokihara, H. Hamada, N. Mukaida, S. Sone, Nuclear factor-kappaB-dependent expression of metastasis suppressor KAI1/CD82 gene in lung cancer cell lines expressing mutant p53, Cancer Res. 61 (2001) 673–678.
[95] A. Marreiros, K. Dudgeon, V. Dao, M.O. Grimm, R. Czolij, M. Crossley, P. Jackson, KAI1 promoter activity is dependent on p53, junB and AP2: evidence for a possible mechanism underlying loss of KAI1 expression in cancer cells, Oncogene 24 (2005) 637–649.

[96] P. Dong, M. Tada, J. Hamada, A. Nakamura, T. Moriuchi, N. Sakuragi, p53 dominant-negative mutant R273H promotes invasion and migration of human endometrial cancer HHUA cells, Clin. Exp. Metastasis 24 (2007) 471–483.
[97] D.K. Biswas, J.D. Iglehart, Linkage between EGFR family receptors and nuclear factor kappaB (NF-kappaB) signaling in breast cancer, J. Cell. Physiol. 209 (2006) 645–652.
[98] P. Dong, Z. Xu, N. Jia, D. Li, Y. Feng, Elevated expression of p53 gain-of-function mutation R175H in endometrial cancer cells can increase the invasive phenotypes by activation of the EGFR/PI3K/AKT pathway, Mol. Cancer 8 (2009) 103.
[99] L. Sauer, D. Gitenay, C. Vo, V.T. Baron, Mutant p53 initiates a feedback loop that involves Egr-1/EGF receptor/ERK in prostate cancer cells, Oncogene 29 (2010) 2628–2637.
[100] S. Ohashi, M. Natsuizaka, G.S. Wong, C.Z. Michaylira, K.D. Grugan, D.B. Stairs, J. Kalabis, M.E. Vega, R.A. Kalman, M. Nakagawa, A.J. Klein-Szanto, M. Herlyn, J.A. Diehl, A.K. Rustgi, H. Nakagawa, Epidermal growth factor receptor and mutant p53 expand an esophageal cellular subpopulation capable of epithelial-to-mesenchymal transition through ZEB transcription factors, Cancer Res. 70 (2010) 4174–4184.
[101] W.E. Naugler, M. Karin, NF-kappaB and cancer-identifying targets and mechanisms, Curr. Opin. Genet. Dev. 18 (2008) 19–26.
[102] J. Bollrath, F.R. Greten, IKK/NF-kappaB and STAT3 pathways: central signalling hubs in inflammation-mediated tumour promotion and metastasis, EMBO Rep. 10 (2009) 1314–1319.
[103] F. Colotta, P. Allavena, A. Sica, C. Garlanda, A. Mantovani, Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability, Carcinogenesis 30 (2009) 1073–1081.
[104] A. Yoshimura, Signal transduction of inflammatory cytokines and tumor development, Cancer Sci. 97 (2006) 439–447.
[105] D.I. O'Brien, K. Nally, R.G. Kelly, T.M. O'Connor, F. Shanahan, J. O'Connell, Targeting the Fas/Fas ligand pathway in cancer, Expert Opin. Ther. Targets 9 (2005) 1031–1044.
[106] T.D. Gilmore, M. Herscovitch, Inhibitors of NF-kappaB signaling: 785 and counting, Oncogene 25 (2006) 6887–6899.
[107] G.W. Vainer, E. Pikarsky, Y. Ben-Neriah, Contradictory functions of NF-kappaB in liver physiology and cancer, Cancer Lett. 267 (2008) 182–188.
[108] E. Pikarsky, R.M. Porat, I. Stein, R. Abramovitch, S. Amit, S. Kasem, E. Gutkovich-Pyest, S. Urieli-Shoval, E. Galun, Y. Ben-Neriah, NF-kappaB functions as a tumour promoter in inflammation-associated cancer, Nature 431 (2004) 461–466.
[109] B. Yazdanpanah, K. Wiegmann, V. Tchikov, O. Krut, C. Pongratz, M. Schramm, A. Kleinridders, T. Wunderlich, H. Kashkar, O. Utermohlen, J.C. Bruning, S. Schutze, M. Kronke, Riboflavin kinase couples TNF receptor 1 to NADPH oxidase, Nature 460 (2009) 1159–1163.
[110] S.K. Dhar, Y. Xu, D.K. St Clair, Nuclear factor kappaB- and specificity protein 1-dependent p53-mediated bi-directional regulation of the human manganese superoxide dismutase gene, J. Biol. Chem. 285 (2010) 9835–9846.
[111] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899.
[112] K. Pietras, A. Ostman, Hallmarks of cancer: interactions with the tumor stroma, Exp. Cell Res. 316 (2010) 1324–1331.
[113] S.I. Grivennikov, M. Karin, Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer, Cytokine Growth Factor Rev. 21 (2010) 11–19.
[114] O. Warburg, F. Wind, E. Negelein, The metabolism of tumors in the body, J. Gen. Physiol. 8 (1927) 519–530.
[115] P. Ak, A.J. Levine, p53 and NF-{kappa}B: different strategies for responding to stress lead to a functional antagonism, FASEB J. 24 (2010) 3643–3652.
[116] F. Schwartzenberg-Bar-Yoseph, M. Armoni, E. Karnieli, The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression, Cancer Res. 64 (2004) 2627–2633.
[117] K. Bensaad, A. Tsuruta, M.A. Selak, M.N. Vidal, K. Nakano, R. Bartrons, E. Gottlieb, K.H. Vousden, TIGAR, a p53-inducible regulator of glycolysis and apoptosis, Cell 126 (2006) 107–120.
[118] S. Matoba, J.G. Kang, W.D. Patino, A. Wragg, M. Boehm, O. Gavrilova, P.J. Hurley, F. Bunz, P.M. Hwang, p53 regulates mitochondrial respiration, Science 312 (2006) 1650–1653.
[119] K. Kawauchi, K. Araki, K. Tobiume, N. Tanaka, p53 regulates glucose metabolism through an IKK-NF-kappaB pathway and inhibits cell transformation, Nat. Cell Biol. 10 (2008) 611–618.
[120] K. Kawauchi, K. Araki, K. Tobiume, N. Tanaka, Loss of p53 enhances catalytic activity of IKKbeta through O-linked beta-N-acetyl glucosamine modification, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 3431–3436.
[121] S. Rocha, N.D. Perkins, ARF the integrator: linking NF-kappaB, p53 and checkpoint kinases, Cell Cycle 4 (2005) 756–759.
[122] I. Hickson, Y. Zhao, C.J. Richardson, S.J. Green, N.M. Martin, A.I. Orr, P.M. Reaper, S.P. Jackson, N.J. Curtin, G.C. Smith, Identification and characterization of a novel and specific inhibitor of the ataxia-telangiectasia mutated kinase ATM, Cancer Res. 64 (2004) 9152–9159.
[123] J. Grosjean-Raillard, M. Tailler, L. Ades, J.L. Perfettini, C. Fabre, T. Braun, S. De Botton, P. Fenaux, G. Kroemer, ATM mediates constitutive NF-kappaB activation in high-risk myelodysplastic syndrome and acute myeloid leukemia, Oncogene 28 (2009) 1099–1109.
[124] M. Zhang, C. Sun, X. Shan, X. Yang, J. Li-Ling, Y. Deng, Inhibition of pancreatic cancer cell growth by cucurbitacin B through modulation of signal transducer and activator of transcription 3 signaling, Pancreas 39 (2010) 923–929.
[125] H. Hu, H.J. Lee, C. Jiang, J. Zhang, L. Wang, Y. Zhao, Q. Xiang, E.O. Lee, S.H. Kim, J. Lu, Penta-1, 2, 3, 4, 6-O-galloyl-beta-D-glucose induces p53 and inhibits STAT3 in prostate cancer cells in vitro and suppresses prostate xenograft tumor growth in vivo, Mol. Cancer Ther. 7 (2008) 2681–2691.
[126] T.L. Lee, J. Yeh, J. Friedman, B. Yan, X. Yang, N.T. Yeh, C. Van Waes, Z. Chen, A signal network involving coactivated NF-kappaB and STAT3 and altered p53 modulates BAX/BCL-XL expression and promotes cell survival of head and neck squamous cell carcinomas, Int. J. Cancer 122 (2008) 1987–1998.
[127] H. Lee, A. Herrmann, J.H. Deng, M. Kujawski, G. Niu, Z. Li, S. Forman, R. Jove, D.M. Pardoll, H. Yu, Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors, Cancer Cell 15 (2009) 283–293.
[128] T.H. Kim, S.Y. Lee, J.H. Rho, N.Y. Jeong, Y.H. Soung, W.S. Jo, D.Y. Kang, S.H. Kim, Y.H. Yoo, Mutant p53 (G199V) gains antiapoptotic function through signal transducer and activator of transcription 3 in anaplastic thyroid cancer cells, Mol. Cancer Res. 7 (2009) 1645–1654.
[129] A. Dey, V. Tergaonkar, D.P. Lane, Double-edged swords as cancer therapeutics: simultaneously targeting p53 and NF-kappaB pathways, Nat. Rev. Drug Discov. 7 (2008) 1031–1040.
[130] A. Dey, E.T. Wong, P. Bist, V. Tergaonkar, D.P. Lane, Nutlin-3 inhibits the NFkappaB pathway in a p53-dependent manner: implications in lung cancer therapy, Cell Cycle 6 (2007) 2178–2185.
[131] A.S. Azmi, P.A. Philip, A. Aboukameel, Z. Wang, S. Banerjee, S.F. Zafar, A.S. Goustin, K. Almhanna, D. Yang, F.H. Sarkar, R.M. Mohammad, Reactivation of p53 by novel MDM2 inhibitors: implications for pancreatic cancer therapy, Curr. Cancer Drug Targets 10 (2010) 319–331.
[132] S. Shangary, S. Wang, Small-molecule inhibitors of the MDM2-p53 protein–protein interaction to reactivate p53 function: a novel approach for cancer therapy, Annu. Rev. Pharmacol. Toxicol. 49 (2009) 223–241.
[133] A. Adhikary, S. Mohanty, L. Lahiry, D.M. Hossain, S. Chakraborty, T. Das, Theaflavins retard human breast cancer cell migration by inhibiting NF-kappaB via p53-ROS cross-talk, FEBS Lett. 584 (2010) 7–14.
[134] Y. Peng, C. Li, L. Chen, S. Sebti, J. Chen, Rescue of mutant p53 transcription function by ellipticine, Oncogene 22 (2003) 4478–4487.
[135] C. Lu, W. Wang, W.S. El-Deiry, Non-genotoxic anti-neoplastic effects of ellipticine derivative NSC176327 in p53-deficient human colon carcinoma cells involve stimulation of p73, Cancer Biol. Ther. 7 (2008) 2039–2046.
[136] W. Wang, W.S. El-Deiry, Restoration of p53 to limit tumor growth, Curr. Opin. Oncol. 20 (2008) 90–96.
[137] J. Terzic, I. Marinovic-Terzic, F. Ikeda, I. Dikic, Ubiquitin signals in the NF-kappaB pathway, Biochem. Soc. Trans. 35 (2007) 942–945.
[138] F. Renner, M.L. Schmitz, Autoregulatory feedback loops terminating the NF-kappaB response, Trends Biochem. Sci. 34 (2009) 128–135.
[139] L.R. Dick, P.E. Fleming, Building on bortezomib: second-generation proteasome inhibitors as anti-cancer therapy, Drug Discov. Today 15 (2010) 243–249.
[140] P. Baumann, K. Muller, S. Mandl-Weber, J. Leban, R. Doblhofer, A. Ammendola, R. Baumgartner, F. Oduncu, R. Schmidmaier, The peptide-semicarbazone S-2209, a representative of a new class of proteasome inhibitors, induces apoptosis and cell growth arrest in multiple myeloma cells, Br. J. Haematol. 144 (2009) 875–886.
[141] O.H. Krämer, HDAC2: a critical factor in health and disease, Trends Pharmacol. Sci. 30 (2009) 647–655.
[142] M. Buchwald, O.H. Krämer, T. Heinzel, HDACi—targets beyond chromatin, Cancer Lett. 280 (2009) 160–167.
[143] S.J. Strauss, K. Higginbottom, S. Juliger, L. Maharaj, P. Allen, D. Schenkein, T.A. Lister, S.P. Joel, The proteasome inhibitor bortezomib acts independently of p53 and induces cell death via apoptosis and mitotic catastrophe in B-cell lymphoma cell lines, Cancer Res. 67 (2007) 2783–2790.
[144] Y. Yang, J. Kitagaki, R.M. Dai, Y.C. Tsai, K.L. Lorick, R.L. Ludwig, S.A. Pierre, J.P. Jensen, I.V. Davydov, P. Oberoi, C.C. Li, J.H. Kenten, J.A. Beutler, K.H. Vousden, A.M. Weissman, Inhibitors of ubiquitin-activating enzyme (E1), a new class of potential cancer therapeutics, Cancer Res. 67 (2007) 9472–9481.
[145] O.H. Krämer, D. Baus, S.K. Knauer, S. Stein, E. Jager, R.H. Stauber, M. Grez, E. Pfitzner, T. Heinzel, Acetylation of Stat1 modulates NF-kappaB activity, Genes Dev. 20 (2006) 473–485.
[146] G. Imre, V. Gekeler, A. Leja, T. Beckers, M. Boehm, Histone deacetylase inhibitors suppress the inducibility of nuclear factor-kappaB by tumor necrosis factor-alpha receptor-1 down-regulation, Cancer Res. 66 (2006) 5409–5418.
[147] P. Kaler, T. Sasazuki, S. Shirasawa, L. Augenlicht, L. Klampfer, HDAC2 deficiency sensitizes colon cancer cells to TNFalpha-induced apoptosis through inhibition of NF-kappaB activity, Exp. Cell Res. 314 (2008) 1507–1518.
[148] M.R. Trus, L. Yang, F. Suarez Saiz, L. Bordeleau, I. Jurisica, M.D. Minden, The histone deacetylase inhibitor valproic acid alters sensitivity towards all trans retinoic acid in acute myeloblastic leukemia cells, Leukemia 19 (2005) 1161–1168.
[149] M.V. Blagosklonny, S. Trostel, G. Kayastha, Z.N. Demidenko, L.T. Vassilev, L.Y. Romanova, S. Bates, T. Fojo, Depletion of mutant p53 and cytotoxicity of histone deacetylase inhibitors, Cancer Res. 65 (2005) 7386–7392.
[150] P. Munster, D. Marchion, E. Bicaku, M. Schmitt, J.H. Lee, R. DeConti, G. Simon, M. Fishman, S. Minton, C. Garrett, A. Chiappori, R. Lush, D. Sullivan, A. Daud, Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study, J. Clin. Oncol. 25 (2007) 1979–1985.
[151] R. Hubaux, F. Vandermeers, C. Crisanti, V. Kapoor, A. Burny, C. Mascaux, S.M. Albelda, L. Willems, Preclinical evidence for a beneficial impact of valproate on the response of small cell lung cancer to first-line chemotherapy, Eur. J. Cancer 46 (2010) 1724–1734.
[152] S.S. Ramalingam, M.L. Maitland, P. Frankel, A.E. Argiris, M. Koczywas, B. Gitlitz, S. Thomas, I. Espinoza-Delgado, E.E. Vokes, D.R. Gandara, C.P. Belani, Carboplatin

and Paclitaxel in combination with either vorinostat or placebo for first-line therapy of advanced non-small-cell lung cancer, J. Clin. Oncol. 28 (2010) 56–62.
[153] R. Ralhan, M.K. Pandey, B.B. Aggarwal, Nuclear factor-kappa B links carcinogenic and chemopreventive agents, Front. Biosci. (Schol Ed) 1 (2009) 45–60.
[154] L. Lin, B. Hutzen, M. Zuo, S. Ball, S. Deangelis, E. Foust, B. Pandit, M.A. Ihnat, S.S. Shenoy, S. Kulp, P.K. Li, C. Li, J. Fuchs, J. Lin, Novel STAT3 phosphorylation inhibitors exhibit potent growth-suppressive activity in pancreatic and breast cancer cells, Cancer Res. 70 (2010) 2445–2454.
[155] A. Goel, A.B. Kunnumakkara, B.B. Aggarwal, Curcumin as "Curecumin": from kitchen to clinic, Biochem. Pharmacol. 75 (2008) 787–809.
[156] T.E. Kraft, D. Parisotto, C. Schempp, T. Efferth, Fighting cancer with red wine? Molecular mechanisms of resveratrol, Crit. Rev. Food Sci. Nutr. 49 (2009) 782–799.
[157] S.K. Manna, J.S. Bose, V. Gangan, N. Raviprakash, T. Navaneetha, P.B. Raghavendra, B. Babajan, C.S. Kumar, S.K. Jain, Novel derivative of benzofuran induces cell death mostly by G2/M cell cycle arrest through p53-dependent pathway but partially by inhibition of NF-kappaB, J. Biol. Chem. 285 (2010) 22318–22327.
[158] W. Chen, J. Hou, Y. Yin, J. Jang, Z. Zheng, H. Fan, G. Zou, alpha-Bisabolol induces dose- and time-dependent apoptosis in HepG2 cells via a Fas- and mitochondrial-related pathway, involves p53 and NFkappaB, Biochem. Pharmacol. 80 (2010) 247–254.
[159] A.R. Amin, F.R. Khuri, Z.G. Chen, D.M. Shin, Synergistic growth inhibition of squamous cell carcinoma of the head and neck by erlotinib and epigallocatechin-3-gallate: the role of p53-dependent inhibition of nuclear factor-kappaB, Cancer Prev. Res. Phila Pa 2 (2009) 538–545.
[160] V.S. Thakur, A.R. Ruhul Amin, R.K. Paul, K. Gupta, K. Hastak, M.K. Agarwal, M.W. Jackson, D.N. Wald, H. Mukhtar, M.L. Agarwal, p53-Dependent p21-mediated growth arrest pre-empts and protects HCT116 cells from PUMA-mediated apoptosis induced by EGCG, Cancer Lett. 296 (2010) 225–232.
[161] G. Dasmahapatra, N. Yerram, Y. Dai, P. Dent, S. Grant, Synergistic interactions between vorinostat and sorafenib in chronic myelogenous leukemia cells involve Mcl-1 and p21CIP1 down-regulation, Clin. Cancer Res. 13 (2007) 4280–4290.
[162] M. Terashima, K. Mishima, K. Yamada, M. Tsuchiya, T. Wakutani, M. Shimoyama, ADP-ribosylation of actins by arginine-specific ADP-ribosyltransferase purified from chicken heterophils, Eur. J. Biochem. 204 (1992) 305–311.
[163] J.A. Schmid, A. Birbach, IkappaB kinase beta (IKKbeta/IKK2/IKBKB)—a key molecule in signaling to the transcription factor NF-kappaB, Cytokine Growth Factor Rev. 19 (2008) 157–165.
[164] G. He, G.Y. Yu, V. Temkin, H. Ogata, C. Kuntzen, T. Sakurai, W. Sieghart, M. Peck-Radosavljevic, H.L. Leffert, M. Karin, Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation, Cancer Cell 17 (2010) 286–297.
[165] H. Song, R. Wang, S. Wang, J. Lin, A low-molecular-weight compound discovered through virtual database screening inhibits Stat3 function in breast cancer cells, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 4700–4705.
[166] G. Giaccone, P. Zatloukal, J. Roubec, K. Floor, J. Musil, M. Kuta, R.J. van Klaveren, S. Chaudhary, A. Gunther, S. Shamsili, Multicenter phase II trial of YM155, a small-molecule suppressor of survivin, in patients with advanced, refractory, non-small-cell lung cancer, J. Clin. Oncol. 27 (2009) 4481–4486.
[167] T.N. Chonghaile, A. Letai, Mimicking the BH3 domain to kill cancer cells, Oncogene 27 (Suppl 1) (2008) S149–S157.
[168] E.M. Michalak, C.J. Vandenberg, A.R. Delbridge, L. Wu, C.L. Scott, J.M. Adams, A. Strasser, Apoptosis-promoted tumorigenesis: gamma-irradiation-induced thymic lymphomagenesis requires Puma-driven leukocyte death, Genes Dev. 24 (2010) 1608–1613.
[169] V. Labi, M. Erlacher, G. Krumschnabel, C. Manzl, A. Tzankov, J. Pinon, A. Egle, A. Villunger, Apoptosis of leukocytes triggered by acute DNA damage promotes lymphoma formation, Genes Dev. 24 (2010) 1602–1607.
[170] K.W. Caldecott, Single-strand break repair and genetic disease, Nat. Rev. Genet. 9 (2008) 619–631.
[171] K.K. Frese, D.A. Tuveson, Maximizing mouse cancer models, Nat. Rev. Cancer 7 (2007) 645–658.
[172] T. Iwakuma, G. Lozano, Crippling p53 activities via knock-in mutations in mouse models, Oncogene 26 (2007) 2177–2184.
[173] H. Algul, M. Treiber, M. Lesina, H. Nakhai, D. Saur, F. Geisler, A. Pfeifer, S. Paxian, R.M. Schmid, Pancreas-specific RelA/p65 truncation increases susceptibility of acini to inflammation-associated cell death following cerulein pancreatitis, J. Clin. Invest. 117 (2007) 1490–1501.
[174] K.A. Steinbrecher, E. Harmel-Laws, R. Sitcheran, A.S. Baldwin, Loss of epithelial RelA results in deregulated intestinal proliferative/apoptotic homeostasis and susceptibility to inflammation, J. Immunol. 180 (2008) 2588–2599.
[175] D.S. Basseres, A. Ebbs, E. Levantini, A.S. Baldwin, Requirement of the NF-kappaB subunit p65/RelA for K-Ras-induced lung tumorigenesis, Cancer Res. 70 (2010) 3537–3546.
[176] K. Kawauchi, K. Araki, K. Tobiume, N. Tanaka, Activated p53 induces NF-kappaB DNA binding but suppresses its transcriptional activation, Biochem. Biophys. Res. Commun. 372 (2008) 137–141.
[177] B.K. Nayak, G.M. Das, Stabilization of p53 and transactivation of its target genes in response to replication blockade, Oncogene 21 (2002) 7226–7229.
[178] R. Beckerman, C. Prives, Transcriptional regulation by p53, Cold Spring Harbor Perspect. Biol. 2 (2010) a000935.
[179] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, Cell 100 (2000) 57–70.