Phosphorylation of the NF-κB regulators

Subjects: Biochemistry & Molecular Biology

Contributor: Tao Lu, Aishat Motolani, Matthew Martin, Mengyao Sun

The nuclear factor kappa B (NF-κB) is a ubiquitous transcription factor central to inflammation and various malignant diseases in humans. The regulation of NF-κB can be influenced by a myriad of post-translational modifications (PTMs), including phosphorylation, one of the most popular PTM formats in NF-κB signaling. The regulation by phosphorylation modification is not limited to NF-κB subunits, but it also encompasses the diverse regulators of NF-κB signaling. The differential site-specific phosphorylation of NF-κB itself or some NF-κB regulators can result in dysregulated NF-κB signaling, often culminating in events that induce cancer progression and other hyper NF-κB related diseases, such as inflammation, cardiovascular diseases, diabetes, as well as neuro-degenerative diseases, etc.

Keywords: cancer signaling ; NF-κB ; phosphorylation ; PRMT5 ; YBX1

1. Brief Overview of Cancer and Key Signaling Pathways

Cancer is a diverse and multifactorial genetic disease that arises through a multistep accumulation of genetic alterations, which causes genomic instability in a cell. This genomic instability results in aberrant cellular functions, such as uncontrolled growth, cell death resistance, increased cell migration and invasion, evasion of immune surveillance, metabolic reprograming, *etc.* [1]. The progression of cancer is further driven by the complex interaction of malignant cells with neighboring cells in their microenvironment [2].

Genetic mutations in multiple signaling pathways have been linked to cancer progression. Several typical examples include the receptor tyrosine kinase/Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (RTK/KRAS) pathway, tumor protein P53 (p53) pathway, transforming growth factor β (TGFβ) pathway, and phosphoinositide 3-kinase/Akt (PI-3-kinase/Akt) pathway, *etc*. Interestingly, ample evidences suggest that these signaling pathways frequently promote cancer progression through the nuclear factor κB (NF-κB) activation [3][4]. For example, KRAS oncogenic mutation and p53 loss of function mutation, which is present in approximately 25% and 50% of human tumors, respectively, leads to the constitutive activation of NF-κB, thereby promoting cell survival in multiple cancers. [4]. Similarly, mutations in the PI-3-Kinase/Akt pathway, which exist in over 30% of solid tumors, promotes the activation of components in NF-κB pathway [5]. These examples, among many others, demonstrate the complex signaling interactions in cancer and the pivotal role that NF-κB plays in enabling cancer progression. Hence, it is of great clinical importance to fully understand the different facets of NF-κB regulation in cancer. In this review, we will further elaborate on the complexity of NF-κB regulation in cancer, with the goal of providing deep insight and aiding the development strategies of novel NF-κB targeted cancer therapeutics.

2. Overview of NF-κB Signaling

Gene transcription plays a fundamental role in mediating several biological processes. Thus, strict regulation of transcription factors is necessary to maintain cellular homeostasis. One such transcription factor is NF-κB. The omnipresent NF-κB is a group of homo- and hetero-dimeric proteins, which was discovered about three decades ago in B lymphocytes. NF-κB was found to bind to a B motif at the enhancer element of the κ light-chain gene to regulate its expression [6][7]. The κB motif, as it is currently termed, consists of the following sequence: 5′-GGGRNNYYCC-3′; wherein Y = pyrimidine, R = purine, and N, any nucleotide. After years of continuous studies on NF-κB, additional mechanistic insights into the roles of NF-κB and its signaling cascade—beyond B-cells—have been elucidated [8]. Mammalian NF-κB is composed of five-member subunits that dimerize at gene promoters to control differential gene expression. The members of the NF-κB family include p65/RelA, RelB, c-Rel, p50/p105 (NF-κB1), and p52/p100 (NF-κB2) [9]. These subunits are characterized by the Rel-homology domains in their N-terminal, which contains a DNA-binding domain, a nuclear localization sequence, and a dimerization domain. Additionally, p65, RelB, and c-Rel contain a transactivation domain in their C-terminal, enabling their transcriptional activity. In contrast, the C-terminal region of p105 and p100, the precursors of p50 and p52 respectively, lacks a transactivation domain but contains several ankyrin repeat sequences that function to inhibit NF-κB [10]. As shown in Figure 1, the mechanism of NF-κB induction is grouped into two pathways:

canonical and non-canonical pathways. In the canonical pathway, external stimuli such as growth factors and cytokines bind to NF-κB cell-surface receptors to activate the phosphorylation of Inhibitor of κB (IκB) by Inhibitor of κB kinase (IKK). This phosphorylation results in IκBα degradation, causing the translocation of p65/p50 dimer to the nucleus and enabling its binding to the respective κB elements on the genes [11][12][13] (Figure 1). Comparably, the non-canonical pathway involves signaling *via* Cluster of differentiation 40 (CD40) receptor, Lymphotoxin-β receptor (LTβR), and BLyS receptor 3 (BR3) receptors, triggering NF-κB -inducing kinase (NIK) phosphorylation of IKKα dimers, and subsequent phosphorylation of p100 by IKKα . This phosphorylation cascade triggers the translocation of RelB/p52 dimers into the nucleus to modulate gene transcription [14] (Figure1).

3. Implication of NF-κB Signaling in Cancer

Considering the unique mechanism of gene regulation, NF-κB has been implicated in a diverse range of cellular processes such as inflammation, cell survival, and cell differentiation. Notably, there has been a growing amount of evidence indicating the pivotal role of NF-κB in cancer initiation and progression [15]. NF-κB is highly involved in cell proliferation via the regulation of cell cycle proteins. For instance, NF-κB was reported to trigger cyclin D1 expression in breast carcinoma cells and was found to interact with cyclin-dependent kinase 2 (CDK2) and cyclin E complex in lymphocytes [16][17]. Additionally, NF-κB has been shown to contribute to most cancer hallmarks including promoting metastasis, enabling angiogenesis, altering the tumor microenvironment, evading apoptosis, among others, in different tumor types [18]. Cytokines such as interleukin-17A (IL-17A) was shown to cause metastasis in hepatocellular carcinoma (HCC) by upregulating the levels of metalloproteinases (MMP) 2 and 9 through NF-κB induction [19]. Additionally, the constitutive activity of NF-κB in human prostate tumors was reported to be associated with the expression of key angiogenesis promoters such as vascular endothelial growth factor (VEGF), MMP 9, and interleukin-8 (IL-8) [20]. Unsurprisingly, the tumor microenvironment, which consists of various immune cells, is invariably transformed into a pro-tumorigenic microenvironment through NF-κB signaling. NF-κB activates the expression of distinct pro-inflammatory cytokines that engage in a feedback-loop to promote NF-κB dependent transcription of oncogenes [21]. Alongside enabling tumor growth, NF-κB also plays a vital role in preventing apoptosis in many cancers. For instance, inhibition of NF-κB activity triggered apoptosis in both lung cancer and colorectal cancer cell lines [22][23]. Cancer cells can evade apoptosis by upregulating a number of NF-κB-dependent anti-apoptotic genes such as B-cell lymphoma-extra-large (Bcl-xL), FLICE-inhibitory protein (FLIP), cellular inhibitor of apoptosis protein (c-IAP), and mouse double minute 2 homolog (Mdm2), a negative regulator of p53. [23][24][25][26]. p53 plays a key role in preserving the genomic integrity of a cell in response to cellular stress by activating cell cycle arrest or inducing apoptosis. Thus, NF-κB signaling has been speculated to hinder p53-induced apoptosis in response to chemotherapeutic agents used for cancer treatment [26].

References

1. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The Next Generation. Cell 2011, 144, 646–674.
2. Sever, R.; Brugge, J.S. Signal Transduction in Cancer. Cold Spring Harb. Perspect. Med. 2015, 5, a006098.
3. Freudlsperger, C.; Bian, Y.; Contag, S.; Burnett, J.; Coupar, J.; Yang, X.; Chen, Z.; Van Waes, C. TGF-β and NF-κB sig nal pathway cross-talk is mediated through TAK1 and SMAD7 in a subset of head and neck cancers. Oncogene 2013, 32, 1549–1559.
4. Xia, Y.; Shen, S.; Verma, I.M. NF-κB, an active player in human cancers. Cancer Immunol. Res. 2014, 2, 823–830.
5. Samuels, Y.; Ericson, K. Oncogenic PI3K and its role in cancer. Curr. Opin. Oncol. 2006, 18, 77–82.
6. Sen, R.; Baltimore, D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell 1986, 46, 70 5–716.
7. Sen, R.; Baltimore, D. Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanis m. Cell 1986, 47, 921–928.
8. Tripathi, P.; Aggarwal, A. NF-κB transcription factor: A key player in the generation of immune response. Curr. Sci. 200 6, 90, 519.
9. Zhang, Q.; Lenardo, M.J.; Baltimore, D. Leading Edge Review 30 Years of NF-κB: A Blossoming of Relevance to Huma n Pathobiology. Cell 2017, 168, 37–57.
10. Giuliani, C.; Bucci, I.; Napolitano, G. The role of the transcription factor Nuclear Factor-kappa B in thyroid autoimmunity and cancer. Front. Endocrinol. 2018, 9, 471.

11. Oeckinghaus, A.; Ghosh, S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb. Perspect. Biol. 2009, 1, a000034.
12. Lu, T.; Stark, G.R. Cytokine overexpression and constitutive NF-κB in cancer. Cell Cycle 2004, 3, 1114–1117.
13. Wei, H.; Prabhu, L.; Hartley, A.-V.; Martin, M.; Sun, E.; Jiang, G.; Liu, Y.; Lu, T. Methylation of NF-κB and its Role in Gene Regulation. In Gene Expression and Regulation in Mammalian Cells—Transcription from General Aspects; IntechOpen: London, UK, 2018; 291.
14. Sun, S.C. The noncanonical NF-κB pathway. Immunol. Rev. 2012, 246, 125–140.
15. Dolcet, X.; Llobet, D.; Pallares, J.; Matias-Guiu, X. NF-κB in development and progression of human cancer. Virchows Arch. 2005, 446, 475–482.
16. Chen, E.; Li, C.C.H. Association of Cdk2/cyclin E and NF-κB complexes at G1/S phase. Biochem. Biophys. Res. Commun. 1998, 249, 728–734.
17. Hinz, M.; Krappmann, D.; Eichten, A.; Heder, A.; Scheidereit, C.; Strauss, M. NF-κB Function in Growth Control: Regulation of Cyclin D1 Expression and G0/G1-to-S-Phase Transition. Mol. Cell. Biol. 1999, 19, 2690–2698.
18. Park, M.; Hong, J. Roles of NF-κB in Cancer and Inflammatory Diseases and Their Therapeutic Approaches. Cells 2016, 5, 15.
19. Li, J.; Lau, G.K.-K.; Chen, L.; Dong, S.; Lan, H.-Y.; Huang, X.-R.; Li, Y.; Luk, J.M.; Yuan, Y.-F.; Guan, X. Interleukin 17A Promotes Hepatocellular Carcinoma Metastasis via NF-κB Induced Matrix Metalloproteinases 2 and 9 Expression. PLoS ONE 2011, 6, e21816.
20. Huang, S.; Pettaway, C.A.; Uehara, H.; Bucana, C.D.; Fidler, I.J. Blockade of NF-κB activity in human prostate cancer cells is associated with suppression of angiogenesis, invasion, and metastasis. Oncogene 2001, 20, 4188–4197.
21. Inoue, J.I.; Gohda, J.; Akiyama, T.; Semba, K. NF-κB activation in development and progression of cancer. Cancer Sci. 2007, 98, 268–274.
22. Kim, Y.A.; Lee, W.H.; Choi, T.H.; Rhee, S.H.; Park, K.Y.; Choi, Y.H. Involvement of p21WAF1/CIP1, pRB, Bax and NF-kappaB in induction of growth arrest and apoptosis by resveratrol in human lung carcinoma A549 cells. Int. J. Oncol. 2003, 23, 1143–1149.
23. Wang, C.Y.; Cusack, J.C.; Liu, R.; Baldwin, A.S. Control of inducible chemoresistance: Enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-κB. Nat. Med. 1999, 5, 412–417.
24. Luo, J.-L.; Kamata, H.; Karin, M. IKK/NF-k κB signaling: Balancing life and death-a new approach to cancer therapy. J. Clin. Investig. 2005, 115, 2625–2632.
25. Sevilla, L.; Zaldumbide, A.; Pognonec, P.; Boulukos, K.E. Transcriptional regulation of the bcl-x gene encoding the an-ti-apoptotic Bcl-xL protein by Ets, Rel/NFkappaB, STAT and AP1 transcription factor families. Histol. Histopathol. 2001, 16, 595–601.
26. Tergaonkar, V.; Pando, M.; Vafa, O.; Wahl, G.; Verma, I. p53 stabilization is decreased upon NFκB activation: A role for NFκB in acquisition of resistance to chemotherapy. Cancer Cell 2002, 1, 493–503.