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Research Progress on the NF-κB Signaling Pathway and Tumor Microenvironment

Zihan Su [1,*]

[1]Department of Pharmaceutical and Food Science, Southwest Minzu University, Chengdu, China
*corresponding author: xsldiwjm@outlook.com

Abstract:

Cancers are major threats in the global health field with increased cases of occurrences. It progresses through several different steps, with all of them intricate chemical signaling. Recent progress in tumor microenvironment studies have revealed that tumors are robust communities that are constituted by tumor cells, immune cells and other stromal cells. The tumor immune microenvironment is central to the tumor microenvironment and has a fundamental influence on tumor progression and prognosis and directly on the effectiveness of anti-tumor therapy. In case the malfunction of immune cells occurs, that will result in dysfunction of the immune system, and it will be harder to treat. The NF-κB family of key transcription factors is one of the numerous signal transduction pathways involved in the tumor immune microenvironment and has received significant attention because of its involvement in the survival of cells, immunity, and inflammation. Canonical NF-κB is directly related to the progression of malignancies. Their state of functional activities and cytokine secretion can be fine-tuned by it to affect the malignant states of cancer cells and reconfigure the immune microenvironment of tumors. This writing guideline attempts to delve into the regulatory mechanism of the NF-κB pathway in the tumor microenvironment and the consequences in cancer therapy through immunotherapy. It also addresses the existing issues and gives suggestions about the clinical applications in the future.

Keywords: NF-κB signaling pathway; Immune evasion; Tumor microenvironment.

1. Introduction

The tumor microenvironment (TME) is an intricate dynamic local microenvironment. It enhances the development, growth, and progression of tumor cells. The TME enables immune evasion, enhances the difficulty of treatment, and affords nutritional and metabolic aid. Rather, it is a very critical niche in tumor formation. Pro-angiogenic agents and immune checkpoint inhibitors are some of the strategies in

clinical practice aiming to combat the TME. The immune cells and cytokines in TME are suppressive and they have a crucial role to play in promoting immune escape. They can create a network of repression that suppresses the anti-tumor activity of certain protecting immune cells, including the CD8+ T cells. NF-κB signaling pathway is the main controller of this network.

NF-κB signaling pathway is a significant pathway in cell survival, inflammatory response, and defense response. Its deviant activation is an important component of immunosuppressive microenvironment formation and maintenance in the TME, and is linked with cancer and inflammatory diseases. NF-κB contains 5 subunits and the most common heterodimer is p65/p50. NF-κB is sequestered by the IκB family in the cytoplasm to ensure that it always remains in the inactive state. Two different pathways, the canonical pathway where inflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-1 initiate the IKK complex, and the non-canonical pathway where particular receptors on the cell surface prompt the activation of the IKK complex, are possible.

Preexisting literature has validated that NF-κB can mediate recruitment, differentiation, and functional activation of regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs), and M2-type tumor-associated macrophages (M2 -TAM). At the same time, it directly controls the transcriptional secretion of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta) as well as programmed death-ligand 1 (PD-L1).

The paper will be based on the literature review approach to methodically organize the mechanism of regulatory action of the NF-κB signaling pathway in the TME and profoundly discern the principles of its action on suppressive immune cells, cytokines, and regulatory networks. The aim is to enrich the knowledge of NF-κB immunosuppression nature, give theoretical opportunities to develop a specific immunotherapeutic regimen, and create new avenues in the treatment of tumors.

2. Tumor Microenvironment

The local microenvironment in the TME is complex and robust. It enhances the growth, development and progression of tumor cells. They are its aggressor cells (inflammatory cells), cancer-associated fibroblasts (CAFs), and other stromal cells. Also, the surrounding tumor associated vascular endothelial cells, the capillary network, as well as the variety of cytokines and chemokines are also factors affecting the formation of the TME [1]. The key roles of the TME include augmenting treatment resistance, encouraging tumor progression, immunological avoidance, as well as favoring tumor growth [2]. It can be added that NF-κB signaling pathway is closely linked to the above-mentioned key biological processes of TME [3]. The NF-κB signaling pathway plays a crucial role in the regulation of the above-mentioned significant physiological processes in the TME. This pathway enhances the development of the immunosuppressive microenvironment within the TME, and as a result of this, tumor progression occurs. It is important to note that the whole process is substantially controlled by the NF-κB signaling pathway [4].

3. NF-κB Signaling Pathway

The fundamental elements of this pathway are the IKK complex and the IκB family (which traps NF-κB in cytoplasm). Both the canonical and the non-canonical pathways require IKK. In particular, the inflammatory signals that cause the activation of the canonical pathway include TNF and IL-1. It promotes the activity of certain proteins which destroys the NF-κB inhibitory protein. Then the critical subunits of NF-κB will be transported to the nucleus and this will control the expression of the inflammatory factor and the anti-apoptotic genes. The non-classical pathway is activated by specific receptors on the cell surface. It releases the key signaling molecule NIK via the degradation of TRAF3, which in turn activates IKKα and induces the processing of p100 into p52. This forms the p52/RelB dimer that translocates into the nucleus, regulating genes related to the function of immune cells. Notably, the non-canonical NF-κB pathway serves as a core regulatory hub for humoral immune responses by precisely regulating key B cell activation genes . Its dysfunction can lead to dual effects of humoral immunity in tumors: either anti-tumor or pro-tumor. Meanwhile, by modulating the differentiation and function of various immune cells including MDSCs, T cells, and natural killer (NK) cells, this pathway maintains the “immune activation-inhibition” homeostasis of the tumor immune microenvironment [5]. The above activation pathways can be seen in Figure 1. This pathway establishes an immunosuppressive state by remodeling the tumor microenvironment, ultimately facilitating tumor immune escape.

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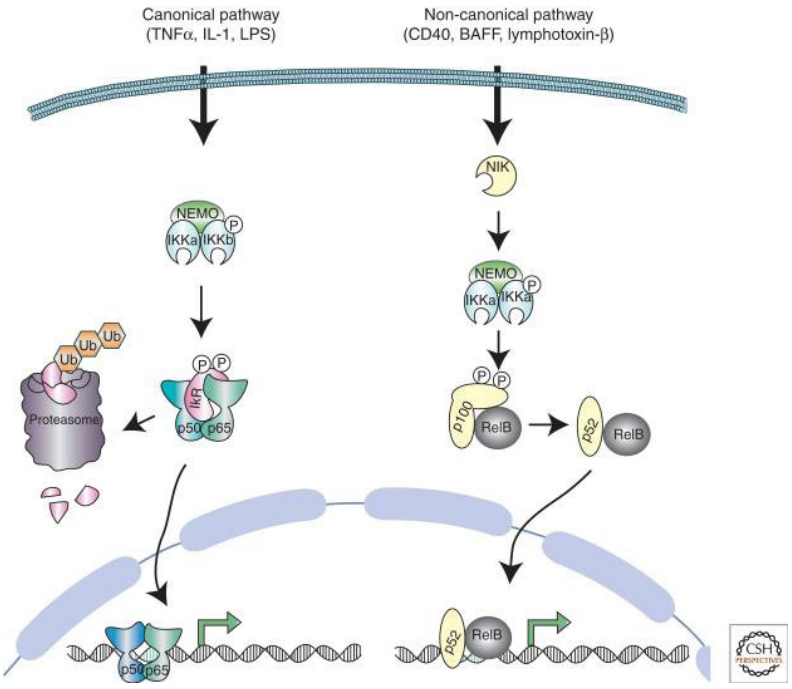

Fig. 1 Two activation pathways of NF-κB [5]

4. Regulatory Mechanism of the NF-κB Signaling Pathway in TME

4.1 Regulate the Recruitment, Differentiation and Functional Activation of Immune Cells

The NF-κB signaling pathway can drive the recruitment, differentiation, and functional activation of three types of suppressive immune cells: Tregs, MDSCs and TAMs can also directly bind to the gene promoters of IL-10, TGF-β, and PD-L1 to regulate their transcription and secretion. Under stress conditions, the upregulated PD-L1 expression may further lead to resistance to PD-1/PD-L1 inhibitors [6, 7]. Based precisely on this multi-level regulatory network, the three types of cells can synergistically reshape the tumor immune microenvironment (TIME) from different dimensions and establish a stable immunosuppressive barrier through specific functional activation.

4.1.1 Regulation of MDSCs

Take MDSCs for example. As the core immunosuppressive cells regulated by the NF-κB signaling pathway, the functional activation of MDSCs is highly dependent on the NF-κB-mediated recruitment and differentiation cascade. In the TME, NF-κB first activates tumor cells to secrete chemokines such as C-X-C Motif Chemokine Ligand 1 (CXCL1), establishing a chemotactic gradient to guide the directed migration of MDSCs from the bone marrow and peripheral blood to the tumor site [8]. Meanwhile, this pathway regulates the differentiation signaling network of bone marrow precursor cells, ensuring that MDSCs acquire a mature immunosuppressive phenotype and functional potential [9]. The basis of the immunosuppressive effect of MDSCs centers on impairing the activity of effector immune cells, and the expression and secretion of key effector molecules are directly regulated by NF-κB [10]. First, the NF-κB pathway can significantly upregulate the expression levels of arginase1 and inducible nitric oxide synthase (iNOS) in MDSCs. ARG1 competitively depletes L-arginine in the tumor microenvironment — an essential amino acid substrate for the proliferation of $CD8^+$ T cells and natural killer (NK) cells — thereby causing cell cycle arrest and a reduction in the number of these core anti-tumor effector cells. In contrast, iNOS catalyzes the production of large amounts of nitric oxide (NO), which irreversibly impairs the anti-tumor cytotoxic capacity of $CD8^+$ T cells and NK cells by directly damaging their DNA structure.

Second, NF-κB can activates the IL-10 gene promoter region in MDSCs, promoting IL-10 transcription. IL-10 blocks the initiation of the adaptive immune response by inhibiting the maturation and antigen-presenting function of dendritic cells (DCs). On the one hand, TGF-β induces the differentiation of naive T cells into Treg; on the other hand, it inhibits the secretion of Th1-type cytokines, thereby forming a dual immunosuppressive network.

Third, under stress conditions such as hypoxia, radiotherapy, and chemotherapy, NF-κB can promote the high ex-

pression of PD-L1 on the surface of MDSCs. The specific binding of PD-L1 to the PD-1 receptor on the surface of $CD8^+$ T cells transmits inhibitory signals, shuts down the T cell activation pathway, and ultimately leads to significant impairment of their anti-tumor effector function [11, 12]. Collectively, these regulatory mechanisms constitute the core pathway of NF-κB-MDSCs-mediated tumor immune escape, providing key therapeutic targets.

4.1.2 Closed-Loop Suppressive Network of MDSCs-Treg-M2-TAMs

The functional activation of the three types of cells does not exist independently, but forms a synergistic network under the unified regulation of NF-κB. TGF-β secreted by MDSCs under the regulation of NF-κB can promote the proliferation of Treg cells. NF-κB also regulates the secretion of vascular endothelial growth factor (VEGF) by M2-TAMs, which provides vascular support for the infiltration of MDSCs and Treg cells. Meanwhile, it regulates the secretion of IL-10 by Treg cells, which in turn maintains the polarized state of M2-TAMs. Ultimately, this forms the "MDSCs-Treg-M2-TAM" closed-loop suppressive network [4]. More importantly, the continuous reinforcement of this network will exacerbate the transcriptional regulation of PD-L1 by NF-κB. Under stress conditions, it further elevates the expression level of PD-L1 in the microenvironment. This not only puts the tumor immune microenvironment in a vicious cycle of: (a) effector cell dysfunction, (b) impaired immune initiation, and (c) tumor continues to proliferate and survive,but also results in resistance to PD-1/PD-L1 inhibitors, thus, a stable environment of immune sanctuary for tumor growth and metastasis. Moreover, this communication has a conclusive effect on controlling the equilibrium of activation/inhibitory cell growth in the effector immune cell and this directly influences variations in immunotherapeutic effectiveness. NF- κB aberrantly activated in the TME causes exhaustion of CD8+T cells. It does so by increasing the expression of exhaustion in CD8+ T cells including PD-1 and Tim-3, as well as, restricting the release of cytotoxic cytokines like IFN- gamma and TNF- alpha. This eventually leads to failure of the CD8 + T cells to recognize and kill tumor cells [13].

4.2 Mechanism of NF-κB Regulating Immune Cells to Activate Antitumor Immunity

At the level of anti-tumor immune activation, NF-κB is a key node for T cell activation. After the T cell receptor (TCR) recognizes tumor antigens, NF-κB is phosphorylated and activated, which regulates the transcriptional expression of cytokines such as IL-2 and IFN-γ, promotes the proliferation, differentiation, and activation of effector T cells including $CD8^+$ cytotoxic T cells, and simultaneously upregulates the expression of costimulatory molecules such as CD28, thereby maintaining the activated state of T cells and preventing their exhaustion [14]S. E.</author><author>Wang, Y.</author><author>Chen, L.</author><author>Molinero, L. L.</author><author>Gajewski, T. F.</author><author>Evaristo, C.</author><author>Alegre, M. L.</author></authors></contributors><auth-address>Department of Medicine, The University of Chicago, 924 E. 57th St. JFK-R312, Chicago, IL 60637 USA.
Genentech, Inc., 1 DNA Way MS: 245c, South San Francisco, CA 94080 USA.
Department of Medicine, The University of Chicago, 924 E. 57th St. JFK-R312, Chicago, IL 60637 USA ; Department of Pathology, The University of Chicago, 927 E. 57th St, Chicago, IL 60637 USA.</auth-address><titles><title>T cell-NF-κB activation is required for tumor control in vivo</title><secondary-title>J Immunother Cancer</secondary-title></titles><periodical><full-title>J Immunother Cancer</full-title></periodical><pages>1</pages><volume>3</volume><number>1</number><edition>20150120</edition><keywords><keyword>Cytokine production</keyword><keyword>Cytotoxicity</keyword><keyword>Effector function</keyword><keyword>Nf-κb</keyword><keyword>Priming</keyword><keyword>T cell</keyword><keyword>Tumor rejection</keyword></keywords><dates><year>2015</year></dates><isbn>2051-1426 (Print. In DCs, NF-κB is activated by tumor antigens or danger signals, which drives DC maturation, upregulates the expression of molecules such as MHC-II, CD80, and CD86, enhances antigen presentation efficiency, and provides the critical "Signal 1 + Signal 2" for the initiation of immune response [15]. In addition, it can also regulate the polarization of macrophages towards the M1 type, promote the secretion of pro-inflammatory cytokines such as TNF-α and IL-12, recruit and activate innate immune cells including NK cells and neutrophils, and enhance non-specific cytotoxicity [1].

5. Modulation of the NF-κB Signaling Pathway in Tumor Therapy

Given that both the formation of the "MDSCs-Treg-M2-TAM" closed-loop suppressive network and PD-1/PD-L1 inhibitor resistance take the sustained activation of the NF-κB pathway as their core driver. This pathway serves not only as the "regulatory hub" for the formation of the closed-loop network, but also as a key therapeutic target for disrupting immunosuppression and reversing therapeutic resistance [7]. Its underexplored application

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potential has become a research focus in the field of tumor immunology.

From the perspective of the precision of intervention targets, the functional specificity of NF-κB family subunits lays a crucial molecular foundation for "precision intervention" strategies in the field of tumor immunology. In-depth and systematic studies have clarified that the 5 subunits contained in the NF-κB family exhibit distinctly differential regulatory mechanisms. Among them, different subunits demonstrate clear functional differences in the activation process of the NF-κB pathway and the specificity of target gene binding. This core characteristic significantly breaks through the limitations of traditional "pan-NF-κB inhibition" strategies: traditional pan-NF-κB inhibitors such as glucocorticoids, due to lacking subunit selectivity, exert non-selective inhibition on the overall activity of the NF-κB pathway. This often disrupts the normal immune homeostasis of the organism, thereby inducing severe toxic reactions such as increased susceptibility to infections and autoimmune diseases. In contrast, intervention strategies based on the functional specificity of subunits can achieve a dynamic balance of "targetedly blocking the immunosuppressive effect in the TME while preserving the immune function of the organism under physiological conditions" [5]. For instance, relevant studies have confirmed that oxaliplatin can specifically downregulate the activity of specific subunits in the NF-κB family, thereby selectively inhibiting the immunosuppressive function of MDSCs. This process not only effectively attenuates the immunosuppressive microenvironment in the TME but also does not significantly interfere with the activity of normal peripheral immune cells in the organism, fully verifying the unique advantages of NF-κB subunit-targeted intervention strategies in tumor immunotherapy [11].

In the design of combined therapeutic regimens, based on the regulatory network of the NF-κB pathway, the synergistic strategy of "NF-κB inhibitors + multi-dimensional immunotherapy" has demonstrated potential. Inhibition of NF-κB can reduce the recruitment of Treg in the TME while enhancing the Treg clearance effect mediated by CTLA-4 inhibitors; the combined use of these two approaches can produce a dual effect of "reducing inhibitory cells and clearing residual inhibitory cells" [13]. Furthermore, NF-κB can directly regulate the transcriptional expression of PD-L1; therefore, the combination of NF-κB inhibitors and PD-1 inhibitors can reverse immune checkpoint inhibitor resistance from the dual perspectives of "downregulating PD-L1 expression + blocking PD-1/PD-L1 binding", further expanding the application scenarios of combined therapy [7].

Meanwhile, the application of biomarkers provides a pathway for improving treatment precision. When summarizing the interaction mechanism between NF-κB and the TME, it has been proposed that NF-κB pathway activity such as IKKβ phosphorylation level and p65 nuclear translocation efficiency can serve as a key biomarker for screening potential beneficiary populations. For instance, the efficacy of subunit-specific inhibitors combined with immune checkpoint inhibitors in tumor patients with high NF-κB activity is significantly superior to that in patients with low NF-κB activity. The specific detection methods for these biomarkers remain unclear, even though relevant technical approaches (e.g., IHC for assessing p65 nuclear translocation and WB for quantifying IKKβ phosphorylation level) have been tentatively mentioned [4].

6. Conclusion

The NF-κB signal transduction pathway plays a central regulatory role in the homeostasis of TME. This pathway participates in the function regulation of TME through both classical and non-classical activation modes, and has been identified as an important molecular target for promoting immunosuppression and malignant progression of tumors. The contribution of this study can be considered from three perspectives. At the mechanistic level, it elucidates the multi-molecular architecture underlying NF-κB-mediated TME remodeling, thereby enhancing the understanding of this complex regulatory network. At the translational level, the therapeutic potential of targeting NF-κB in the TME is supported by experimental evidence, reinforcing its utility in precision medicine and treatment strategy development. At the clinical level, this approach offers a promising avenue for overcoming resistance to immunotherapy, particularly resistance to PD-1/PD-L1 inhibitors. To advance this research direction, we recommend the following: development of NF-κB-targeting inhibitors with subunit specificity; exploration of combination therapies involving NF-κB inhibitors and immune checkpoint blockers; identification of potential biomarkers indicative of NF-κB pathway activity; and systematic investigation of other key molecular nodes within the TME regulatory network.

The current study has laid an important foundation for achieving the accurate intervention of TME and facilitating the advancement of tumor immunotherapy. Further implementation of the corresponding thorough research work will contribute to the eradication of the existing cancer treatment barriers and encourage the advance of clinical cancer prevention and treatment methods.

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