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TNF-α, NF-kb and NLRP3 in Relation to Tumor Development

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Abstract. With the development of society, cancer has become one of the major diseases with a high incidence and fatality rate in the world.Scientists have proved that TNF-α,NF-kb and NLRP3 plays an important role in the tumor microenvironment (TME), especially their dual effects in regulating inflammation and tumor progression. However, there is still a lack of a comprehensive understanding of the specific mechanisms of these molecules in different tumor types and their interactions, which also limits their potential application in tumor immunotherapy. Therefore, the study of the relationship between inflammatory factors and tumor development has become a hot topic in today's society. For example, the inflammatory factor TNF-α secreted by NF cells and T cells can directly annihilating tumor cells, and can indirectly kill tumor cells by activating the immune system's response, NF-kb and NLRP3 also inhibit tumor growth, invasion and metastasis under specific conditions. In conclusion, inflammatory cytokines are closely related to the development of tumors, and this study also provides a solid foundation for future immunotherapy of tumors. This article focuses on the promotion and inhibition effects of inflammatory factors TNF-α, NF-kb and inflammatory body NLRP3 on tumors, providing evidence and conclusions for researchers.

Keywords: Tumor; inflammatory factor; TNFα; NF-kb; NLRP3.

1. Introduction

TME refers to the internal environment in which tumor cells live, and is closely related to the occurrence, growth and metastasis of tumor in the late stage of tumor development, it mainly includes fibrocytes, EC, and PC, the most important part of the TME is the IME. When CI is caused, LYM and Mac accumulate at the very heart of the inflammatory site. Once activated, Mac produces reactive oxygen species (ROS) and IC. Toward the increased activation of NF-kB pathway and cyclooxygenase-2 (COX-2). In some tumors, the inflammasome NLRP3 and cell necrosis factor (TNF) may influence the aggressiveness of tumors by influencing the elevation of IL-1β and IL-6 [1]. In addition, inflammatory cells can also produce cytokines, which can activate different effectors such as NF-kb, STAT transcription factors, and produce pro-tumor factors to promote the growth and invasion of tumor cells. So inflammatory cytokines have a dual effect on tumor cells.

The NLRP3 is a consists of pro-Caspase-1, cysteine protease caspase-1, the pro-inflammatory cytokines proIL-18 and interleukin-1β split to produce an active form that triggers apoptosis [2]. The action mechanism of NLRP3 is mainly divided into two stages, including the primer stage and the activation stage. Primer stage: The NLRP3 receives the start signal, include Pattern recognition receptors (PRRs) recognition of pathogen signals. Interactions between PRRs and related molecular patterns lead to activation of the NF-kb pathway. The NF-kb pathway induces NLRP3 gene and IL-1β transcription, IL-1β is a cytokine that is essential for the inflammatory response. Caspase-8 mediated FADD is involved in the initiation phase by modulating the NF-kappa B pathway. NLRP3 can be activated after translation. Activation phase: The initiation signal comes from multiple triggers, resulting in the triggering of the NLRP3 inflammasome. When the inflammasome sensor detects a signal of disease or injury, it causes changes in cellular ion concentration, especially intracellular potassium ion efflorescent, which activates the NLRP3 to change its structure, thus interacting with ASC to form the inflammasome complex. ASC recruits the original caspase-1 into the complex, causing it to automatically split and activate into caspase-1. Then Activated caspase-1 breaks down immature proil-1β and proIL-18 into mature active forms, IL-1β and IL-18. And then these cytokines

are secreted out of the cell, triggering an inflammatory response [3]. TNF-α is produced by activated macrophages, NK cells and T cells. It can directly kill tumor cells, but also can mediate the body's immune response to achieve the effect of tumor treatment. It is a key component of the normal immune response, and it can activate the immune system for regulation [4]. However, TNF-α is also the earliest and most important inflammatory factor in the inflammatory response process. It affects tumor cell growth, epithelial mesenchymal transformation, invasion and metastasis. At the same time, TNF-α is also a key factor in the signaling pathway, It can induce glial forming cells and vascular endothelial cells to express intercellular adhesion molecules and promote the migration of activated T cells [5]. NF-kb can control the transcription of target genes occurs through binding to specific DNA elements [6]. There are two types of NF-kb pathways: non-classical signaling pathway and classical signaling pathway. The activation of non-classical signaling pathways is slow, It mainly induces the synthesis of activated enzymes by NF-kb. NF-kb dimers activate target genes by binding to specific DNA binding sites. The major signaling target genes of NF-kb include genes encoding pro-inflammatory factors (e. g. TNF, IL-1), growth factors, chemokines and NF-kb signal inhibition sites. The activation process of classical signaling pathways is rapid and can activate pro-inflammatory cytokines instantaneously. PAMPs and DAMPs work through specific receptor ligand molecules [7]. NK-kb regulates related proteins to affect tumor growth, proliferation and metastasis.

This paper mainly adopts the methods of literature review and theoretical analysis, by combing and analyzing the relevant theories and literatures on the influences of TNF-α, NF-kb and NLRP3 on tumor cells, the author mainly summarized TNF-α. The effect of NF-kb and NLRP3 on tumor. At the same time, combined with specific cases, a deeper understanding of the interaction between inflammatory factors and tumors will provide the basis for tumor immunotherapy. This paper analyzes the current situation, problems and causes, and also provides reference for relevant researchers.

2. TNF-α and Tumor Cell Invasion and Metastasis

When TNF-α was first discovered, it induced hemorrhagic necrosis of tumors. And multiple studies have shown that TNF-alpha does indeed fight cancer, Exogenous TNF-α can directly interact with malignant tumor cells by inducing apoptosis, but toxic effects can also occur. TNF-α can also cause indirect necrosis of tumor cells by increasing vascular permeability in synergy with liposome mediated chemotherapy, but most experiments have not proved its effectiveness, so further experiments are needed to prove it [8]. Therefore, TNF-α has an inhibitory effect on most tumor cells.

In the TME of a solid tumor of breast cancer, using experiments in mice, the researchers found that the various subunits of the NF-kB transcription factor exhibit disparate levels of expression across the distinct subtypes of BC affecting patients. NF-kB primarily relies on the RELA subunit as a pivotal subcellular pathway for its regulatory functions. A positive correlation was observed between the expression of specific subunits of NF-kB and elevated levels of TNF-α in BC patients. The decline of LYRM7 induced by TNF-a leads to a reduction in the assembly of mitochondrial supercomplexes and an increase in the levels of ROS, thereby increasing the invasion and migration potential of these cells are phenomena that I am meticulously examining, making sure that I am acutely aware and vigilant towards any changes or progress in this regard. TNF-α is a key factor in the induction of LYRM7, which in turn regulates mitochondrial function under inflammatory conditions [6]. Therefore, the level of TNF-α determines the growth of breast cancer. In stomach cancer, research has indicated that the concentration of TNF-α in the peritoneal serum of individuals with gastric cancer is substantially elevated, and during the progression of chronic gastritis with Hp infection to precancerous lesions and then to gastric cancer, the higher the level of TNF-α, the more serious the lesion of gastric mucosa (figure 1). The abnormal expression of TNF-α may be one of the mechanisms by which Hp promotes the occurrence and development of gastric cancer [9]. For a few tumor cells, such as breast cancer tumor cells, TNF-α affects the metastasis of tumor cells mainly by regulating the expression of LYRM7.

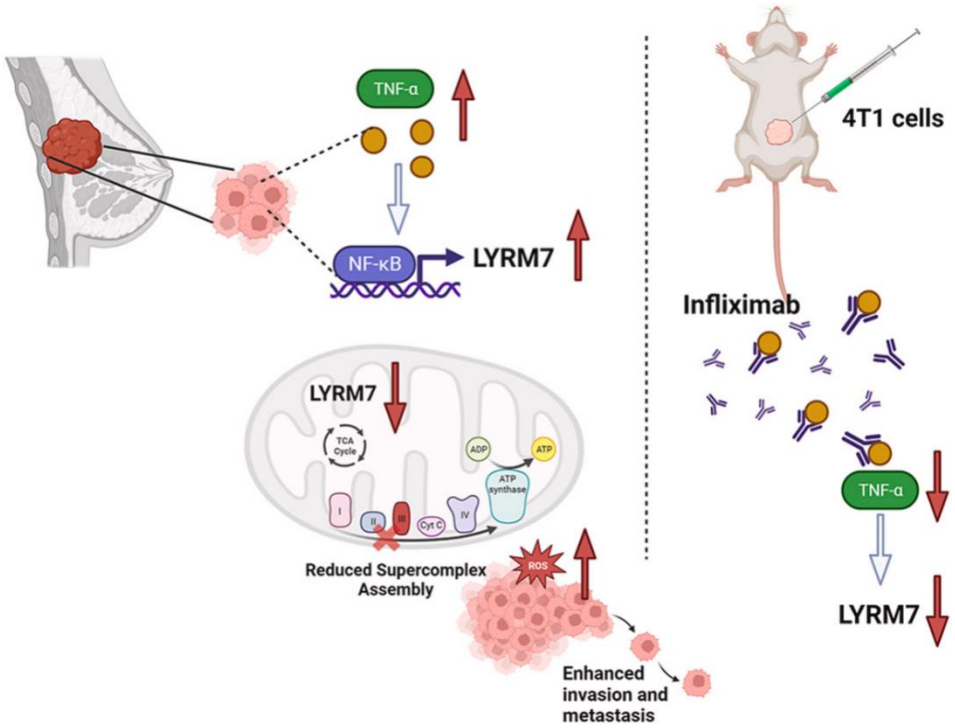

Fig. 1 Pathogenesis of BC [6].

3. NF-kb and Tumor Growth and Metastasis

Whether the abnormal expression of NF-kb affects a range of solid tumors (like GC, BC and cervical cancer), The inflammatory microenvironment of TME mainly rises the gene mutation rate by dependent manner of active nitrogen and reactive oxygen intermediates to promote tumor growth. In inflammatory cells like macrophages, neutrophils and lymphocytes, NF kb promotes malignant tumor parenchymal and stromal cells to induce the impression of TNF-α, IL-6 and IL-1β [10]. For example, NF-kb is a key survival factor that inhibits TNF-α induced apoptosis signaling, so inhibition of NF-kb and its related regulatory factors can greatly reduce the tumor-promoting effect of TNF-α. C. orbiculatus ethyl acetate extract (COE) can inhibit TNF-α induced NF-kb pathway, by reducing the expression of NF-kb and phosphorylation of IkBα in GCC, epithelial mesenchymal transformation and invasion of gastric cancer were inhibited. Therefore, inhibiting the survival signal mediated by NF-kB and promoting the expression of Caspase 3 can release the death signal [11]. Although it has been shown to have significant anticancer effects, the specific mechanism is not fully understood. In addition, for malignant cells (TNF-α), pro-inflammatory cytokines activate classical NF-κB, promoting the expression of Bcl-2, EBI, IAP and other related anti apoptotic cells, thus promoting tumor cell survival and cancer development. For example: In CAC mouse experiments, mice with IKKβ deletion in intestinal cells, inducing tumor development through AOM and DSS, showed a significant reduction in the growth and mortality rate of tumors, but the size of the tumor remains unchanged. Intestinal cells lacking Ikkβ are prone to undergo apoptosis within a few days subsequent to their exposure to AOM and DSS. This phenomenon can be attributed, at least in part, to the depletion of IKKβin MC. Because impaired BCL-X expression leading to a marked decrease in the quantity and dimensions of the tumors has been observed, indicating a favorable response to the treatment regimen. This is the outcome that arises from the unchecked proliferation of impairments, due to decreased production of NF-kb rely on pro-inflammatory cytokines in myeloid cells [10]. In gastric cancer, NF-kb can activate cytokines and promote the increase of proteins, thus promoting the proliferation of tumor cells.

In addition, the inflammatory mediator prostaglandin E2 (PGE2) also activates NF-κB through the EP4-MAPK and phosphoinositol 3-kinase (EP4-PI3K) pathways in colorectal CSC, thereby promoting tumor growth, invasion, and metastasis [12]. In the TME environment, the nuclear factor

kappa-light-chain-enhancer of activated B cells (NF-kB) exerts a regulatory influence over the programmed cell death ligand 1 (PD-L1) expression, which helps link together the immune-related markers of cancer. In lung cancer, There exists a direct regulatory connection between the expression of PD-L1 and EGFR by NF-kB pathway. This intricate crosstalk not only plays a pivotal role in modulating the cell proliferation, survival, and differentiation but is also intricately involved in orchestrating the immune evasion strategies of cancer cells. The Mutations in EGFR that result in constant tyrosine kinase-driven phosphorylation contribute to the activation of NF-kB and the induction of PD-L1 expression. Therefore, TK inhibitors are commonly used to reduce the expression levels of PD-L1, interventions targeting NF-kB pathway can be employed. In terms of specific mechanisms, EGFR triggers phosphorylation of AKT, IκBα, and ERK, leading to accumulation of PD-L1 and HIF-1α. Thus, The activation of EGFR has the potential to significantly enhance the expression of PD-L1 by phosphorylation through hypoxia inducible factor-1. In addition, HIF-1αcan support activation of the NF -kB pathway through transcription of IKKβwhile directly inducing p65 [13]. Therefore, in colon and lung cancer, NF-kb primarily functions to suppress the expression of PD-L1 or use other drugs through the NF-kb signaling pathway to inhibit the growth of tumor cells with low levels of PD-L1 (Figure 2).

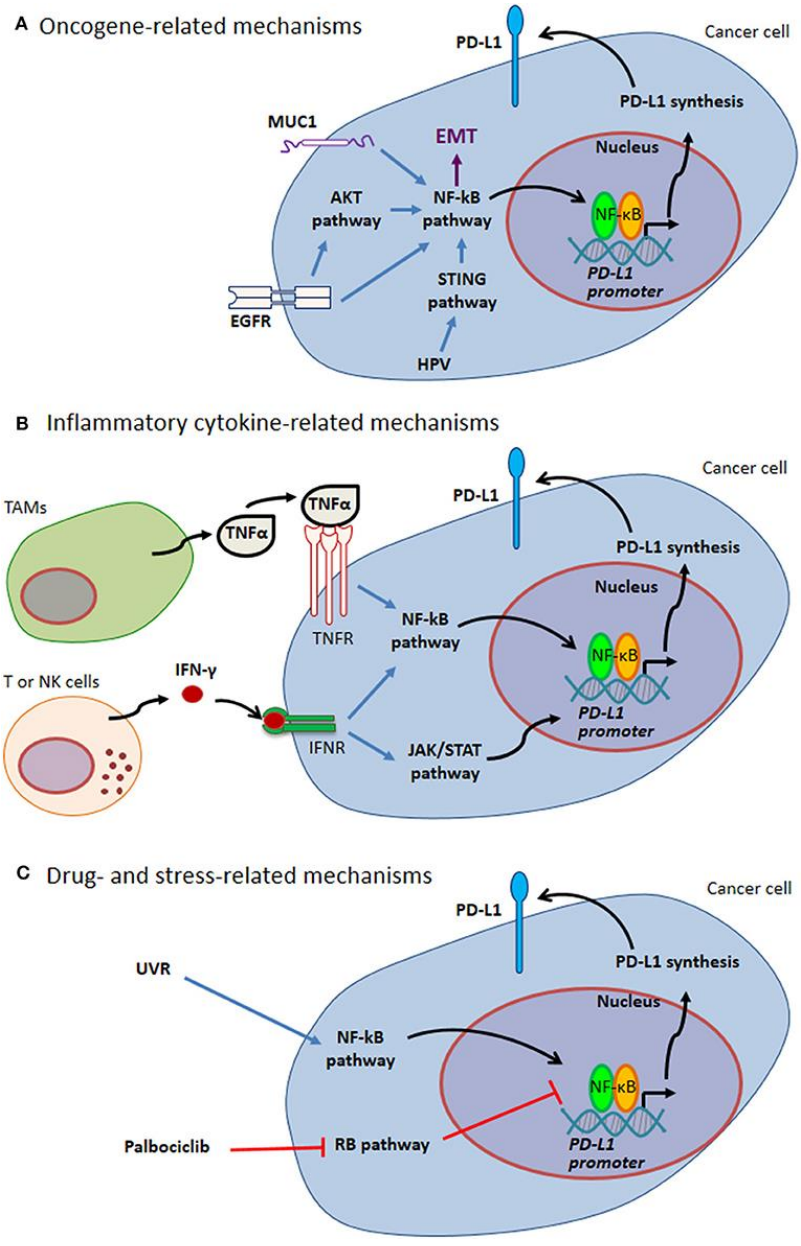

Fig. 2 Mechanism of NF-kb expression of PD-L1 in tumors [13].

4. NLRP3 and Tumor Invasion and Metastasis

In rectal cancer, NLRP3 activation inhibits metastatic growth by triggering immune system activation, acting as an inhibitor of tumor formation. [14], Inflammasomes, which are pivotal in the activation of the innate immune response, exhibit a dysregulated expression in NLRP3-deficient mice is involved in the secretion of IL-18, and delivering recombinant IL-18 to NLRP3-deficient mice led to a reduction in tumor formation that The development of tumors following AOM and DSS treatment indicates that Interleukin-18, facilitated by NLRP3, plays a protective role in the context of CAC and potentially in other cancer types. In addition, NLRP3 deficient mice have been shown to increase. The CRC has invaded the liver, manifesting as a metastatic proliferation that exhibits unchecked malignancy, this is caused by a disruption in IL-18 signaling, which adversely impacts the maturation of liver NK cells, their surface presentation of the death ligand FasL, and their capacity to eliminate FASL-sensitive tumors [15]. In addition, it has been shown that knocking out the NLRP3 inflammasome can increase the risk of liver metastasis of colorectal cancer in mice by reducing the expression of IL-18, suggesting that activating the NLRP3 inflammasome can inhibit liver metastasis of colorectal cancer [16]. However, mice lacking ASC or CASP1 further supported the critical role of NLRP3 inflammatosomes in preventing tumor development compared to blank controls, demonstrating that NLRP3 acts protectively in CRC inflammation models by promoting the formation of inflammasomes [17]. IL-1 signaling plays a pivotal role in orchestrating the intricate dance of cellular processes that ultimately determines the trajectory of tumor development. The IL-1R signaling in T cells and EC contributes to tumor promotion, whereas the pro-tumorigenic effects are mitigated by the AT properties of IL-1R signaling in MY [15]. So in colon cancer, NLRP3 can inhibit tumor cells primarily by affecting interleukin.

While the NLRP3 inflammasome acts as a tumor suppressor gene in colon cancer, it may play a promoting role in other kinds of tumors (Figure 3). Mice lacking NLRP3 or CASP1 in in-situ breast cancer had a reduced number of lung metastases. It has been shown that the triggering of inflammasome and consequent generation of IL-1β in PT establishes a supportive TME for tumor metastasis by recruiting myeloid SC and TA Mac are actively recruited into tumor tissues, where they perform critical functions in modulating the TME and suppressing immune responses [11]. In addition to breast cancer in situ, among other types of cancer, Doxycycline can curtail the activation of the NLRP3 inflammasome, which is provoked by lipopolysaccharides, in PC3 and A549 cells, inhibit cell proliferation and promote cell apoptosis, and slow down tumor development. Studies have also shown that inhibiting the expression of NLRP3 inflammasome can reduce the activation of Caspase-1 and the subsequent release of IL-1B are critical steps in the signaling cascade that orchestrates the inflammatory response and IC activation, thus inhibiting the rampant proliferation and far-reaching metastasis of liver cancer cells [16]. Therefore, for in-situ breast cancer, lung cancer, liver cancer, etc. Some drugs or cytokines can reduce the level of NLRP3 and inhibit the growth and metastasis of tumor cells.

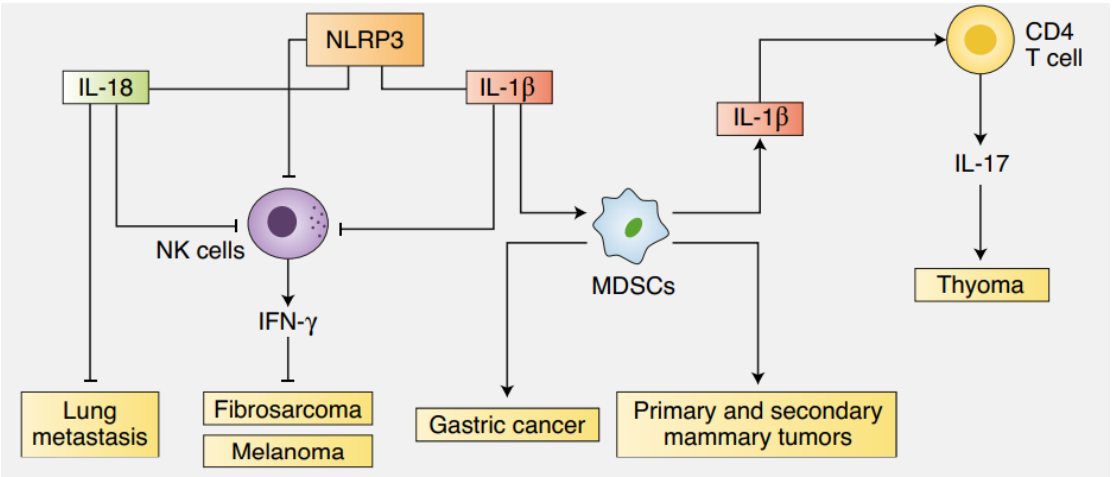

Fig. 3 The role of NLRP3 inflammasome in cancer [16].

5. Conclusion

The impacts of TNF-a, NF-kb and NLRP3 on tumor cells are different in different tumor environments. In some cancers like colon cancer stomach cancer , BC, TNF-α, NF-kb and NLRP3 can inhibit tumor growth, invasion and metastasis through different cytokines and signaling pathways, it was inversely proportional to tumor cells. But in other malignancies, like liver cancer, LC and BC, under the influence of certain proteins and cytokines, TNF-a, NF-kb and NLRP3 proliferates to create an environment for tumor cells to grow and develop. When tumor cells are in equilibrium with TNF-q, NF-kb, and NLRP3, the manifestation of these inflammatory mediators is curtailed, thus inhibiting tumor growth and invasion, But at the same time, the inhibition of these inflammatory factors will also induce a decrease in the level of T cells, which will make the body's immunity decline. Therefore, in the future, we can inhibit the expression of these inflammatory factors while keeping the level of T cells at a normal level, so as to maintain the body's immunity in a normal state, which is worth our efforts to study.

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