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Relation Between Tumour Microenvironment And NF-κb Pathway

Sejal Saraf, Anurupa Das, Sajal Somankar

Guide: Ms Megha Chaturvedi (Assistant Professor)

Department of Biotechnology, Kalinga University, Raipur, Chhattisgarh, India

Abstract

The tumour microenvironment (TME) is essential for the advancement, spread, and resistance to therapy of cancer. The NF-κB pathway is a crucial regulatory mechanism in the tumour microenvironment (TME) that influences several biological processes, including as inflammation, immunity, cell proliferation, and survival. This abstract examines the complex connection between the tumour microenvironment (TME) and the nuclear factor kappa B (NF-κB) pathway, emphasizing their combined impact on cancer progression and treatment outcomes.
The tumour microenvironment (TME) consists of a diverse range of cellular and non-cellular constituents, such as immune cells, fibroblasts, extracellular matrix, and signaling molecules. Together, these components form an intricate and interrelated system that facilitates the development of tumours. In this particular situation, the NF-κB pathway is often activated in an unusual way, leading to the creation of an inflammatory environment that supports the growth and survival of cancer cells. Persistent activation of NF-κB in cancer cells may trigger the activation of genes that promote angiogenesis, suppress apoptosis, and create an inflammatory milieu that supports tumour proliferation.Moreover, the interaction between cancer cells and the supporting elements of the tumour microenvironment (TME) via NF-κBsignaling pathways might influence immunological responses, resulting in evasion and inhibition of the immune system. Tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which are often found in the tumour microenvironment (TME), play a crucial role in boosting NF-κBsignaling, hence influencing this process significantly. Consequently, they improve the settings that inhibit the immune system inside the microenvironment.Therapeutically, focusing on the NF-κB pathway offers a hopeful strategy to disrupt the supporting function of the tumour microenvironment (TME) in cancer development. Preclinical investigations have shown that NF-κBsignaling inhibitors have the ability to decrease tumour development and enhance the effectiveness of conventional therapy. Due to the intricate structure of the tumour microenvironment (TME) and the many impacts of the nuclear factor kappa B (NF-κB), it is crucial to thoroughly evaluate possible adverse reactions and devise techniques to accurately target the route inside the TME.

Gaining insight into the correlation between the tumour microenvironment (TME) and the NF-κB pathway is crucial for acquiring information about cancer biology and formulating efficient treatment approaches. The ongoing interaction between NF-κBsignalling and the elements of the tumour microenvironment (TME) underscores the need for comprehensive approaches in cancer therapy that target both internal and external features of the tumour.

Keywords: Tumour proliferation, chronic inflammation, activation of NF-Kb pathway

Introduction

Tumour metabolism mainly includes glycolysis. Cancer cells switch from “cellular respiration” to very inefficient glycolysis for their ATP needs, a phenomenon describes by Otto Warburg in 1924. This unique way of energy consumption leads to proliferation of tumour cells. The rate of glycolysis is faster when compared to healthy cell glycolysis rate. It creates the conditions favourable for tumours to grow and in this way tumour creates a microenvironment around itself. TME provides a barrier against the immune system reactions present in the body. TME is formed due to the presence and accumulation of pro inflammatory cytokines. Therefore, provides inflammatory reactions due to the presence of inflammatory cells. Tumours have activated pathway known as Nuclear factor NF-kb pathway which is responsible to provide immunity to the pathogens which promotes tumour survival. NF-kb is a transcriptional factor which is responsible for inflammation. When the inflammatory cells interferetumour growth, it is recognized by immune surveillance of tumours. The main motive of this pathway is to provide the hypoxic conditions by producing cytokines. There are 5 transcriptional factors which forms various hetero/homo dimmers of Rel proteins and bind to the promoter region to carry out transcription. The canonical pathway responsible for activation of NF-kb pathway includes the activation of the inhibitor of Kb (IkB) kinase (IKK) complex.

Components of tumour microenvironment

Tumour microenvironment has proliferating tumour cells, blood vessels,tumour stroma and infiltrating inflammatory cells. Immune cells present are T lymphocyte, dendritic cells, occasional B cells, macrophages, PMNL and NK cells. Tumour cells frequently downgrade the expression of HLA (Human Leukocyte Antigen) and are enriched in MICA and MICB (both are ligands of MHC that express NKG2D molecules) their presence is the reason of the protection of tumour from the immune system. These features make tumour cells susceptible to NK cell mediated cytotoxicity.

TIL (tumour infiltrating lymphocytes) consist of major components in TME, CD3+ CD4+ and CD3+ CD8+ T cells. Effector T cells is a proof of immune surveillance but it is not effective to stop tumour growth. Treg cells suppress proliferation of other T cells by IL-10 and TGFβ secretion.

Tumour Associated Macrophages(TAM) produces inhibitory lymphocyte response and releases IL10,prostaglandins and reactive oxygen species(ROS).

Myeloid Suppressor Cells (MSC) suppresses the immune response by production of an enzyme Arginase 1 that synergizes with iNOS to increase superoxide and NO production. MSC recruitment is by tumour itself as tumour produces IL10, VEGF. GMSCF and block DC and lymphocyte functions.

PMNL are infrequently seen in infiltrates of tumour. Granulocyte is seen as a major component in infiltrates of murine tumours.

Chronic inflammation

Chronic inflammation is a slow inflammation, response by our immune system that sticks around long after an infection/ injury. TME undergoes changes which resembles to the process of chronic inflammation which starts with ischemia followed by interstitial and cellular edema that leads to appearance of immune cells and finally tissue repair. Chronic inflammation is involved in proliferating the tumour cells. Accumulation of Treg cells in TME downregulates response against "self" which leads to suppression of antitumour immunity.

Hypoxic environment of tumour by the action of NF-kb pathway

Hypoxic conditions are created early in the stages of tumour formation. It allows entering of the inflammatory cells that depend upon glycolytic pathway for its survival.They also contribute to the hyperproduction of ROS (Reactive Oxygen Species). The inhibitory activities of ROS are mediated by NF-kb pathway.

NF-kb pathway is responsible for the production of cytokines which are important for tumour growth. The cytokines are secreted by the action of TNFα and other proinflammatory cytokines that activates the cytokine genes for proliferation. The infiltration of leukocytes continuously releases these growth factors that causes growth of tumour.

NF-kb pathway mechanism

Nuclear Factor- kb is a major contributor of inducing and maintaining a chronic inflammatory microenvironment. It is a master transcription factor made up of 5 transcription factors, NF-kb1, NF-kb2, RelA, RelB, C Rel. These transcription factors which forms various hetero/homo dimers and bind to the promoter region to start transcription. This pathway can be activated by various factors like cytokines (TNFα), growth factors (EGF), bacterial and viral products(LPS, dsRNA), UV and ionising radiations, DNA damage and oncogenic stress. This pathway is involving in diseases like cancer, arthritis, asthma, multiple sclerosis, inflammatory bowel diseases, atherosclerosis.

The canonical pathway of this NF-kb leads to activation of Rel A and c-Rel complexes. An alternative NF-kb pathway is activated by Lymphotoxinβ(TNF family cytokine), BAFF and TNFSF13B(B cell activating Factor), CD40 ligand, resulting is the activation of RelB/p52 complexes.

The regulation of pathway depends upon different requirement of IKK subunits. It has 2 types of kinase subunits, IKKα and IKKβ and a regulatory subunit IKKϒ. The IKKβ and IKKϒ are required for the activation of canonical pathway that includes phosphorylation of IkB. IKKα is required for the alternative pathway of NF-kb which includes phosphorylation of p100(precursor of p50). The proteins present are translocated to the nucleus where it can activate the transcription of its targeted genes.

The production of proinflammatory cytokines is dependent upon NF-kb pathway. It is difficult to interpret the association of NF-kb with inflammatory disease as production of both, anti-inflammatory as well as pro inflammatory mediators occurs. By the help of Cre/lox gene targeting technology, it shows that Nf-kb is involved in the inflammatory response which is tissue specific. The studies have also confirmed that NF-kb causes leukocyte apoptosis during inflammatory response.

Studies have also shown that NF-kb proteins have roles both in pro and anti-inflammatory responses. In a knockout mousehomodimer p50 was seen in the resting T cells and decreased responses of p50 was seen in activated T cells. Overexpression of p50 was seen to repress IL-2 expression and increased

response of p50 lead to suppression of TNFα. These studies suggests that NF-kb can have anti-inflammatory roles by directly suppressing the pro inflammatory genes.

The alternative NF-kb pathway activates IKKα by a kinase called NIK(NF-kb Inducing Kinase). Studies in mice has shown that this pathway plays an important role in formation of lymphoid organs and B lymphocyte functions. A study was conducted in a transgenic mouse in which the activation loop of the kinase was mutated and alanine residues were added in place of serine ($IKK\alpha^{AA}$). It was observed that the IKK complex lacked NIK inducible activity of IKKα. Studies have shown that IKKα deficient macrophages showed an increased level of expression of proinflammatory cytokines and also induced an increase proliferation of T cells. Rel B deficient mice have shown an anti-inflammatory role but it is not connected with NF-kb hence suggesting that other components of alternative NF-kb pathway can cause anti-inflammatory responses. Rel B has also shown a role in endotoxin tolerance suggesting that other components of alternative NF-kb pathway can have anti-inflammatory roles. The mechanism of anti-inflammatory response is still not clear. Rel B also seems to regulate the stability of IkBα and limits canonical Nf-kb activation.

Other effects of NF-kb pathway

Other than inducing a chronic inflammatory microenvironment, it is also involved in various other processes which contribute to the growth and proliferation of the tumour.

- **Prevents apoptosis**:

It is found that NF-kb pathway inhibits apoptosis by expressing anti apoptotic genes (caspase-8 inhibitor of FLIP), c-IAP1/2 and XIAP(inhibitor of apoptosis protein). Tumour cells may rely on NF-kb pathway to avoid apoptosis.

NF-kb has shown to inhibit pathogen induced apoptosis in macrophages (invitro). Studies have shown that inhibition of NF-kb pathway decreased Fas(CD95) ligand expression, important for Activation Induced Cell Death(AICD).

- **Promotes angiogenesis:**

An angiogeneticfactor, VEGF(Vascular Endothelial Growth Factor), found responsible for angiogenesis which is regulated by HIF-1α and by cytokines and oncogenes are considered mediators of NF-kb activators. Inhibition of NF-kb seems to abolish production of VEGF in a variety of conditions which results in inhibition of angiogenesis. Various factors like basic fibroblast growth factor(bFGF), IL-8, matrix metalloproteinease-9 (MMP-9) and other NF-kb targeted genes are involved in the process of angiogenesis.

- **Promotion of Metastasis:**

Epithelial Mesenchymal Transition (EMT) is seen in the early stages of metastasis. Twist1 is a transcription factors which is seen as NF-kb target during the stimulation of TNFα in breast cancer. CAM like integrins, selectins are mostly regulated by NF-kb pathway. NF-kb plays a role is providing a suitable environment for the proliferation of primary tumour cells during the pre-metastatic stage.

- **Regulation of tumour metabolism:**

Studies show that activation of NF-kb in p53 mouse embryonic fibroblast(MEF) increases the expression of the transporter GLUT 3 and maintains a high glycolytic flux. High level of glycolysis is proven to activate the NF-kb pathway via an O linked N- acetylglucosamine(O-GlcNAc) modification of IKK2. NF-kb regulates cytochrome c oxidase(SCO2) which is involved in mitochondrial respiration. The mediation is done by p53. In the absence of p53, NF-kb translocate to the nucleus and blocks the mitochondrial oxidative phosphorylation, causing the Warburg effect.

NF-kB, Kras and p53:

Mutations of Kras and p53 are found in highly in colorectal and pancreatic cancer. Nf-kB is highly regulated by Kras and p53 genes. The activation of Kras mutation and deficiency of p53 resulted in the activation of Nf-kB pathway(lung adenocarcinoma in mouse studied by Jack and colleagues). Kras mutation alone is sufficient to activate Nf-kB pathway in-vitro as well as in-vivo.

The canonical pathway of Nf-kB required activation of IKK2, non-canonical pathway similarly requires IkB kinase, TBK1, seen in Kras mutant tumours. Glycogen synthase kinase (GSK3α) is also seen in the Kras mutated tumour. Inhibition of the same suppresses the growth of pancreatic tumour. GSKα not only stabilize the TAK1/TAB complex, it also controls the level of NF-Kb 2 (p100, non-canonical pathway) in the nucleus. Apoptosis of colon tumour (Kras induced) is seen due to inhibition of TAK1 complex. p62 deficient mice are seen to have an effect in protection of ROS induced cell death. Kras increases p62 expression which protects the cell. p62 is having 2 Nf-Kb binding sites, sustains NF-kb activation, downstream of Kras.

PRO AND ANTI-TUMEROGENESIS:

As we have discussed NF-kB can be a contributor to tumorigenesis. However, in very specific cases, it can be a tumour suppressor, liver tumour being the prime example. In studies related to HCC [Hepatocellular Carcinoma] model, Nf-Kb is being proven as a promoter of tumorigenesis but in DEN[Diethyl Nitrosamine] induced HCC model deletion of IKK2 resulted in the promotion of tumour growth. Similar cases are seen in skin where inhibition of Nf-kB in keratinocytes increased the chance of SCC[Squamous Cell Carcinoma].

Interestingly there are 2 signalling mechanisms, Nf-Kb and JNK that counter regulate one another. If Nf-kB is inhibited, JNK signalling increases oxidative stress and the damage to the DNA.

Relationship between TME and NF- kb pathway

It discusses the relationship between the tumor microenvironment (TME), autophagy, and immune responses in cancer, emphasizing the important role of the NF-κB pathwy . Autophagy's dual role in modulating the NF-κB pathway and influencing the polarization of tumor-associated macrophages (TAMs) is highlighted. Moreover, the natural compound Baicalin is identified as selectively targeting M2 macrophages, promoting TAM repolarization towards an M1-like phenotype and inhibiting hepatocellular carcinoma (HCC) growth in vivo. These conditions illuminate the mechanisms governing the TME and suggest promising avenues for cancer therapy, particularly in HCC management.

Conclusion:

The advancements in technology led to discoveries of many contributors of cancer whether it be physical or a chemical reaction inside our body. Our immune responses play a vital role in our body. Excessive inflammation could be a reason for the proliferation of tumour. Nuclear Factor, Nf-kB, is found as an active contributor towards cancer. It's canonical as well as non-canonical pathway factors result in excessive inflammation by increasing the level of hormone cytokine which thereby create a hypoxic environment, favourable for the growth of tumour. Many tests have been done which also states that Nf-kB could also be a suppressor of tumour in many cancers, for example lung adenocarcinoma, skin cancer. Due to its dual action purposes the Nf-kB pathway is extensively studied. Suppression of Nf-kB pathway could be a very possible way of reducing the growth as well as life span of tumour in a short period of time.

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TL Whiteside Professor of Pathology, Immunology and Otolaryngology, University of Pittsburgh School of Medicine and the Hillman Cancer Center, Pittsburgh, PA, USA.

Toby Lawrence Inflammation Biology Group, Centre d'Immunologie Marseille-Luminy, Parc Scientifique de Luminy, Case 906, 13288 Marseille, France.

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