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Inflammation, Immunity, and Cancer: The Role of Transcription Factors NF-κB and STAT3

Khie Khiong,* Oeij Anindita Adhika, Melisa Chakravitha*****

**Biology Departement, Immunology Division of Central Research for Medicine Sciences, Faculty of Medicine, Maranatha Christian University, Bandung*
***Anatomy Departement, Faculty of Medicine, Maranatha Christian University, Bandung*
****Faculty of Medicine, Maranatha Christian University, Bandung*

Abstract: *A link between inflammation and cancer has long been suspected. Recent studies have identified the role of transcription factors nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) in inflammation-induced tumor. In this review, we focus on the role of NF-κB and STAT3 in regulating functions of cancer cells and surrounding non-tumorigenic cells to create a tumor microenvironment that enhance tumor promotion and progression.*
Key word: *inflammation, cancer, NF-κB, STAT3*

Inflamasi, Imunitas dan Kanker: Sebuah Tinjauan Mengenai Peranan Faktor Transkripsi NF-κB dan STAT3

Khie Khiong,* Oeij Anindita Adhika,** Melisa Chakravitha***

**Bagian Biologi dan Divisi Imunologi, Pusat Penelitian Ilmu Kedokteran (PPIK), Fakultas Kedokteran, Universitas Kristen Maranatha, Bandung*
***Bagian Anatomi Fakultas Kedokteran, Universitas Kristen Maranatha, Bandung*
****Fakultas Kedokteran, Universitas Kristen Maranatha, Bandung*

Abstrak: *Sejak lama telah diduga bahwa terdapat hubungan yang erat antara proses inflamasi dan kanker. Penelitian-penelitian mengenai* ***transcription factors nuclear factor-κB*** *(NF-κB) menunjukkan bahwa NF-κB dan* ***signal transducer and activator of transcription 3*** *(STAT3) memiliki peranan dalam proses tumorigenesis yang diinduksi oleh inflamasi. Pada tinjauan sekarang, kami menitik-beratkan peranan NF-κB dan STAT3 dalam meregulasi sel-sel kanker dan sel-sel yang berdekatan dengan sel-sel kanker dalam menciptakan lingkungan mikro yang akan memicu timbulnya kanker dan perkembangan tumorigenesis.*
Kata kunci*: inflammation, kanker, NF-κB, STAT3*

Introduction

Cancer is a hyperproliferative disorder that involves morphological cellular transformation, dysregulation of apoptosis, and metastasis.[1] For about two millennia, a causal relationship between inflammation and cancer has been suspected. It was Galen who first noted this relationship and later in the 19th century Rudolf Virchow had demonstrated the presence of leukocytes in malignant tissues and claimed that tumors arise from regions of chronic inflammation.[2]

Clinical observations also support the idea, for example chronic inflammations induced by hepatitis C virus (HCV), *Helicobacter pylori*, and ulcerative colitis (UC) are important risk factors for malignancies such as hepatocellular carcinoma (HCC), gastric cancer, and colon cancer, respectively. The finding that the long-term use of non-steroidal antiinflammatory drugs (NSAIDs) decreases cancer risk (40-50% reduction in the case of colon cancer) strengthens the proposed link between inflammation and cancer.[1,3-6] Furthermore, several non-infectious causes of chronic inflammation such as cigarette smoke, asbestos, and silica also increase the risk of developing cancer.[7]

In cancers, many of the cell types active in chronic inflammation were found in the surrounding stroma and also within the neoplasm itself.[8] Now, it has been realized that the development of cancers from inflammatory condition might be a process driven by inflammatory cells as well as a variety of mediators, including cytokines, chemokines and enzymes, which altogether establish an inflammatory microenvironment.[9] The immune system has been called a 'double-edged sword' because it serves as tumor suppressor as immune surveillance on the one hand and as an initiator and/or promoter of tumors on the other.[7,9] The innate immune response is thought to promote tumor growth, whereas the adaptive immune response is thought to suppress tumor growth.[1] The direction in which the balance is tipped, either towards tumor suppression or progression depends partly on cell types and partly on the cytokines profile that is predominantly expressed in the tumor microenvironment.[6]

Commensurate with their ability to regulate genes encoding key-cancer promoting inflammatory mediators, activation of transcription factors nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) are central in determining whether immune responses in the tumor microenvironment promote or inhibit tumorigenesis.[10] In myeloid cells, NF-κB and STAT3 regulate production of inflammatory mediators, cytokines, and growth factors. Whereas in target tumors or pretumorous cells, these transcription factors regulate cell proliferation, antiapoptosis, immune regulation, and invasion. Therefore, these transcription factors play multiple roles in inflammation-linked tumor development.[7] An understanding of these transcription factors signaling pathways would be beneficial to find new targets for cancer treatment and prevention.

NF-κB

NF-κB is a sequence-specific transcription factor that is known to be a key molecule in inflammation,[11,12] because it regulates the proinflammatory transcriptional programs that organize and execute inflammatory responses.[13] Recent evidence also indicates that NF-κB and the signaling pathways that are involved in its activation are important for tumor development.[11] This hypothesis was based on a large body of circumstantial evidence, such as the frequent presence of constitutively activated NF-κB in diverse solid malignancies and the well established ability of NF-κB to upregulate production of key proinflammatory cytokines and enzymes, including TNF-α, IL-1, IL-6 and COX-2,[5] which provide newly emerging tumors with an inflammatory microenvironment that supports tumor progression, invasion of surrounding tissues, angiogenesis, and metastasis.[1] NF-κB also regulates the expression of many genes whose products can suppress tumor cell death, enhance epithelial to mesenchymal transition (which has an important role in tumor invasiveness), and stimulate tumor cell cycle progression.[1]

The mammalian NF-κB family consists of 5 members: NF-êB1 (p50), NF-κB2 (p52), c-Rel, RelB, and RelA (p65). Most members of this family can homodimerize, as well as form heterodimers with each other. In unstimulated cell, inhibitor of NF-κB (IκB) proteins sequester the NF-κB dimer in the cytoplasm. During chronic infection, NF-κB becomes activated in response to production of pathogen associated molecular patterns (PAMPs) or through proinflammatory cytokines such as TNF-α and IL-1, during persistent inflammation.[5] The key regulatory event in NF-κB activation is the phosphorylation of IκB proteins by the IκB kinase (IKK) complex, which leads to IκB protein ubiquitylation and subsequent degradation. Released NF-κB dimers translocate to the nucleus and bind to κB sites in the promoters which leads to their transcription.[13]

The IKK complex comprises two catalytic subunits IKKα and IKKβ which induce two NF-κB activation pathways, the classical (canonical pathway) and the alternative (non-canonical pathway) respectively. The classical pathway is triggered by proinflammatory stimuli including proinflammatory cytokines, bacterial-cell wall components, viruses, and DNA-damaging agents. The classical NF-κB activation depends on IKKα activity which leads to phosphorylation of the inhibitory protein IκB, allowing NF-κB (which are mostly comprised of RelA:p50 heterodimers) to translocate to the nucleus and to exert their function as transcriptional regulators. By contrast, the non-canonical NF-κB activation is triggered by certain TNF-family member, depends on IKKα, and induces the processing of NF-κB2/p100:RelB dimers. Owing to the variety of target genes of the classical pathway, which include those encoding mediators of inflammation, cytokines, chemokines, proteases and inhibitors of apoptosis, it has been proposed that the classical

NF-κB activation pathway might link inflammation to tumor promotion and progression.[4]

The first evidence of NF-κB having a direct and indirect role in tumorigenesis came from the colitis-associated cancer (CAC) model through the deletion of IKKβ in intestinal epithelial cells (IECs) (which are the cells that undergo malignant progression) or the inhibition of NF-κB signaling in myeloid cells[7]. This model showed different mechanisms of NF-κB in regulating function of IECs and myeloid cells to create a microenvironment that enhance tumor promotion and progression.

Tanaka's group established an inflammation-dependent colon tumor-model in mice, in which tumors developed after a single dose of genotoxic colonic carcinogens, azoxymethane (AOM) followed by dextran sulfate sodium (DSS) in drinking water. In this model, deletion of IKKβ in intestinal epithelial cells did not decrease inflammation, but rather, led to a dramatic decrease in tumor incidence without affecting tumor size. So, the tumor-promoting function of NF-κB in IECs is not associated with its ability to activate proinflammatory genes, but rather with its ability to suppress the apoptosis of pre-neoplastic progenitors.[4,7,12] NF-κB inhibits apoptosis by inducing the expression of antiapoptotic genes, such as Bcl-2 family members and caspase inhibitor.[14]

Nonetheless, a second mechanism through which NF-κB can affect tumor promotion results from its ability to induce the production of proinflammatory factors by myeloid cells. Deletion of IKKβ in myeloid cells resulted in a significant decrease not only in tumor number, but also in tumor size. The decrease in tumor size is a consequence of diminished proliferation of transformed epithelial cells, which requires growth factors that are produced by myeloid cells including TNF-α and IL-6, which can act on mutant cells to affect tumor incidence and tumor size.[4,7,12]

NF-κB also has the ability to promote tumor metastasis and angiogenesis. NF-κB induces production of matrix metalloproteinases (MMPs), proteolytic enzymes that promote tumor invasion or surrounding tissue. Recent evidence showed that IKKα promotes metastasis in prostate cancer through inhibition of mammary serine protease inhibitor (maspin), a critical suppressor of metastasis.[5,15] NF-κB activation was also found to stimulate angiogenesis, possibly by inducing expression of IL-8 and vascular endothelial growth factor (VEGF).[11]

STAT3

Immune cells in the tumor microenvironment not only fail to mount an effective antitumor immune response, but also interact intimately with the transformed cells to promote oncogenesis actively. STAT3 which is a point of convergence for numerous oncogenic signaling pathways is constitutively activated both in tumor cells and immune cells in the tumor microenvironment. The constitutive activation of STAT3 can be propagated, in part through STAT3-regulated factors such as VEGF and IL-10, from tumor cells to diverse immune cells, mediating a crosstalk between the two, which, in turn, generates immunosuppression involving both innate and adaptive immunity. Because STAT3 is also crucial for tumor-cell proliferation and survival, tumor angiogenesis, and invasion, a direct link between traditional oncogenesis and immunosuppression is embodied in the STAT3 pathway.[16]

STAT3 was first identified as a DNA-binding factor that is activated by IL-6 to regulate gene expression in the acute-phase inflammatory response.[17] The activation of STAT signaling pathways requires tyrosine phosphorylation of STAT proteins. But because many cytokine receptors do not have intrinsic tyrosine-kinase activity, ligand engagement leads to the activation of receptor-associated tyrosine kinases, which are usually members of the Janus kinase (JAK) family. In addition to cytokines, STAT3 are also activated by many growth factor receptors with intrinsic tyrosine-kinase activity and non-receptor tyrosine kinases such as SRC and ABL. After tyrosine phosphorylation, STAT3 molecules dimerize and translocate to the nucleus, where they directly regulate gene expression.[6,16]

In normal cells and under physiological conditions, the activation of STATs is rapid and transient, because they are negatively regulated by proteins such as suppressor of cytokines signaling (SOCS) and protein inhibitor of activated STAT (PIAS).[16] However, in tumorigenesis, STAT3 induces the expression of many cytokines, chemokines and other mediators, such as IL-6 and COX-2, that are associated with cancer-promoting inflammation. Importantly, receptors for many of these cytokines, chemokines and mediators in turn further activate STAT3, thus forming autocrine and paracrine feedforward loops that result in a stable change to the genetic program and the promotion of cancer inflammation.[10]

As STAT3 mediates both the expression of and response to inflammatory cytokines, it is thought that STAT3 activity in tumor cells could promote cytokine-induced tumor growth, whereas STAT3 activity in immune cells could modulate cytokine production to inhibit tumor specific-immune responses or inflammation.[18] *In vitro* and *in vivo* findings show that STAT3 activity in tumor cells can negatively influence the expression of immune-stimulating molecules. Further work revealed a cascade of events in which proinflam-matory mediators produced by tumor cells owing to STAT3 blockade could activate innate immune cells, including macrophages and neutrophils, leading to their further secretion of proinflammatory mediator and increased cytotoxicity against tumor cells.[16]

STAT3 mediates tumor-immune escape through inhibition of dendritic cell (DC) maturation. DCs in the tumor microenvironment are usually immature, being characterized by an insufficient level expression of MHC class II complexes, co-stimulatory signals such as CD80 and CD86, and IL-12. Not only are these DCs incapable of activating anti-

gen-specific $CD8^+$ T cells, but they can also induce immune tolerance. The STAT3-associated inhibition of DC maturation was mediated, by VEGF, IL-6 and IL-10. STAT3 also induce regulatory T (T_{Reg}) cells proliferation, which have an important role in sustaining the immunosuppressive environment in tumors. In addition to secreting IL-10, T_{Reg} cells also secrete TGFβ, thereby suppressing $CD8^+$ T cell activation directly or indirectly through DCs.[19] Moreover, it appears that the tumor microenvironment promotes the generation of $FOXP3^+$ (forkhead box P3) T_{Reg} cells that mediate IL-10-dependent, cell-contact independent suppression.[20] In addition, STAT3 activation in macrophages, neutrophils and natural killer (NK) cells decrease their anti-tumor cytotoxic-activity.[16]

Crosstalk Between NF-κB and STAT3

As discussed above, both STAT3 and NF-κB have crucial and integrated roles in inflammatory responses that promote cancer development and growth.[10] Although NF-κB and STAT3 signaling pathways are persistently activated in various malignancies, as yet, no activating mutations have been found in the genes encoding these transcription factors in solid tumors. Instead, mutations occur either in upstream receptors such as *GP130*, which encodes a subunit of the IL-6 receptor (the activation of which results in STAT3 hyperactivation in liver tumors) or in genes encoding negative regulators of STAT3 signaling, such as SOCS3 in lung cancer. However, the most common mechanism by which NF-κB and STAT3 transcriptional programs are induced is not through mutation of proteins in their pathways, but by an excess of activating cytokines provided in an autocrine or paracrine manner.[6]

Translocation of NF-κB dimers to the nucleus results in the transcription of a myriad of proinflammatory genes, such as cytokines, chemokines, proangiogenic factors, adhesion molecules, antiapoptotic proteins, and inducible enzymes. Most of them overlap with the target genes of STAT3. This is because the promoter region of many of those genes contains GAS (Gamma activated sequence) or ISRE (STAT-binding elements) in addition to κB (NF-κB binding element) sites.[6]

Recent evidence also suggests that accumulation of RelA in the nucleus can be promoted through acetylation by p300, which required STAT3 activation. Consequently, persistent activation of RelA in tumor cells, as well as in non-transformed cells in the tumor microenvironment, requires continuous STAT3 signaling. Just as STAT3 can increase NF-κB activity in cancer, persistent activation of STAT3 in tumors, especially in immune cells of the tumor microenvironment, is dependent on NF-κB (specifically RelA). This reciprocal relationship with RelA stems from the fact that several cytokines and growth factors encoded by RelA target genes are STAT3 activators such as IL-6, IL17, IL-21 and IL-23. Therefore, not only do these two transcription factors need each other for their persistent activation in cancer, they also ensure the continued expression of their activators, facilitating the stable establishment of this feedforward loop and a permanent change in the genetic program.[10]

However, NF-κB is involved not only in procarcinogenic inflammation, but also in antitumor immune responses. STAT3, conversely, is a specific regulator of procarcinogenic inflammation, driving cancer-promoting inflammatory conditions while simultaneously suppressing antitumor immune responses. Intriguingly NF-κB and STAT3 are frequently persistently activated in the same tumor cells, and in tumor associated myeloid cells. STAT3 inhibits the expression of NF-κB target genes involved in Th1 innate immunity and adaptive immune responses important for controlling microbial infections and tumor growth. In this way, STAT3 opposes the activation of anti-tumor immunity programs by NF-κB when both are activated in the same cells. Therefore, STAT3 interacts with NF-κB at multiple levels and the consequence of this interaction is highly context dependent.[10]

Targeting NF-κB and STAT3 for Cancer Therapy

For decades, tumor therapies have concentrated on cytotoxic regimens aimed at killing tumor cells directly. A better understanding of the molecular changes that occur in the tumor microenvironment and their importance during tumor development paved the way for strategies that target specific cytokines or the recruitment of inflammatory cells. But, instead of inhibiting cytokines and chemokines, targeting the central regulators NF-κB and STAT3 seems to be a good alternative. However, there is one caveat to the potential of NF-κB and STAT3 as drug targets: the unwarranted effects that the long term suppression of the STAT3 and/or NF-κB pathways could have on the immune system.[6]

Ablation of IKK shows that this kinase has a role in the inflammatory response but, surprisingly, it is also necessary for tissue repair, including in conditions in which inflammation is the main mediator of tissue injury. Subsequent work has shown that ablation of IKK activity, through either deletion of the gene that encodes IKKγ or of the genes that encode IKKα and IKKβ, is crucial for the maintenance of the colonic epithelium. Therefore, although NF-κB fulfills its expected role in inducing pro-inflammatory gene-expression programs, it also surprisingly has an important role in the resolution of inflammation and in tissue repair process[13].

STAT3 is an important factor in T cell migration and its blockade could have undesirable effects on the antitumor immune response.[6] A recent study involving conditional ablation of *Stat3* gene showed that STAT3 has a role in facilitating wound healing. The ability of STAT3 to inhibit inflammation, induce growth, block apoptosis, and stimulate migration, invasion, and angiogenesis as shown in cancer, therefore, reflects its role in orchestrating wound healing.[16]

The development of specific delivery methods as the use of selective compounds might help to limit such side effects. Several NF-κB or STAT3 inhibitors have been developed and provided promising results in pre-clinical models. Specific IKKâ inhibitors demonstrated great efficacy in lymphoid malignancies, such as multiple myeloma and a subgroup of diffuse large B-cell lymphoma, and could therefore represent invaluable novel theurapeutics. However their potential to treat solid tumor is yet to be clarified. Specific inhibitors of STAT3 including antisense oligonucleotides, peptides, peptidomimetics, small molecule inhibitors and platinum complexes have also been developed. One such small-molecule inhibitor, STA-21, prevents STAT3 dimerization and DNA binding, and inhibited the growth of breast cancer cells. However, it will be exciting to see how well this specific inhibitors perform in the clinic and whether they will be superior to targeting single cytokines and chemokines in terms of efficacy and side effects.[6]

Concluding Remark

From the earliest pathology studies dating back to the 1800s, cancer has been known to be associated with inflammation. Indeed, many human cancers arise and progress in the setting of chronic inflammatory states. NF-κB and STAT3 are among the most frequently activated oncogenic transcription factors and both regulate cancer-associated inflammation. For this reason, there is considerable interest in the therapeutic inhibition of NF-κB and STAT3 in cancer disease. However, recent reports suggest that severe harmful consequences could result from the inhibition of NF-κB and/or STAT3. Therefore a better understanding in NF-κB and STAT3 signaling pathways is needed to find new strategies for cancer prevention and treatment.

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