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REVIEW

NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer

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ABSTRACT

Although links between cancer and inflammation were firstly proposed in the nineteenth century, the molecular mechanism has not yet been clearly understood. Epidemiological studies have identified chronic infections and inflammation as major risk factors for various types of cancer. NF-κB transcription factors and the signaling pathways are central coordinators in innate and adaptive immune responses. STAT3 regulates the expression of a variety of genes in response to cellular stimuli, and thus plays a key role in cell growth and apoptosis. Recently, roles of NF-κB and STAT3 in colon, gastric and liver cancers have been extensively investigated. The activation and interaction between STAT3 and NF-κB play vital roles in control of the communication between cancer cells and inflammatory cells. NF-κB and STAT3 are two major factors controlling the ability of pre-neoplastic and malignant cells to resist apoptosis-based tumor-surveillance and regulating tumor angiogenesis and invasiveness. Understanding the molecular mechanisms of NF-κB and STAT3 cooperation in cancer will offer opportunities for the design of new chemo-preventive and chemotherapeutic approaches.

KEYWORDS inflammation, tumorigenesis, NF-κB, STAT3

INTRODUCTION

The functional relationship between inflammation and cancer was initially proposed in 1863 by Rudolf Virchow based on his observation that a high number of leukocytes presented in tumor samples (Balkwill and Mantovani, 2001). About 17% of the global cancer burden is attributable to infectious agents, and inflammation is a major component of these chronic infections (Parkin, 2006). Most, if not all, solid tumors are infiltrated with immune and inflammatory cells (Grivennikov and Karin, 2008). Inflammation is involved in different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis (Grivennikov et al., 2009). Therefore, cancer-related inflammation (CRI) has been suggested to represent the seventh hallmark of cancer (Colotta et al., 2009) (Fig. 1). Additional with other six hallmarks (self-sufficient proliferation, insensibility to anti-proliferative signals, evasion of apoptosis, unlimited replicative potential, sustained angiogenesis, tissue invasion and metastasis) are required for cancer development (Fig. 1) (Hanahan and Weinberg, 2000).

The strong associations between inflammation and cancer are concluded from both clinical and epidemiological studies. Infectious agents, such as *Helicobactro pylori* and *Papillomaviruses*, promote carcinogenesis (Psyrri and DiMaio, 2008; Marusawa and Chiba, 2010; Polk and Peek, 2010). Obesity, tobacco smoke and inflammatory bowel disease that act as non-infectious agents can also increase the risk of cancer development (Park et al., 2010). Studies show that inflammatory microenvironment is as important as the tumor cell population (Mantovani, 2009). During carcinogenesis, the host antitumor activity is suppressed, and therefore, tumor-promoting immune activity supports tumor growth, angiogenesis, invasion and metastasis (de Visser et al., 2006). Nevertheless, how inflammation promotes tumor growth and how cancerous cells suppress anti-tumor immunity remain a significant challenge. Characterization of signal pathways involved in cancer-related inflammation will help to find novel targets for cancer prevention and treatment. Recently, genetic knockout mice models and biochemical studies have revealed that two transcription factors, NF-κB and STAT3, are major factors linking inflammation to cancer.

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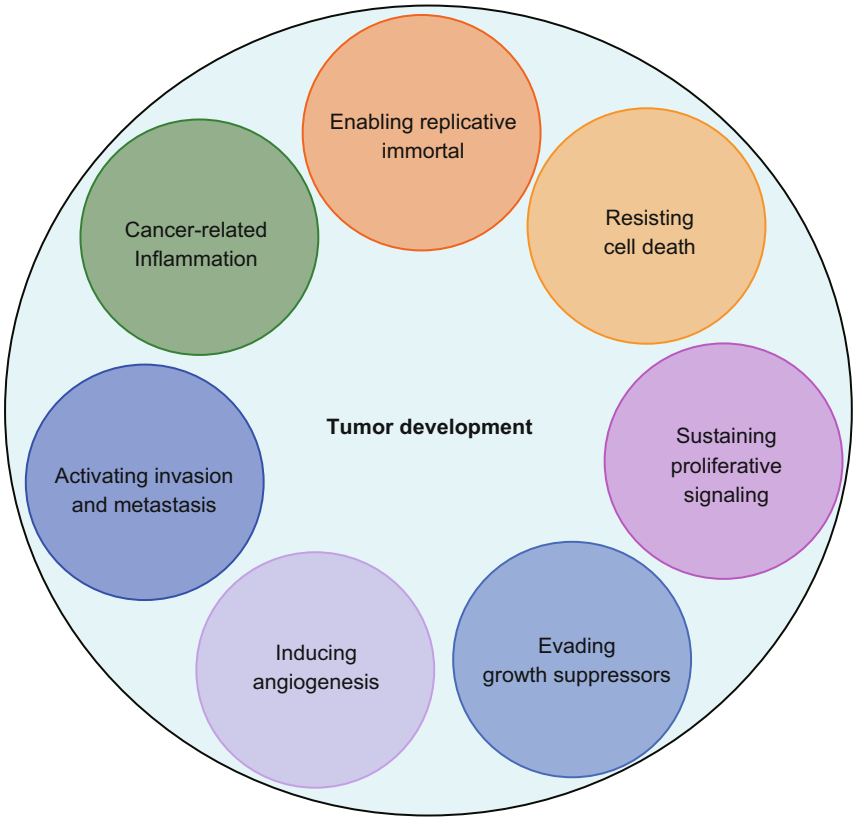

Figure 1. Seven hallmarks of cancer.

INTERPLAYS BETWEEN INFLAMMATION AND TUMORIGENESIS

The immune system interacts with tumor throughout its development (Fig. 2). Several types of inflammation may inhibit tumor growth and progression, but most of types promote tumorigenesis. Infections with *Helicobacter pylori*, hepatitis B/C, Schistosoma or bacteroides are linked to gastric cancer, hepatocellular carcinoma, bladder cancer and colon cancer, respectively (Karin, 2006; Wu et al., 2009). Another type of chronic inflammation that precedes tumor development is inflammatory bowel disease (IBD) which greatly increases the risk of colorectal cancer (Waldner and Neurath, 2009). Recent work has shown that tobacco smoke acts as tumor promoter via triggering chronic inflammation (Takahashi et al., 2010). Similarly, obesity promotes tumorigenesis in the liver and pancreas partially through obesity-induced chronic inflammation (Khasawneh et al., 2009, Park et al., 2010). However, not all of chronic inflammatory diseases increase cancer risk. Several studies show that psoriasis, one type of chronic inflammatory diseases, even reduces the cancer risk (Nickoloff et al., 2005). To date, it is still not clear how inflammation interacts with tumorigenesis. One fact is that inflammation does impact every single step of tumorigenesis, from initiation to metastatic progression (Fig. 2).

The tumor microenvironment contains innate immune cells,

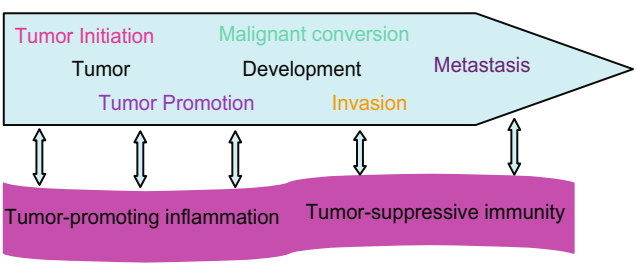

Figure 2. Tumor-promoting inflammation and tumor-suppressive immunity are involved in every single step of tumorigenesis.

adaptive immune cells, cancer cells and their surrounding stroma (de Visser et al., 2006). During tumor initiation, an inflammatory microenvironment can enhance the proliferation of mutated cells (Hussain and Harris, 2007; Polyak et al., 2009; Wang et al., 2010). In addition, inflammatory cells can also increase mutation rates through serving as sources of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) that are able to induce DNA damage and genomic instability (Miletic et al., 2007; Faux et al., 2009; Pan et al., 2009; Hursting and Berger, 2010; Zargan et al., 2011). The process of tumor growth from a single initiating cell into a fully developed primary tumor is called tumor promotion, which is stimulated by inflammation-driven mechanism. Based on current investiga-

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tions, inflammation-induced tumor promotion may occur early or late in tumor development through production of tumor-promoting cytokines by immune/inflammatory cells (Moore et al., 1999; Eferl and Wagner, 2003; Yu et al., 2007; Grivennikov et al., 2009; Yu et al., 2009; Grivennikov and Karin, 2010). Angiogenesis, which is required for growth of large tumors, is triggered by tumor hypoxia. In hypoxic conditions, tumor associated macrophages are recruited to tumor sites and in turn produce chemokines and proangiogenic factors (Kujawski et al., 2008). Hypoxia also induces the expression of HIF-1α, which further stimulates expression of CXCL12. CXCL12 then activates and recruits endothelial cells in a CXCR4-dependent manner (Murdoch et al., 2008). In clinic, metastasis is the most critical step of tumorigenesis, because over 90% of cancer mortality is caused by metastasis. The process of metastasis can be grossly divided into four major steps: (1) Epithelial-mesenchymal transition (EMT); (2) Invasion into blood vessels; (3) Traveling through the circulation; (4) Proliferation of single metastatic progenitor cells. The level of many proinflammatory cytokines is elevated in cancer patients and increases the probability of cancer cells to successfully metastasize to other sites. TNFα and IL-6 can promote metastasis and the survival of circulating metastatic seeds (Nguyen et al., 2009). TGFβ activates SMAD transcription factors and MAPKs to regulate EMT and elevated TGFβ is often associated with poor prognosis (Yang and Weinberg, 2008; Yang et al., 2008).

Rag2-deficient mice, which lack mature lymphocytes and show enhanced development of a variety of spontaneous cancers by 14–16 months old, provided the first experimental evidence of tumor immunosurveillance (Shankaran et al., 2001). While, in the vast majority of established tumors, tumor-infiltrating lymphocytes are insufficient for curtailing tumor growth, resulting in a revised version of the immunosurveillance theory called immunoediting (Dunn et al., 2004; Smyth et al., 2006). In the process of tumorigenesis, cancer cells constantly edit and modulate the host antitumor immune response and the host immune response shapes tumor immunogenicity and clonal selection. Via the immunoediting, the balance between antitumor and tumor-promoting immunity can be tilted in favor of tumor growth. The cancer cells edit their repertoire of tumor antigens toward lower immunogenicity and also reshape the tumor microenvironment to become immunosuppressive. It in part explains the reason why cancers in alymphocytic mice are more immunogenic than that in immunocompetent mice (Shankaran et al., 2001). Also the interplays between inflammation and tumorigenesis are clear. However, how inflammation-associated cells interact and communicate with each other and with cancer cells remains a big challenge. Until recently, genetic knockout mouse models functionally showed two transcription factors (NF-κB and STAT3) are critical regulators in cancer associated inflammation.

NF-κB SIGNALING TRANSDUCTION PATHWAY

NF-kappa B (NF-κB) or Rel proteins comprise a family of structurally-related eukaryotic transcription factors. It has been showed that NF-κB transcription factors are involved in controlling a large number of normal cellular and organismal processes, such as immune and inflammatory responses, developmental processes, cellular growth, and apoptosis (Gilmore et al., 2004; Hoffmann and Baltimore, 2006; Bhoj and Chen, 2009; Vallabhapurapu and Karin, 2009). NF-κB proteins are related through a highly conserved DNA-binding/dimerization domain called the Rel homology (RH) domain and can be divided into two classes. The second class (the Rel proteins) containing C-terminal transcription activation domains, includes c-Rel, RelB and RelA (p65) (Fig. 3). Upon activation, the Rel proteins translocate to nucleus and bind to 9–10 base pair DNA sites (called κB sites) as dimers. Members of the first class (the NF-κB proteins: p105 and p100) have long C-terminal domains that contain multiple copies of ankyrin repeats, which act to inhibit these molecules. They become active and shorter DNA-binding proteins (p105 to p50, p100 to p52) by either limited proteolysis or arrested translation (Fig. 3). As such, members of the first class are generally not activators of transcription, except when they form dimers with members of the second class of NF-κB transcription factors.

NF-κB acts as a “rapid-acting” primary transcription factor to regulate many cellular responses. Many stimuli can induce NF-κB activity, such as tumor necrosis factor alpha (TNFα), interleukin 1-beta (IL-1β), bacterial lipopolysaccharides (LPS), ionizing radiation, reactive oxygen species (ROS), etc (Osborn et al., 1989; Basu et al., 1998; Kida et al., 2005; Qin et al., 2005). Most of the NF-κB activators induce the degradation of IκB protein via activation of the IκB kinase (IKK) complex (IKKα, IKKβ and IKKγ). With the degradation of IκB, the NF-κB complex is then freed to enter the nucleus where it can 'turn on' the expression of specific genes that have NF-κB DNA-binding sites (canonical NF-κB pathway). However, a select set of cell-differentiating or developmental stimuli, such as BAFF, RNAKL or lymphotoxin, activate the non-canonical NF-κB pathway to induce RelB/P52 dimer in the nucleus. Unlike canonical NF-κB pathway, in non-canonical NF-κB pathway, ligands induce NF-κB inducing kinase (NIK) activation. NIK phosphorylates NF-κB2 protein and leads to proteasomal processing of the NF-κB2 precursor protein p100 into mature p52 subunit. Then p52 dimerizes with RelB to regulate a distinct class of genes (Bonizzi et al., 2004).

The physiological roles of each member of NF-κB family have been studied in knock-out mouse models (Fig. 3). Genetic data showed specific and redundant functions of each member of NF-κB family proteins in the regulation of innate and adaptive immune responses and cell survival (Fig. 3). RelA deficiency in mice causes embryonic lethality due to extensive apoptosis in the liver (Beg et al., 1995). Mice lacking p50, p52, c-Rel or RelB respectively, are immunodeficient, but develop normally to adulthood (Kontgen et al., 1995; Sha et al., 1995; Weih et al., 1995; Caamano et al., 1998) (Fig. 3). Besides their physiological roles, aberrant activation of the NF-κB pathway is involved in the pathogenesis of a number of human

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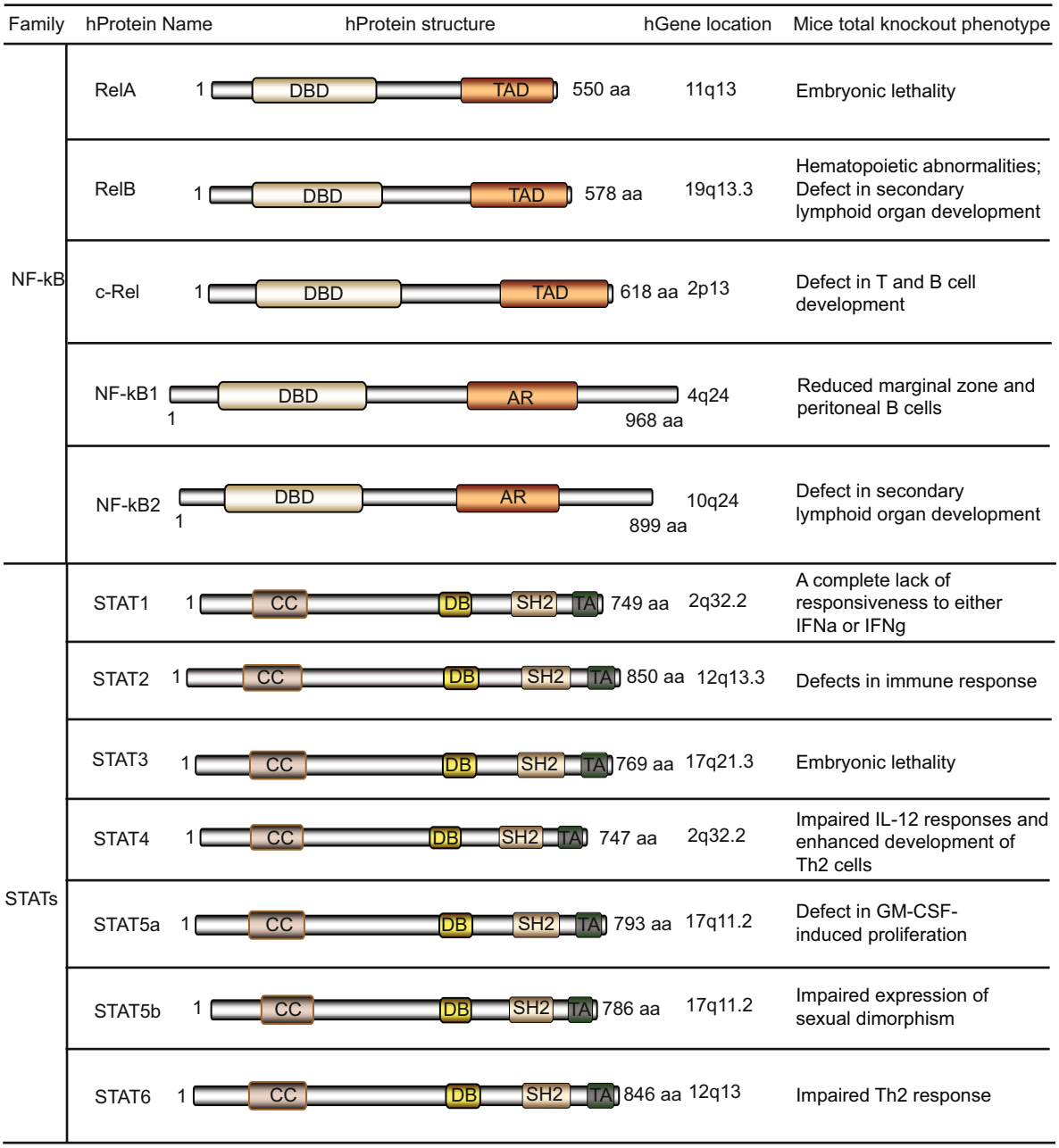

Figure 3. Phenotypes of total knockout mice of each member of NF-κB and STATs families.

diseases including cancer. V-Rel, a highly oncogenic retroviral homologue of c-Rel, causes carcinogenesis in avian lymphoid cells which provided the first evidence for a role of NF-κB in tumorigenesis (Hoelzer et al., 1979). Indeed, constitutive NF-κB activity has been observed in a number of human cancers (Staudt).

CRITICAL ROLES OF NF-κB IN INFLAMMATION AND CANCER

Constitutive activation of NF-κB, which is defined as persistence of NF-κB in the nucleus, is shown in a wide variety of tumor types, such as lymphoma, liver cancer, lung cancer, breast cancer, etc (Mann et al., 2006; Qiao et al., 2006; Baby et al., 2007; Lenz et al., 2008). Besides, NF-κB is activated in response to tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli that commonly contribute to carcinogenesis. Furthermore, NF-κB controls the expression of the genes linked with proliferation, invasion, angiogenesis, and metastasis of cancer. Based on these evidences, NF-κB is believed to be closely connected to

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the whole process of tumorigenesis (Prasad et al., 2010). The mechanism of expression of constitutively active NF-κB is not fully understood. Several mechanisms, for example activation of kinases, overproduction of cytokines, infected virus proteins have been suggested to be involved in. Constitutive NF-κB activation further upregulates major inflammatory factors, such as TNFα, IL-6, IL-1, IL-8. Such inflammatory factors are potent activators for NF-κB. Thus it is believed that NF-κB and inflammation constitute a positive feedback loop to induce cellular and DNA damage, to promote cell proliferation and transformation.

NF-κB is engaged in tumorigenesis by promotion of cell proliferation and suppression of cell death. NF-κB controls some key cell cycle regulatory genes, including cyclin D1, cyclin D2, cyclin D3, cyclin E1, c-myc, CDK2, CDK4 and CDK6 (Naugler and Karin, 2008). Recent biological evidences showed that the pro-survival function of NF-κB is related to its functional interaction with the PI3K-AKT-mTOR signaling pathway, one of the key elements in promoting cell proliferation and cell growth. When cells treated with cytokines and growth factors, AKT engages mainly IKKα in promoting NF-κB activation (Dan et al., 2008). The anti-apoptotic function of NF-κB is mainly achieved through the transcriptional regulation of an array of anti-apoptotic proteins, which can be divided into two groups. The first group mainly includes inhibitor of apoptosis proteins (IAPs), Ciap1, Ciap2, XIAP and CFLIP (Srinivasula and Ashwell, 2008). The second group mainly refers to Bcl-2 family members, including Bcl-2 and Bcl-xL (Luo et al., 2005).

Cancer metastasis, a complex cascade of biological events, finally allows tumor cells to escape from primary site and invade and proliferate at ectopic environments. NF-κB regulates the process via its transcriptional activation of target genes, including VCAM-1, ICAM-1, MMPs and CXCR4 (Helbig et al., 2003). More importantly, IKKβ/IkBα/NF-κB pathway is required for the induction and maintenance of epithelial mesenchymal transition (EMT) in the mouse model (Huber et al., 2004). IKK-dependent but NF-κB transcription-independent function is also involved in the control of metastasis. It has been shown that genetic inhibition of IKKα kinase activity promotes Maspin expression and reduces metastatic potential of the cancer cells (Luo et al., 2007). Moreover, NF-κB is involved in angiogenesis by controlling key angiogenesis factors such as VEGF, IL-6, MCP-1 and MMPs (Schmidt et al., 2007). Similar to IKK-dependent but NF-κB transcription independent control of metastasis, there is also a specific link between IKK and angiogenesis. It has been showed that IKKβ upregulates mTOR activity through direct phosphorylation of TSK1 at ser487 and ser511 (Lee et al., 2007).

STATs SIGNALING TRANSDUCTION PATHWAY

The STAT (Signal Transducer and Activator of Transcription) proteins regulate many aspects of growth, survival and differentiation in cells. The first two STAT proteins were identified in the interferon system. There are seven mammalian STAT family members who have been identified: STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5α and STAT5β), and STAT6 (Fig. 3). STAT proteins were originally described as latent cytoplasmic transcription factors that require phosphorylation for nuclear retention and activation. Structurally, each of the STAT proteins has several conserved domains which are critical for its functions. DNA binding domain is observed in the central region of each STAT protein (except STAT2) and regulates DNA binding specificity (Horvath et al., 1995). There is a conserved SH2 domain in the region between 600 and 700 amino acid residues of all seven members. Once phosphorylated, STAT proteins form homo-or hetero-dimers through interactions of phosphorylated tyrosine of one STAT and SH2 domain of another, then translocate into the nucleus. Extracellular binding of cytokines to their cognate receptors induces activation of the intracellular Janus kinase (JAK) that phosphorylates a specific tyrosine residue in the STAT protein, promoting the dimerization of STAT monomers via their SH2 domain (Aaronson and Horvath, 2002).

Biological roles of each STAT family protein have now been elucidated through studies of gene targeted mice (Fig. 3). Stat1 knockout mice are quit sensitive to infection with viral and microbial pathogens and macrophages from Stat1 knockout mice show impaired responses to IFNα and IFNδ (Durbin et al., 1996; Meraz et al., 1996) (Fig. 3). Stat2 null mice exhibit a number of defects in immune response, including an increased susceptibility to viral infection and the loss of a type I IFN autocrine/paracrine loop (Park et al., 2000) (Fig. 3). Unlike other STAT family knockout mice, Stat3 knockout mice are embryonic lethal by rapid degeneration of embryos due to the impaired functions of visceral endoderm such as nutritional insufficiency (Park et al., 2000) (Fig. 3). Stat4 knockout mice show impaired IL-12-mediated increases in IFN-γ production, cellular proliferation, and NK cell cytotoxic activity of lymphocytes (Kaplan et al., 1996; Thierfelder et al., 1996) (Fig. 3). Stat5α knockout females show impaired lobuloalveolar outgrowth during pregnancy and defective lactation, while Stat5β knockout males show a loss of sexually dimorphic pattern (Liu et al., 1997; Udy et al., 1997) (Fig. 3). Further, female mice lacking both Stat5α and Stat5β were infertile due to the impaired development of functional corpora lutea in the ovary (Teglund et al., 1998) (Fig. 3). In Stat6 knockout mice, IL-4-mediated increases in surface expression of MHC class II and IL-4 receptor a chain, cellular proliferation, IgE class switching and IL-4-induced development of Th2 cells are impaired (Libikova et al., 1975; Grusby, 1997) (Fig. 3).

FUNCTION OF STAT3 IN INFLAMMATION AND CANCER

Recent evidences suggest a crucial role for STAT family proteins, especially STAT3, in inducing and maintaining a procarcinogenic inflammatory microenvironment. Tissue specific inactivation has revealed STAT3 has complex physiological roles. Besides, STAT3 was originally identified as an acute phase

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response factor that is activated after stimulation by interleukin-6 (IL-6). It can be activated by a wide range of cytokines, growth factors, and oncogenes. Stat3-deficient T cells show severely impaired IL-6-induced cell proliferation due to the lack of IL-6-mediated prevention of apoptosis of T cells. Stat3 is also involved in IL-2 and IL-6-induced T cell proliferation (Akaishi et al., 1998). Its activation in macrophages and neutrophils has been shown to be indispensable for prevention of chronic inflammation in mice. The mutant mice are highly susceptible to endo-toxin shock with increased serum concentration of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, IL-1β, and IFN-δ. Most of the described functions of STAT3 depend on the phosphorylation status, which promote STAT3 dimerization and translocation to the nucleus or mitochondria (Gough et al., 2009).

Among the diverse functions of STAT3, it is now known that STAT3 promotes oncogenesis. STAT3 is required for cell transformation mediated by Src oncogene, which has been directly linked to human cancer (Bowman et al., 2001). Moreover, STAT3 suppresses anti-tumor immunity by antagonizing the expression of anti-tumor T helper 1 cytokines such as IL-12 and interferon-γ, which are necessary for both innate and T cell-mediated anti-tumor immunity (Kortylewski et al., 2005). And it promotes tumor growth by mediating T regulatory cell expansion in tumor and the development of Th17 T cells (Matsumura et al., 2007). In addition, STAT3-mediated malignant property is also associated with chronic inflammation. STAT3 is frequently activated in malignant cells and capable of inducing the expression of a large number of genes involved in tumorigenesis. STAT3 signalling is a major intrinsic pathway in cancer-associated inflammation. Cytokines, chemokines and other mediators are crucial for inducing and maintaining a cancer promoting inflammatory environment, and STAT3 is critical for regulating their expression. Persistent activation of STAT3 in tumor cells activates cytokines, chemokines and growth factors, which in turn activate STAT3 in stromal cells. Stromal and inflammatory cells are the main resource for inflammation mediators. Therefore, the IL6-JAK-STAT3 pathway is an important mediator of cancer inflammation in intrinsic pathway. It is also crucial for extrinsic pathway by environmental factors.

NF-κB AND STAT3 COLLABORATIVELY MEDIATE THE INTERPLAYS BETWEEN INFLAMMATION AND TUMORIGENESIS

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 mediators or in genes encoding negative regulators. However, the most common mechanism by which NF-κB and STAT3 transcriptional activities are induced is through the activating cytokines provided in an autocrine or paracrine manner. NF-κB and STAT3 act as two major transcriptional factors to link inflammation with tumorigenesis, and they functionally interact with each other at many different layers. First, the members of NF-κB like RelA can physiologically interact with STAT3 and their association can modify their transcriptional activity (Yu et al., 2002; Lee et al., 2009). Second, as two important transcriptional factors, NF-κB and STAT3 cooperatively bind at a subset of gene promoters to collaboratively induce their target genes expression (Yang et al., 2007). Third, many cytokines like IL-6 induced by NF-κB or STAT3 can feedback to induce STAT3 and NF-κB activation (Gao et al., 2007; Sansone et al., 2007; Grivennikov and Karin, 2008). Through their functional interaction, NF-κB and STAT3 collaboratively promote tumor development via induction of pro-tumorigenic genes including genes in angiogenesis and hypoxia, chemokines and immunosuppressive cytokines (Bollrath and Greten, 2009; Atkinson et al., 2010; He and Karin, 2011).

FUTURE DIRECTIONS

Although, the role of inflammation in tumorigenesis is now generally accepted and it has become evidence that inflammatory responses play decisive role at different stages of tumor development, the molecular mechanisms about how inflammation is involved in tumorigenesis are far from being completely understood (Fig. 4). The distinctions between tumor-promoting inflammation and tumor-suppressive immunity are still not clear. Clearly a better insight into following aspects will help us to develop the effective cancer therapy or even prevention: (1) Distinguish tumor-promoting inflammation and tumor-suppressive immunity in each step of tumor development including tumor initiation, promotion, malignant conversion, invasion and metastasis (Fig. 4); (2) Identify which cell type performs tumor-promoting inflammation and which cell type performs tumor-suppressive immunity in each step of tumor development (Figure 4); (3) Identify which signal transduction pathway mediates the cell-type specific tumor-promoting inflammation or tumor-suppressive immunity (Fig. 4); (4) Construct the dynamic functional interaction map involved
in innate immune cells, adaptive immune cells, stroma and cancer cells (Fig. 4).

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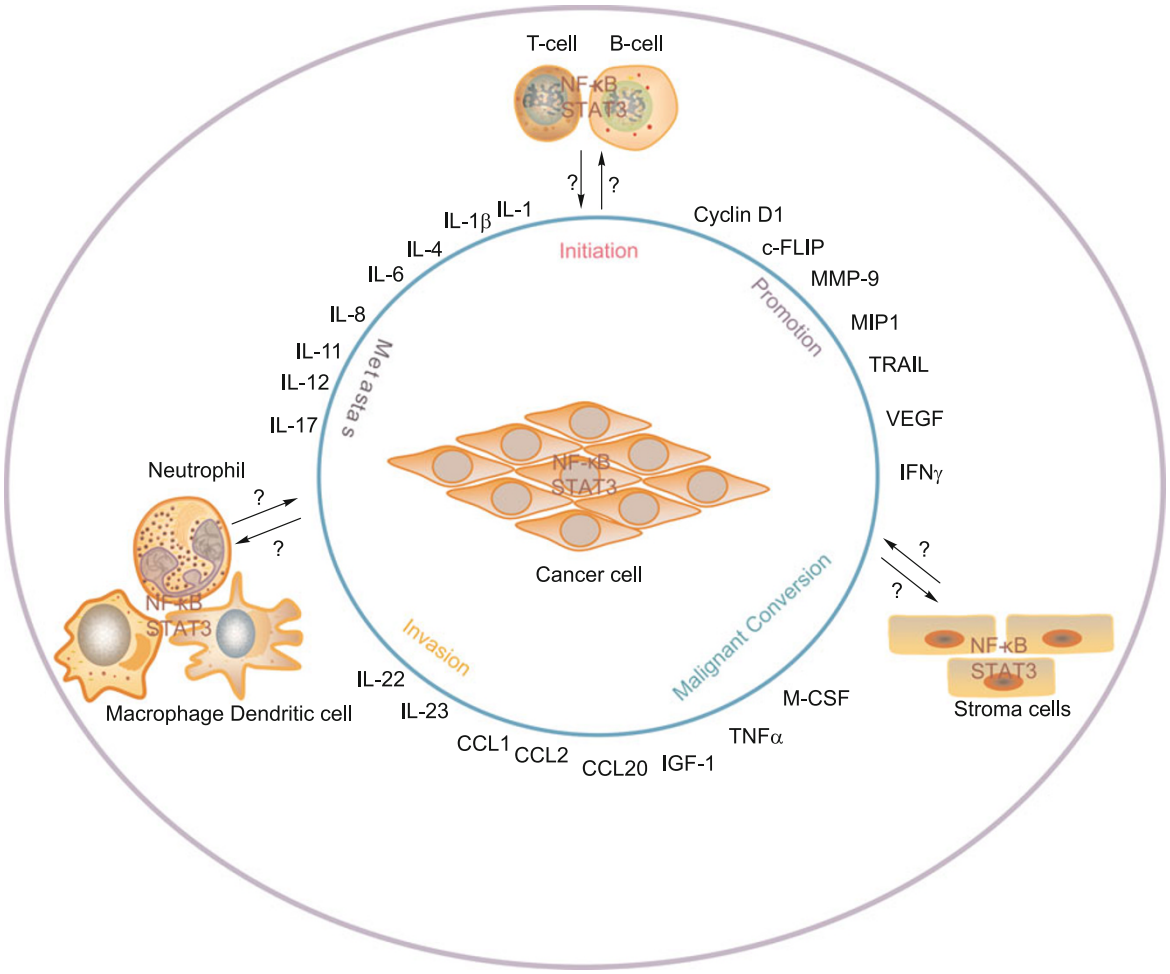

Figure 4. The role of inflammation in tumorigenesis is much complicated and it is pivotally important to dissect the role of distinct cell type in each step of cancer development.

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