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Signaling Pathways that Facilitate Chronic Inflammation-Induced Carcinogenesis

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Abstract

Recently, growing evidences have shown that chronic inflammation is the major cause of carcinogenesis. Inflammation signaling pathways can facilitate evolution and development of cancers in a variety of aspects, such as proliferation, metastasis, and apoptosis, etc. Nuclear factor-kappa B (NF-κB), janus-activated kinase (JAK)-signal transducers and activators 3 (STAT3), mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase/ protein kinase B (PKB, also known as Akt)/ mammalian target of rapamycin (PI3K/Akt/mTOR), Wnt/ β-catenin, and transforming growth factor (TGF)-β/Smad signaling pathways have been well studied, which are implicated in inflammation-induced carcinogenesis. Although tremendous of researches have reported these signaling pathways, few has explained the mechanism by which inflammation signaling pathways sustain activation during carcinogenesis. In this review, we summarized the present knowledge of 6 well known inflammation signaling pathways, especially their roles in chronic inflammation-induced carcinogenesis, reasons for the persistent inflammation, and potential inhibitors targeting key molecules for cancer therapy. This review will help in improving our understandings of how these inflammation signaling pathways take part in carcinogenesis, thus paving the way for the prediction of occurrence and prognosis as well as targeting therapy of cancers.

Keywords: Carcinogenesis; NF-κB; JAK-STAT3; MAPK, PI3K/Akt/mTOR; Wnt/β-catenin, TGF-β/Smad

Abbreviations

AP-1: Apoptosis Protein 1; APOBECs: Apolipoprotein B mRNA Editing Enzyme Catalytic Polypeptides; cPLA2α: Cytosolic Phospholipase A2α; CRC: Colorectal Cancer; EMT: Epithelial-to-Mesenchymal Transition; Evo-Dev: Evolution-Development; GC: Gastric Cancer; HBV: Hepatitis Virus B; HCC: Hepatocellular Carcinoma; hiNOS: Human Inducible Nitric Oxide Synthase; IKK: IκB Kinase; IL-1: Interleukin-1; IL-R: IL-1 Receptor; JAK-STAT3: Janus-Activated Kinase-Signal Transducers and Activators 3; JNK: c-Jun N-Terminal Kinase; MAPK: Mitogen-Activated Protein Kinase; MKK: MAPK Kinase; MMP-9: Matrix Metalloproteinase-9; NF-κB: Nuclear Factor-Kappa B; PDAC: Pancreatic Ductal Adenocarcinoma; PH: Pleckstrin Homologous; PI3K: Phosphatidylinositol-3-Kinase; PI(3,4)P2: Phosphatidylinositol 3,4-Bisphosphate; PI(3,4,5)P3: Phosphatidylinositol 3,4,5-Trisphosphate; PI(4)P: Phosphatidylinositol 4-Phosphate; PI(4,5)P2: Phosphatidylinositol 4,5-Bisphosphate; PKB: Protein Kinase B, also known as Akt; PTEN: Phosphatase and Tensin Homolog; PTK: Tyrosine Kinase; RHD: Rel Homology Domain; RXRα: Retinoid X Receptor α; SAPK: Stress Activated Protein Kinase; SH2: Scr Homology 2; SHP1/2: Src Homology-Containing Phosphatase1/2; SOCS: Suppressor Of Cytokine Signaling; TAK1: TGF-β-Activated Kinase 1; TGF-β: Transforming Growth Factor-β; TLR: Toll-Like Receptors; TNF-α: Tumor Necrosis Factor-α; TNFR: TNF-α Receptor

Introduction

The cause of malignant tumors has not been fully understood. Epidemiological studies and clinical observations have demonstrated that the environment has an important influence on the occurrence of human malignant tumors. It is estimated that more than 80% of the malignant tumors are closely related to environmental factors, such as microbial infection, chronic stimulation with chemicals, ionizing radiation, and toxin, etc. In addition to the impact of environmental factors, the occurrence of cancers is also associated with internal agents such as genetic predisposition, immune conditions, endocrine states, etc. When the organism is stimulated by persistent environmental factors whose impacts cannot be efficiently eliminated by the immune system, chronic inflammation might occur. Many chronic inflammatory diseases can lead to increased risks of cancers. Chronic hepatitis, for instance, are closely related to the occurrence of most hepatocellular carcinomas (HCC) in the world [1]. Inflammatory colonic diseases such as Crohn's disease and ulcerative colitis can also lead to an increased risk of colon adenocarcinoma [2-4]. Chronic pancreatitis caused by heavy alcohol consumption is responsible for an increased risk of pancreatic cancer [5,6]. Chronic inflammation of esophagus such as gastroesophageal reflux disease and Barrett's esophagus can cause a serious of somatic and epigenetic changes, which may ultimately lead to the occurrence of esophageal carcinoma [7]. Chronic bronchitis and emphysema increase the risks of lung cancer [8,9]. *Helicobacter pylori* infection and colonization can lead to chronic gastritis related gastric cancers [10]. Parasites infections such as *Schistosoma hematobium* in bladder, *Opisthorchis viverrini*, *Opisthorchis felineus*, and *Clonorchis sinensis* in gallbladder can cause local chronic inflammation, which can ultimately lead to the occurrence of cancers [11, 12]. Chronic inflammation contributes to

cancer initiation and progression *via* generating a tumor-supporting microenvironment. It initiates cancer development *via* inducing reactive oxygen and nitrogen species which are usually associated with DNA mutations. Because the persistent inflammation exists, mutations accumulate, of which some are driver mutations that can promote cell growth, survival, or reduce cell apoptosis [13]. During chronic inflammation, a variety of inflammation signaling pathways remain persistent activation. These include the nuclear factor-kappa B (NF-κB), Janus-activated kinase (JAK)-signal transducers and activators 3 (STAT3), mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K)/ Protein Kinase B (PKB, also known as Akt)/ mammalian target of rapamycin (PI3K/Akt/mTOR), Wnt/β-catenin, and transforming growth factor (TGF)-β/ Smad signaling pathways. In order to prevent and control inflammation-caused cancers potently, it is quite important to learn how internal inflammatory signaling pathways affect the occurrence and development of cancers.

NF-κb Signaling Pathway and Carcinogenesis

In mammal cells, NF-κB family contains 5 members, namely p65 (RelA), p50 (NF-κB1), p52 (NF-κB2), RelB, and cRel. These proteins have a same amino terminal, which is composed of about 300 amino acid residues, called Rel homology domain (RHD), with DNA binding site and dipolymerization site inside. IκB is a kind of repressor protein of 36kDa, which can interact with the amino acid residues of RHD, masking the translocation signal nuclear sequence in RHD, and preventing NF-κB translocation to preserve it in the cytoplasm. The mechanism of NF-κB activation is a complex process. Upon stimulation, Ser32/36 in the regulation region of IκB amino terminal is phosphorylated by the inhibitor of IκB kinase (IKK) complex, which results in IκB ubiquitination and subsequent degradation induced by proteasome complex [14,15]. Free from IκB, NF-κB dimmers can translocate to the nucleus and activate the expression of genes encoding cytokines, chemokines, and antiapoptotic factors which play a key role in several cellular functions, like inflammation, cell survival, proliferation, apoptosis, angiogenesis, and innate and acquired immunity [16]. When the NF-κB is continually activated, chronic inflammation occurred, which contributes to the tumor-supporting microenvironment formation. Since NF-κB is a potent inducer of the caspase-8 homolog FLICE-interacting protein, a repressor of death receptor-induced apoptosis, under chronic inflammation circumstances, it can bring abnormal transcription of this apoptosis repressor gene [17]. Thus, abnormal NF-κB activation can facilitate carcinogenesis *via* promoting cell growth as well as decreasing apoptosis. A recent research showed that the inhibition of NF-κB and MAPK signaling pathways could result in strong inhibition of pancreatic tumor cell growth but not apopotosis [18]. The extract from Sabdariffa leaf displays an inhibition function on the expression of matrix metalloproteinase-9 (MMP-9) which facilitates cancer invasiveness *via* inhibiting Akt/NF-κB/MMP-9 cascade pathway [19]. These two studies give us good examples that inhibiting NF-κB signaling pathways continued activation brings results in carcinogenesis suppression. It confirmed that blocks the chronic inflammatory process, tumor initiation or development encounters a big issue because the loss of tumor-supporting microenvironment. Supernatant of tumor-infiltrating c isolated from the resection of colorectal cancer (CRC) patients increases the growth rate of CRC cell lines *via* activating NF-κB and STAT3 signaling pathways, which indicates that abnormal activation of NF-κB and STAT3 signaling pathways can facilitate carcinogenesis [20]. Hepatocyte IKK/NF-κB promotes HCC development by maintaining liver inflammatory responses [21]. The inflammatory process triggers hepatocyte NF-κB through upregulation of TNF-α in adjacent endothelial and inflammatory cells. NF-κB inhibition by anti-TNF-α treatment or induction of IκB super repressor in later stages of tumor development results in apoptosis of transformed hepatocytes and failure to progress to HCC, which confirmed that abnormal activation of NF-κB signaling pathway contributes to HCC development [22]. Serum levels of IL-6 and TNF-α have been found to be significantly higher in HBV-infected patients with liver cirrhosis and HCC than those without and in accordance with the progress of the disease phases [23,24]. All of these researches proved that chronic inflammation induced by persistent activation of NF-κB signaling pathway facilitates carcinogenesis.

Importantly, NF-κB signaling pathway has complex interactions with other signaling pathways. Stimuli that can activate NF-κB pathway include lipopolysaccharide and anti-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which work *via* binding to toll-like receptors (TLRs) and to the TNF-α receptor (TNFR) or IL-1 receptor (IL-1R), respectively [14,25]. Upon stimulated by the corresponding ligands, TNFR-associated death domain, TNFR-associated factor, and receptor-interacting protein 1 can be rapidly assembled at the TLR/IL-1R or TNFR to form complexes, which recruit and activate TGF-β-activated kinase (TAK) 1. TAK1 subsequently phosphorylates IKK-β and MAPK kinase 4/7 (MKK4/7), which in turn cause the activation of NF-κB and c-jun-NH2-kinase (JNK) [26-28]. Since JNK signaling pathway promotes cell proliferation and inhibits apoptosis, the interaction of this pathway with NF-κB signaling pathway might amplify the tumor-promoting effects. That is to say, chronic inflammation may bring activation of different signaling pathways *via* interaction between them, resulting in amplify pro-tumorigensis results.

JAK-STAT3 Signaling Pathway and Carcinogenesis

JAK family contains four members including JAK1-3, molecules belonging to tyrosine kinase (PTK) family [29]. Once IL-6 binds to its receptor, the intracellular portion of the receptor were dipolymerized, after which JAK binds to the box function region of the receptor dimer and is activated *via* phosphorylation. Activated JAK further induces the activation of substrates surrounding the receptor dimer, including other JAK family members and STATs. STATs belong to substrates of JAK, and at the same time are kinds of DNA binding proteins with scr homology 2 (SH2) function domain. STAT can bind to tyrosine site of receptor dimer as well as KLD functional domain of JAK *via* SH2 domain. JAK phosphorylates tyrosine sites in the Y function region of STATs, causing STATs activation. With the help of SH2 functional regions, such as SIF-A (composed of STAT3 and P48), SIF-B (composed of STAT3 and STAT1), and SIF-C (composed of two STAT1s), activated STATs in the cytoplasm forms homologous or heterologous dimmers. These dimers are shifted to the nuclei and activate a variety of targeted oncogenes, leading to malignant progression of cancers [21,30]. One of the most investigated STATs molecules is STAT3. A zebrafish tumorigenesis model has been applied to explore the relationship between IL-6/STAT3 signaling pathway and hepatocarcinogenesis. Overexpression of IL-6 specifically in zebrafish livers results in a massive infiltration of inflammatory cytokines and cells, which facilitates hepatocarcinogenesis. PI3K/Akt and JAK-STAT3 pathways are activated in this model. Of the pathways, PI3K/Akt is mostly reactive to the infiltrated inflammatory cells, whereas the JAK-STAT3 is mostly implicated in hepatocarcinogenesis.

Taking the results stated above together, it is clear that JAK-STAT3 and PI3K/Akt pathways are related to inflammation-induced HCC [31]. In addition, the activation of STAT3 can also predict poor prognosis. For instance, long-term use of indomethacin leads to activation of NF-κB and JAK-STAT3 pathways which in turn results in poor prognosis of HCC [32]. STAT3 signaling pathway not only predict prognosis of cancer, but also serve as a therapeutic target. For instance, the high level of STAT3 has been associated with advanced tumor stage and decreased survival in patients with pancreatic ductal adenocarcinoma (PDAC). Inactivation of STAT3 leads to tumor growth inhibition in animal model.

Inhibition of STAT3 increases the therapeutic response in PDAC, which will be a potential adjuvant therapy for PDAC [33]. MiR-34a can inhibit STAT3 signaling pathway for cancer treatment. It has been shown that miR-34a induced by p53 inhibits epithelial-to-mesenchymal transition (EMT). Activation of IL-6R/STAT3/miR-34a feedback loop promotes EMT, invasion, and metastasis *in vitro* and *in vivo*. The expression of miR-34a can suppress tumor progression *via* inhibiting chronic inflammation induced by STAT3 signaling pathway [34]. Thus, activation of STAT3 signaling pathway promotes cancer occurrence, and prognosis, while inhibition of this pathway may lead to cancer regression.

STAT3 signaling pathway has interactions with other signaling pathways. In human liver cancer tissues, for instance, STAT3 and IκB signaling pathways are negatively correlated to each other [30]. Src homology-containing phosphatase1/2 (SHP1/2) takes part in feedback inhibition of STAT3 activation. Blocking of NF-κB leads to the oxidation of SHP1/2 *via* elevating reactive oxygen species level. Oxidized SHP1/2 has no enzymatic activity on JAK2 substrate, resulting in continued activation of JAK-STAT3 pathway [35]. Thus, JAK-STAT3 may promote malignant transformation *via* interacting with other signaling pathways.

MAPK Signaling Pathway and Carcinogenesis

MAPK, a kind of serine/threonine kinases, can phosphorylate various cytoplasmic proteins and move from the cytoplasm to the nucleus to regulate the activities of some transcription factors. MAPK activation is a critical step in the cascade reaction of phosphorylation. The classical MAPK cascade is initiated by MAPKKK activation. MAPKKK belongs to serine/threonine kinase, which can activate MAPKK. MAPKK in turn phosphorylates and activates MAPK. Generally, MAPK has 5 major subgroups, namely ERK (ERK1/ERK2), JNK/SAPK, p38MAPK (p38α, p38β, p38γ and p38δ), ERK3/ERK4 and ERK5 [36]. Mediated by a number of tyrosine kinase and cytokine receptors associated with G proteins, MAPK signaling pathway is involved in regulation of a variety of cell behaviors, like proliferation, differentiation, survival, and apoptosis.

One of the most investigated MAPKs is JNK. JNK proteins are encoded by three genes, *JNK1*, *JNK2*, and *JNK3*. The former two are ubiquitously expressed, whereas the latter one is restricted mainly to testis and brain. JNK plays an important role in cell apoptosis and proliferation. It is normally activated by MKK7 and MKK4 [37]. Like other MAPK cascades, the JNK signaling pathway regulates cell behavior in many ways, among which the cell growth regulation and carcinogenesis function of c-Jun and JNK are widely investigated. Studies have clearly established the role of JNK in cell proliferation or apoptosis induced by some inflammation cytokines, such as TNF-α, IL-10, etc. [38-40]. Under sustained expression of inflammation cytokines, like TNF-α and IL-10, JNK can phosphorylate various substrates, including c-Jun, JunB, JunD, ATF2, p53, Bcl2, Bcl-xL, Bid, Bad, and Bax proteins, thus regulating cell growth and death [41]. Since phosphorylated JunD could stimulate the transcription of potent apoptosis repressor gene *cIAP2*, which contains a composite promoter with tandem apoptosis protein 1 (AP-1) and NF-κB binding sites, JNK activation could bring JunD/Fos and NF-κB dimers cooperation and transcription in a synergistic manner [42]. This generates a positive feedback regulatory circuit. NF-κB and JNK-activated JunD induces cIAP expression, which promotes K63-linked polyubiquitination of upstream signaling molecules, leading to TAK1 activation. TAK1 in turn phosphorylates IKK-β and MKK4/7 to activate NF-κB and JNK [42]. Although the initial JNK activation mediated by TNFR1 promotes cell survival and proliferation transiently, the effect turns to be opposite when JNK activation is sustained for prolonged period. Sustained JNK activation induces Bax/Bak-dependent apoptotic pathway, which can cause mitochondrial outer membrane permeabilization, and subsequently release of cytochrome C, initiating apoptosis [43,44]. JNK can also activate apoptosis *via* transcriptional activation of apoptosis-inducing genes such as *TNF-α, Fas-L and Bak*, or *via* phosphorylation of tumor suppressor p53 and E3 ubiquitin ligase Itch homolog [45-48]. Thus, when JNK is activated for a short time, it promotes cell survival and proliferation transiently, but when JNK activation is sustained for prolonged period, it will results in cell apoptosis or tumor suppression. JNK signaling pathway plays a complex role in carcinogenesis.

Other well-known MAPKs are p38 proteins. The p38 family has four members, namely p38α, p38β, p38γ, and p38δ, also called stress activated protein kinase (SAPK) 2a, 2b, 3, and 4, respectively, which are distributed in different tissues [36]. The p38 MAPK is selectively activated by MAPKK (MKK3/6), mediated by dual phosphorylation at the Thr-Gly-Tyr motif [49]. The p38 MAPK and JNK pathways can interact at several levels. For instance, a research based on the matched primary and metastatic pancreatic cancer tissues from 36 patients discovered that high expression of pp38 MAPK was significantly associated with improved postoperative survival (median overall survival 27.9 months, P=0.041). Inhibition of p38 *via* SB202190 enhances cell proliferation. Meanwhile, p38 activity is related to low levels of pJNK expression, and *vice versa*. Furthermore, inhibition of JNK using SP600125 significantly decreases xenografts growth of tumors with high p38 activity compared with those without p38 expression. In general, p38 MAPK promotes pancreatic cancer malignancy *via* activating JNK signaling pathway [50]. In fact, cytokines including TNF-α, IL-1, IL-6, IL-8, MCP-1, and GM-CSF that are activated in chronic inflammation and tumor angiogenesis, adhesion, invasion and metastasis are all regulated by p38 MAPK. Thus, p38 signaling pathway plays an important role in promoting chronic inflammation and carcinogenesis.

PI3K/Akt/mTOR Signaling Pathway and Carcinogenesis

In the process of carcinogenesis, PI3K/Akt/mTOR pathway often turns to be dysregulated because of mutation, deletion, amplification, methylation, and post-translation modifications. It is an intracellular signaling pathway that promotes tumor progression, metastasis, apoptosis inhibition, malignant transformation, and radioresistance [51,52]. Phosphatase and tensin homolog (PTEN) is a negative regulator of PI3K/Akt/mTOR pathway [53]. It is also a quite effective tumor suppressor and is often mutated, deleted or epigenetically

silenced in different human cancers [54,55]. According to their different structure, regulation function, and *in vitro* lipid substrate specificity, PI3K family can be divided into three major classes, namely class I, class II, and class III [56]. As class I PI3K promotes carcinogenesis, it is well-studied. Class I PI3Ks are heterodimers which are composed of a 110-kDa catalytic subunit (p110) and a regulatory subunit. There are 4 p110 isoforms (p110a, p110b, p110g, and p110d) encoded by different genes and 7 regulatory subunits (p85a, p85b, p55a, p55g, p50a, p101, and p87) produced by a combination of different genes and alternative start codons [57]. The regulatory subunits can inhibit the kinase activity in normal situation by binding to the p110 catalytic subunits and stabilizing the PI3K protein heterodimers. PI3K is responsible for phosphorylating a range of membrane phospholipids including phosphatidylinositol 4-phosphate (PI(4)P) and phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2), catalyzing transfer of ATP-derived phosphate to the D-3 position of the inositol ring of membrane phosphoinositides, thereby forming the second messenger lipid phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) [58]. PI(3,4,5)P3 subsequently recruits a subset of signaling proteins with pleckstrin homologous (PH) domains binding to the membrane, including 3-phosphoinositide-dependent protein kinase-1 and Akt/PKB [59-62]. Continued expression of some inflammation cytokines, like IL-3, IL-6, IL-7, etc. could cause abnormal activation of Akt, which has the ability to phosphorylate a variety of downstream proteins including mTOR, GSK3, and IRS-1 [63], so that PI3K/Akt signaling pathway can join in multiple cellular processes such as apoptosis, therapeutic resistance, glucose metabolism, cell migration, transcription, and cell proliferation [64,65]. In addition, activation of mTOR can up-regulate the expression of multiple proteins such as cyclin D1 [66] and vascular endothelial growth factor (VEGF) [67], leading to increased carcinogenesis. In a recent study enrolling 71 gastric cancer (GC) patients whose lesion samples were tested for the expression of PI3K/AKT/mTOR pathway-related proteins by immunohistochemistry indicated that PI3K, AKT, p-4E-BP1, p-AKT, p-mTOR, eIF-4E, p-eIF-4E, P70S6K1, and p-P70S6K1 proteins were significantly over-expressed in gastric cancer tissues; whereas, the expression of PTEN protein, one of the inhibitors of PI3K, was lower in tumor tissues compared with non-tumoral tissues, indicating that the PI3K/AKT/mTOR pathway is activated in GC [68]. Another similar study raised the hypothesis that the expression of PI3K/AKT/mTOR signaling pathway may promote GC progression [69]. These researches all proved that activation of PI3K/AKT/mTOR is involved in carcinogenesis.

Wnt/β-catenin Signaling Pathway and Carcinogenesis

The name Wnt is combined by two terms, namely int and wg, two highly homologous genes in mice and Drosophila, respectively [70-72]. Wnt protein initiates signaling by binding to the Frizzled protein (a seven-span transmembrane receptor) and either LRP5 or LRP6 (two members of the low-density-lipoprotein receptor-related protein family) proteins. Wnt signaling pathways are divided into two categories, β-catenin-dependent and non-β-catenin-dependent signaling cascades. A hallmark of the β-catenin-dependent signaling is the stabilization of cytoplasmic β-catenin and translocation into nuclei, while the non-β-catenin-dependent signaling is mediated by planar cell polarity pathway and small GTPase proteins. High levels secretion of TNF-α, IL-1β and IL-6 cytokines contribute to Wnt/β-catenin signaling pathway activation. It has been discovered that miR-26b could reduce the secretion of TNF-α, IL-1β and IL-6 cytokines *via* inhibiting Wnt/β-catenin pathway activation, leading to malignant cell proliferation suppression and apoptosis elevation, which proves that chronic inflammation induced by Wnt/β-catenin could promote malignant cell proliferation and reduce cell apoptosis [73]. Indeed, activation of Wnt/β-catenin signaling pathway is evident in various cancers. For instance, a subset of osteosarcoma cell lines displays specific activation of Wnt/β-catenin pathway [74]. Mutations of β-catenin are detected in approximately 30% of primary HCC, raising the possibility that activation of Wnt/β-catenin signaling contributes to hepatocarcinogenesis [75]. It has been found that the expression of CyclinD1 is reduced *via* inhibiting Wnt/β-catenin signaling pathway when Retinoid X Receptor α (RXRα) is knocked down. RXRα can also upregulate the expression of proliferating cell nuclear antigen *via* activating NF-κB signaling pathway and down-regulating the p21 level. Thus abnormal activation of Wnt/β-catenin and NF-κB pathways stimulated by RXRα may promote the proliferation of cholangiocarcinoma [76]. High level expression of miR-1207 can cause activation of Wnt/β-catenin signaling pathway *via* inhibiting negative regulators including AXIN2, secreted Frizzled-related protein 1, and inhibitor of β-catenin and TCF-4 (ICAT), leading to tumorigenesis. Thus, activation of Wnt/β-catenin signaling pathway induced by miR-1207 could promote carcinogenesis *via* inhibiting associated negative regulators [77]. These researches indicate that activation of Wnt/β-catenin signaling pathway could promote carcinogenesis.

It has been discovered that Wnt/β-catenin and NF-κB have complicated interactions. Overexpression of β-catenin is inversely correlated with NF-κB and human inducible nitric oxide synthase (hiNOS) activity. Under the circumstances of β-catenin absence, an increased activation of NF-κB can be seen [78]. Thus, Wnt/β-catenin signaling regulates hiNOS expression through interaction with NF-κB, playing an important role in the athophysiology of inflammation-associated carcinogenesis.

TGF-B/Smad Signaling Pathway and Carcinogenesis

At the early stage of carcinogenesis, TGF-β acts as a tumor suppressor *via* blocking cell growth cycle; during the progression process of carcinogenesis, with the decay of tumor suppressor function, TGF-β turns to promote cell proliferation. For instance, in normal pancreatic cells, high levels of TGF-β can inhibit cell proliferation *via* G1/S phase retardation [79]. While under chronic inflammation circumstances, TGF-β could activate JNK, which contributes to carcinogenesis. Compared with the parental cell line, mitochondrial-depleted ρ0 cells derived from the Hep3B hepatocarcinoma cell line display more aggressive characteristics of invasiveness and migration. This is regulated by TGF-β/Smad pathway *via* induction of c-Jun/AP-1 expression and activity [80], which is the downstream gene in JNK signaling pathway. These data demonstrate that TGF-β acts as a tumor suppressor factor in non-cancer cells, however it may also promote tumorigenesis under chronic inflammation circumstances.

Oncogenic Mechanisms in Chronic Inflammation and Abnormal Activation of Signaling Pathways in Cancer Prediction and Prognosis

Homeostasis is maintained by balance of immune system. Disturbance of homeostasis, caused by tissue injure or infection, will initialize immune response, imbalance of which can lead to chronic inflammation, causing neoplastic transformation [81]. Experiments in

animal models have shown that modulation of the immune system can affect angiogenesis, cell proliferation, tumor volume, and overall cancer incidence [82,83]. Based on our experience of HBV-HCC, the classic example of chronic inflammation induced carcinogenesis, together with the related advances in this field, we presented a scientific hypothesis termed as Cancer Evolution-Development (*Evo-Dev*) [84]. As this hypothesis described, the process of carcinogenesis occurs in the microenvironment of non-resolving inflammation are abided by Darwinian evolution theory: mutation-selection-adaptation. The roles of inflammation signaling pathway alteration in the process of carcinogenesis can be analyzed through the lens of Cancer *Evo-Dev* hypothesis.

First, proinflammatory factors are responsible for the generation of genome instability. As a part of the immune reaction, the activation of inflammation related signaling pathways can be observed in many diseases. Although the temporary stimulation is beneficial, the persistence activation of these inflammation signaling pathways usually leads to side effect. Persistence inflammation can increase DNA mutation rates and cause overall genetic instability, *via* reducing expression and activity of DNA mismatch repair genes mutS homolog 2 and 6. Nucleic acid editing enzymes, such as the human apolipoprotein B mRNA-editing enzyme catalytic polypeptides (APOBECs) family of cytidine deaminases, are powerful endogenous mutagenic factors and can be found in signaling pathways of both innate and acquired immune system [85,86]. The enzymes of this family may increase the number of somatic mutations to a threshold that exceeds the repair ability and starts the cancer Evo-Dev process. That has been validated in transgenic animal models [87]. During the chronic inflammation, pathways like NF-κB are persistently activated, consequently leading to high level of APOBECs expression and human genome injury. Besides, persistent inflammatory response can also increase the expression of DNA methyltransferases, methylating the genome globally. It can lead to promoter silencing of genes including the DNA mismatch repair gene *hMLH1* and tumor suppressor genes such as *APC, CDKN2, BRCA1, Rb* and *MDM2* [88,89]. DNA hypermethylation can be observed in a variety of chronic inflammatory diseases including ulcerative colitis and Barrett's esophagus. Colonization of *H. pylori* in the gastric mucosa can also lead to hypermethylation of tumor suppressor genes [90,91]. These findings suggest that genetic and epigenetic changes induced by proinflammatory factors are involved in the process of carcinogenesis.

Second, somatic mutations confer survival advantages to cells by altering critical inflammation signaling pathways. There are a tremendous number of mutations in cancer genome, which can be categorized as passenger mutations and driver mutations. Most of them belong to passenger mutations which do not contribute to carcinogenesis. In contrast, driver mutations can promote the cancer evolution [92]. These mutations were usually found in evolutionarily conserved signaling pathways as we mentioned above. The alteration of these pathways can promote cell growth, proliferation, and migration, conferring survival advantages to mutant cells. However, the catalogue of driver mutations with similar function varies in different individuals and the incidences of specific mutations in a single gene are not high among patients population. The clinical application of a single mutation is limited by the low detection rate. For example, mutation rates of *ARID1A* and *ARID2*, two genes with classic HCC related genetic variations, are 16.8% and 5.6% respectively in tumor tissues [93].

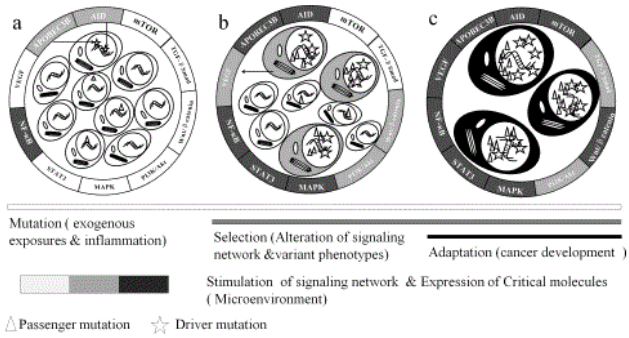

Figure 1: The Schematic figure of the basic framework of Cancer Evo-Dev. a. Inflammation related signaling pathways can be stimulated by different environmental exposures including viral infection, ultraviolet rays, cigarette, injury etc. Persistence inflammation can increase DNA mutation rates and cause overall genetic instability via inducing expression of AID/APOBECs. b. Distinct mutant lineages are selected by inflammatory microenvironment. Most somatic mutations are passenger mutations which do not contribute to carcinogenesis. Only a small part belongs to driver mutations conferring survival advantages to cells by altering critical signaling pathways. c. Mutants with characteristics of stem cells live through the survival selection and evolve to tumor-initialing cells by altering the signaling network. The process of cancer Evo-Dev is triggered consequently and is characterized by "reverse evolution" and "dedifferentiation". (The depth of the color represents the activation degree. The deeper the color is, the greater the activation degree is.)

Therefore, different somatic mutations with similar function may influence the same signaling pathway. Those mutant cells which obtain characteristics of "stemness" by altering these signaling pathways can survive the selection and function as cancer-initiating cells. It is well established in many inflammation induced cancers that the abnormal activation of these signaling pathways can predict effective of therapies and the prognosis of patients. For instance, the alteration of some inflammation signaling pathways, such as PI3K/AKT/mTOR, NF-κB, MAPK, and Wnt/β-catenin is predictive and prognostic for HCC and PDAC [32-34,85,94-96]. The expression of periostin (POSTN) can significantly promote proliferation, growth, invasion, and chemo-resistance of colorectal carcinoma (CRC) cells. It has a high discriminatory performance for the prognosis of CRC. Besides, this evolution promoting effect is counteracted *via* targeting to PI3K/Akt or Wnt/β-catenin signaling pathway [97]. All researches proved that abnormal activation of these inflammation signaling pathways can be utilized in the prediction and therapeutic intervention of cancer occurrence and prognosis.

Mechanisms of Abnormal Activation in Inflammation-Related Signaling Pathways and Cancer Therapy

Although inflammation-related signaling pathways are not specific in cancers, they are more activated in cancers compared with normal tissues. One possible reason is that inflammation-related mutations can persistently activate certain inflammation signaling pathways [75]. Another possible reason causing high activation of inflammation signaling pathways is epigenetic modifications. DNA methylation is

the most extensively studied modification for epigenetic modification. Cluster of methylation in GC rich region termed as CpG island usually happen in promoter region of oncogenes, which frequently cause reduced gene expression. For instance, promoter methylation of suppressor of cytokine signaling *(SOCS)-1* in GC causes *SOCS-1* reduced expression, (SOCS-1 takes part in feedback inhibition of STAT3 activation) which in turn activates JAK/STAT3 signaling [98]. With the increasing maturity of the next generation sequencing technology, increased mutations or epigenetic modifications associated with cancers are discovered. *Via* bench-to-top next generation sequencer and bead array technology, a variety of mutations or DNA methylations occurred in breast cancer that may cause inflammation signaling pathways aberrant activation were discovered. For instance, Wnt pathway is activated possibly by aberrant methylation of negative regulators SFRP1 and DKK3, AKT/mTOR pathway is often activated through *PIK3CA* gene mutation, and Notch pathway is activated potentially by *NOTCH1* and *NOTCH2* gene mutations [99]. Two recent researches investigated the relationship between signaling networks and cancer in a systematic way. To draw a global picture of how signaling pathways influence carcinogenesis, a global analysis method is applied, mainly focusing on accumulation of mutations or determinants of specificity on signaling networks based on ovarian cancer cell lines and global cancer genome repository. A computational platform (ReKINect) is designed to predict the underlying signaling mechanisms or perturbations in cancer, *via* identifying network-attacking mutations and systematically interpreted the exomes and quantitative proteomes. Finally, the newly unknown network-attacking mutations as well as the presence of mutational hotpots were discovered [100,101]. This method may help in elucidating kinome-wide inflammation network-attacking mutations, thus facilitating the understanding between these events and cancers. Since the inflammation signaling pathways are not specifically activated in cancers but also in normal tissues, it's wise to explore the possible treatment focusing on abnormally expressed inflammation pathways. In two cell lines with PIK3CA mutations, after cytosolic phospholipase A2α (*cPLA2α*) is overexpressed, the AKT phosphorylation level and the cell proliferation rate increase. Consistently, after the cell lines stated above are treated with Efipladib or siRNA to silence the expression of *cPLA2α*, the AKT phosphorylation level and the cell proliferation rate decrease. *In vivo* experiments show the similar results. In addition, compared with adjacent normal mucosa, human CRC tissue displays a higher level of *cPLA2α* expression. Thus *cPLA2α* is responsible for sustaining AKT phosphorylation and cell proliferation on conditions that *PI3K* mutation exists, which provides us a potential therapeutic target for CRC [102]. Aspirin consumption is involved in better clinical outcome and prognosis in *PIK3CA*-mutated CRC, which confirm that *PI3CA* mutation is a possible therapeutic target for CRC [103]. JAK2 gain-of-function mutations (V617F) are responsible for myeloproliferative diseases. Thus, it appears that JAK2 will be a fruitful strategy for this kind of diseases [104].

Recently, a unique inhibitor, NT157, which targets STAT3, has been found to contribute to cell malignant inhibition. It can decrease cancer cell proliferation, increase cancer cell apoptosis, and reduce the expression of pro-tumorigenic cytokines, like TGF-β, IL-6, etc [105]. Another TAK1 inhibitor 5Z-7-Oxozeaenol (5Z-O) could inhibit TAK1 activation, leading to the suppression of downstream signaling pathways, including p38, JNK and NF-κB. While knockdown TAK1 binding protein in mice could attenuate tumor growth and metastasis [106]. These two inhibitors targeting TAK1 have efficient effect on cancer treatment stimulated by chronic inflammation. Currently, a specific p38γ pharmacological inhibitor pirfenidone has been found to suppress proinflammatory cytokine expression and colon tumorigenesis, which could be used in colon cancer prevention and treatment [107]. PRT062070 [4-(cyclopropylamino)-2-({4-[4-(ethylsulfonyl)piperazin-1-yl]phenyl}amino)pyrimidi ne-5-carboxamide hydrochloride], an orally active kinase inhibitor targeting JAK has potent antitumor activation *via* inhibiting JAK1-3 associated signaling pathways both *in vivo* and *in vitro*. It has been carried on a phase I dose escalation study in patients with B-cell leukemia and lymphoma, which will be utilized in autoimmune and malignant diseases therapy [108]. TEL03, a dual inhibitor, blocks the expression of both STAT3 and HIF-1α. Since TEL03 could inhibit both HIF-1α and Stat3 simultaneously, it has dramatically inhibition function on tumor growth *in vivo*, which could be a promising strategy for breast and pancreatic cancer therapies [109]. SLC1 is a recombinant inhibitor consisting an E-selectin targeting domain which selectively inhibit NF-κB activation in endothelial cells *in vitro* and *in vivo*. It's a cell type-specific inhibitor of inflammation signaling pathways, which will promote the effectiveness and reduce the risk ratio of inflammatory-induced cancer treatment [110]. Although majority of the novel inhibitors targeting key molecules of inflammation signaling pathways are under preclinical investigation or assessment, we believe that in the near future, more inhibitors targeting abnormally activated inflammation signaling pathways will undergo clinical tests for cancer treatment.

Conclusion

Inflammation signaling pathways play a pivotal role in carcinogenesis. The most investigated inflammation signaling pathways include NF-κB, JAK-STAT3, MAPK, PI3K/Akt/mTOR, Wnt/β-catenin, and TGF-β/Smad. These signaling pathways not only function as biological regulator along, but also interact with each other. For example, the NF-κB and JNK, NF-κB and JAK-STAT3, Wnt/β-catenin and NF-κB, TGF-β and JNK are all pathways with cross-talk effects. All these can contribute to the formation of inflammatory molecular networks. Under normal circumstances, inflammatory molecular networks function well in a balanced way, maintaining the homeostasis. Once the chronic inflammation was induced by the alteration of signaling networks resulted from tissue injury and/or infection, aberrant somatic mutations or epigenetic modifications may occur, increasing the risk of carcinogenesis. Understanding the mechanisms by which inflammation signaling pathways facilitate carcinogenesis can be helpful to explore the possible targets for cancer prediction, prognosis, and treatment. Nowadays, some novel inhibitors targeting inflammation signaling pathways have undergo preclinical investigation or assessment, we believe that in the foreseeable future, cancer patients can benefit from those potent inhibitors.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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