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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].

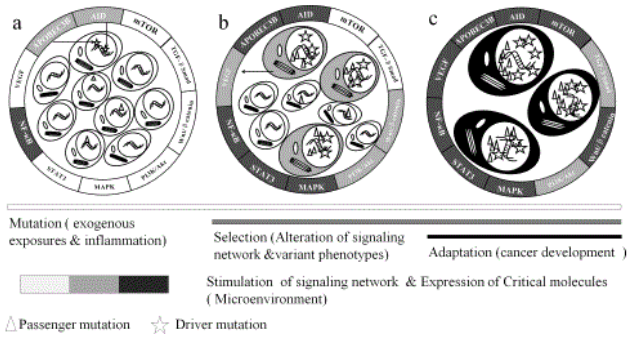

Figure 1: The Schematic figure of the basic framework of Cancer Evo-Dev. a. Inflammation related signaling pathways can be stimulated by different environmental exposures including viral infection, ultraviolet rays, cigarette, injury etc. Persistence inflammation can increase DNA mutation rates and cause 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.

References

1. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, et al. (1993) Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 328: 1797-1801.
2. Ekbom A, Helmick C, Zack M, Adami HO (1990) Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 336: 357-359.
3. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN (1994) Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut 35: 1590-1592.
4. Ekbom A, Helmick C, Zack M, Adami HO (1990) Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 323: 1228-1233.
5. Ekbom A, McLaughlin JK, Nyrén O (1993) Pancreatitis and the risk of pancreatic cancer. N Engl J Med 329: 1502-1503.
6. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, et al. (1997) Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 89: 442-446.
7. Solaymani-Dodaran M, Logan RF, West J, Card T, Coupland C (2004) Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut 53: 1070-1074.
8. Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, et al. (1995) Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol 141: 1023-1032.
9. Mayne ST, Buenconsejo J, Janerich DT (1999) Previous lung disease and risk of lung cancer among men and women nonsmokers. Am J Epidemiol 149: 13-20.
10. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, et al. (1991) Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 325: 1127-1131.
11. Mostafa MH, Sheweita SA, O'Connor PJ (1999) Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev 12: 97-111.
12. Watanapa P, Watanapa WB (2002) Liver fluke-associated cholangiocarcinoma. Br J Surg 89: 962-970.
13. Wang D, DuBois RN (2015) Immunosuppression associated with chronic inflammation in the tumor microenvironment. Carcinogenesis 36: 1085-1093.
14. Oeckinghaus A, Hayden MS, Ghosh S (2011) Crosstalk in NF-κB signaling pathways. Nat Immunol 12: 695-708.
15. Ghosh S, Karin M (2002) Missing pieces in the NF-kappaB puzzle. Cell 109: S81-96.
16. Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-Î°B as the matchmaker. Nat Immunol 12: 715-723.
17. Kreuz S, Siegmund D, Scheurich P , Wajant H (2001) NF-kappaB inducers upregulate cFLIP, a cycloheximide-sensitive inhibitor of death receptor signaling. Mol Cell Biol 21: 3964-3973.
18. Papademetrio DL, Lompardía SL, Simunovich T (2015) Inhibition of Survival Pathways MAPK and NF-kB Triggers Apoptosis in Pancreatic Ductal Adenocarcinoma Cells via Suppression of Autophagy. Target Oncol .
19. Chiu CT, Chen JH, Chou FP, Lin HH (2015) Hibiscus sabdariffa Leaf Extract Inhibits Human Prostate Cancer Cell Invasion via Down-Regulation of Akt/NF-kB/MMP-9 Pathway. Nutrients 7: 5065-5087.
20. De Simone V, Franze E, Ronchetti G, Colantoni A, Fantini M C, et al. (2015) Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. Oncogene 34: 3493-3503.
21. He G, Karin M (2011) NF-κB and STAT3 - key players in liver inflammation and cancer. Cell Res 21: 159-168.
22. Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, et al. (2004) NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature 431: 461-466.
23. Song le H, Binh VQ, Duy DN, Kun JF, Bock TC, et al. (2003) Serum cytokine profiles associated with clinical presentation in Vietnamese infected with hepatitis B virus. J Clin Virol 28: 93-103.
24. Wong VW, Yu J, Cheng AS, Wong GL, Chan HY, et al. (2009) High serum interleukin-6 level predicts future hepatocellular carcinoma development in patients with chronic hepatitis B. Int J Cancer 124: 2766-2770.
25. West AP, Koblansky AA, Ghosh S (2006) Recognition and signaling by toll-like receptors. Annu Rev Cell Dev Biol 22: 409-437.
26. Li S, Wang L, Dorf ME (2009) PKC phosphorylation of TRAF2 mediates IKKalpha/beta recruitment and K63-linked polyubiquitination. Mol Cell 33: 30-42.
27. Adhikari A, Xu M, Chen ZJ (2007) Ubiquitin-mediated activation of TAK1 and IKK. Oncogene 26: 3214-3226.
28. Hayden MS, Ghosh S (2008) Shared principles in NF-kappaB signaling. Cell 132: 344-362.
29. Kisseleva T, Bhattacharya S, Braunstein J, Schindler CW (2002) Signaling through the JAK/STAT pathway, recent advances and future challenges. Gene 285: 1-24.
30. He G, Yu GY, Temkin V, Ogata H, Kuntzen C, et al. (2010) Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. Cancer Cell 17: 286-297.
31. Jung IH, Choi JH, Chung YY, Lim GL, Park YN, et al. (2015) Predominant Activation of JAK/STAT3 Pathway by Interleukin-6 Is Implicated in Hepatocarcinogenesis. Neoplasia 17: 586-597.
32. Xu P, Sun Z, Wang Y , Miao C. (2015) Long-term use of indomethacin leads to poor prognoses through promoting the expression of PD-1 and PD-L2 via TRIF/NF-kappaB pathway and JAK/STAT3 pathway to inhibit TNF-alpha and IFN-gamma in hepatocellular carcinoma. Exp Cell Res 337: 53-60.
33. Nagathihalli NS, Castellanos JA, Shi C, Beesetty Y, Reyzer M L, et al. (2015) STAT3 Mediated Remodeling of the Tumor Microenvironment Results in Enhanced Tumor Drug Delivery in a Mouse Model of Pancreatic Cancer. Gastroenterology.
34. Rokavec M, Öner MG, Li H, Jackstadt R, Jiang L, et al. (2014) IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 124: 1853-1867.
35. Kubo M, Hanada T, Yoshimura A (2003) Suppressors of cytokine signaling and immunity. Nat Immunol 4: 1169-1176.
36. Lei YY, Wang WJ, Mei JH, Wang CL (2014) Mitogen-activated protein kinase signal transduction in solid tumors. Asian Pac J Cancer Prev 15: 8539-8548.
37. Pereira L, Igea A, Canovas B, Dolado I, Nebreda AR (2013) Inhibition of p38 MAPK sensitizes tumour cells to cisplatin-induced apoptosis mediated by reactive oxygen species and JNK. EMBO Mol Med 5: 1759-1774.
38. Dhanasekaran DN, Reddy EP (2008) JNK signaling in apoptosis. Oncogene 27: 6245-6251.
39. Du L, Lyle CS, Obey TB, Gaarde WA, Muir JA, et al. (2004) Inhibition of cell proliferation and cell cycle progression by specific inhibition of basal JNK activity: evidence that mitotic Bcl-2 phosphorylation is JNK-independent. J Biol Chem 279: 11957-11966.
40. Gururajan M, Chui R, Karuppannan AK, Ke J, Jennings CD, et al. (2005) c-Jun N-terminal kinase (JNK) is required for survival and proliferation of B-lymphoma cells. Blood 106: 1382-1391.
41. Bogoyevitch MA, Kobe B (2006) Uses for JNK: the many and varied substrates of the c-Jun N-terminal kinases. Microbiol Mol Biol Rev 70: 1061-1095.
42. Lamb JA, Ventura JJ, Hess P, Flavell RA, Davis RJ (2003) JunD mediates survival signaling by the JNK signal transduction pathway. Mol Cell 11: 1479-1489.

43. Lei K, Nimnual A, Zong WX, Kennedy NJ, Flavell RA, et al. (2002) The Bax subfamily of Bcl2-related proteins is essential for apoptotic signal transduction by c-Jun NH(2)-terminal kinase. Mol Cell Biol 22: 4929-4942.
44. Tournier C, Hess P, Yang DD, Xu J, Turner TK, et al. (2000) Requirement of JNK for stress-induced activation of the cytochrome c-mediated death pathway. Science 288: 870-874.
45. Fuchs SY, Adler V, Buschmann T, Yin Z, Wu X, et al. (1998) JNK targets p53 ubiquitination and degradation in nonstressed cells. Genes Dev 12: 2658-2663.
46. Oleinik NV, Krupenko NI, Krupenko SA (2007) Cooperation between JNK1 and JNK2 in activation of p53 apoptotic pathway. Oncogene 26: 7222-7230.
47. Fan M, Chambers TC (2001) Role of mitogen-activated protein kinases in the response of tumor cells to chemotherapy. Drug Resist Updat 4: 253-267.
48. Chang L, Kamata H, Solinas G, Luo JL, Maeda S, et al. (2006) The E3 ubiquitin ligase itch couples JNK activation to TNFalpha-induced cell death by inducing c-FLIP(L) turnover. Cell 124: 601-613.
49. Cargnello M, Roux PP (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev 75: 50-83.
50. Zhong Y, Naito Y, Cope L, Naranjo-Suarez S, Saunders T, et al. (2014) Functional p38 MAPK identified by biomarker profiling of pancreatic cancer restrains growth through JNK inhibition and correlates with improved survival. Clin Cancer Res 20: 6200-6211.
51. Ni J, Cozzi P, Hao J, Beretov J, Chang L, et al. (2013) Epithelial cell adhesion molecule (EpCAM) is associated with prostate cancer metastasis and chemo/radioresistance via the PI3K/Akt/mTOR signaling pathway. Int J Biochem Cell Biol 45: 2736-2748.
52. Chang L, Graham PH, Hao J, Ni J, Bucci J, et al. (2013) Acquisition of epithelial-mesenchymal transition and cancer stem cell phenotypes is associated with activation of the PI3K/Akt/mTOR pathway in prostate cancer radioresistance. Cell Death Dis 4: e875.
53. Chang L, Graham PH, Hao J, Bucci J, Cozzi PJ, et al. (2014) Emerging roles of radioresistance in prostate cancer metastasis and radiation therapy. Cancer Metastasis Rev 33: 469-496.
54. Sircar K, Yoshimoto M, Monzon FA, Koumakpayi IH, Katz RL, et al. (2009) PTEN genomic deletion is associated with p-Akt and AR signalling in poorer outcome, hormone refractory prostate cancer. J Pathol 218: 505-513.
55. de Muga S, Hernandez S, Agell L, Salido M, Juanpere N, et al. (2010) Molecular alterations of EGFR and PTEN in prostate cancer: association with high-grade and advanced-stage carcinomas. Mod Pathol 23: 703-712.
56. Leevers SJ, Vanhaesebroeck B, Waterfield MD (1999) Signalling through phosphoinositide 3-kinases: the lipids take centre stage. Curr Opin Cell Biol 11: 219-225.
57. Vanhaesebroeck B, Leevers SJ, Ahmadi K, Timms J, Katso R, et al. (2001) Synthesis and function of 3-phosphorylated inositol lipids. Annu Rev Biochem 70: 535-602.
58. Martelli AM, Evangelisti C, Chappell W, Abrams SL, Bäsecke J, et al. (2011) Targeting the translational apparatus to improve leukemia therapy: roles of the PI3K/PTEN/Akt/mTOR pathway. Leukemia 25: 1064-1079.
59. Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C, et al. (2004) PI3K/Akt signalling pathway and cancer. Cancer Treat Rev 30: 193-204.
60. Fruman DA, Meyers RE, Cantley LC (1998) Phosphoinositide kinases. Annu Rev Biochem 67: 481-507.
61. Stephens L, Anderson K, Stokoe D, Erdjument-Bromage H, Painter G F, et al. (1998) Protein kinase B kinases that mediate phosphatidylinositol 3,4,5-trisphosphate-dependent activation of protein kinase B. Science 279: 710-714.
62. Alessi DR, Deak M, Casamayor A, Caudwell FB, Morrice N, et al. (1997) 3-Phosphoinositide-dependent protein kinase-1 (PDK1): structural and functional homology with the Drosophila DSTPK61 kinase. Curr Biol 7: 776-789.
63. Porta C, Paglino C, Mosca A (2014) Targeting PI3K/Akt/mTOR Signaling in Cancer. Front Oncol 4: 64.
64. Chen X, Thakkar H, Tyan F, Gim S, Robinson H, et al. (2001) Constitutively active Akt is an important regulator of TRAIL sensitivity in prostate cancer. Oncogene 20: 6073-6083.
65. Manning BD, Cantley LC (2007) AKT/PKB signaling: navigating downstream. Cell 129: 1261-1274.
66. Grewe M, Gansauge F, Schmid RM, Adler G, Seufferlein T. (1999) Regulation of cell growth and cyclin D1 expression by the constitutively active FRAP-p70s6K pathway in human pancreatic cancer cells. Cancer Res 59: 3581-3587.
67. Abraham RT (2004) mTOR as a positive regulator of tumor cell responses to hypoxia. Curr Top Microbiol Immunol 279: 299-319.
68. Tapia O, Riquelme I, Leal P, Sandoval A, Aedo S, et al. (2014) The PI3K/AKT/mTOR pathway is activated in gastric cancer with potential prognostic and predictive significance. Virchows Arch 465: 25-33.
69. Ying J, Xu Q, Liu B, Zhang G, Chen L, et al. (2015) The expression of the PI3K/AKT/mTOR pathway in gastric cancer and its role in gastric cancer prognosis. Onco Targets Ther 8: 2427-2433.
70. Nusse R, Varmus HE (1982) Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. Cell 31: 99-109.
71. Holland JD, Klaus A, Garratt AN, Birchmeier W (2013) Wnt signaling in stem and cancer stem cells. Curr Opin Cell Biol 25: 254-264.
72. Wend P, Holland JD, Ziebold U, Birchmeier W (2010) Wnt signaling in stem and cancer stem cells. Semin Cell Dev Biol 21: 855-863.
73. Sun J, Yan P, Chen Y, Chen Y, Yang J, et al. (2015) MicroRNA-26b inhibits cell proliferation and cytokine secretion in human RASF cells via the Wnt/GSK-3Î²/Î²-catenin pathway. Diagn Pathol 10: 72.
74. Martins-Neves SR, Corver WE, et al. (2015) Osteosarcoma Stem Cells Have Active Wnt/Î²-catenin and Overexpress SOX2 and KLF4. J Cell Physiol .
75. Miyoshi Y, Iwao K, Nagasawa Y, Aihara T, Sasaki Y, et al. (1998) Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. Cancer Res 58: 2524-2527.
76. Huang GL, Wei Z, Ren HY, Shen XY, Chen QX, et al. (2015) Retinoid X Receptor alpha Enhances Human Cholangiocarcinoma Growth through Simultaneous Activation of Wnt/beta-catenin and NF-κB Pathways. Cancer Sci.
77. Wu G, Liu A, Zhu J, Lie F, Wu S, et al. (2015) MiR-1207 overexpression promotes cancer stem cell-like traits in ovarian cancer by activating the Wnt/Î²-catenin signaling pathway. Oncotarget 6: 28882-28894.
78. Du Q, Zhang X, Cardinal J, Cao Z, Guo Z, et al. (2009) Wnt/beta-catenin signaling regulates cytokine-induced human inducible nitric oxide synthase expression by inhibiting nuclear factor-kappaB activation in cancer cells. Cancer Res 69: 3764-3771.
79. Alvarez C, Bass BL (1999) Role of transforming growth factor-beta in growth and injury response of the pancreatic duct epithelium in vitro. J Gastrointest Surg 3: 178-184.
80. Yi EY, Park SY, Jung SY, Jang WJ, Kim YJ (2015) Mitochondrial dysfunction induces EMT through the TGF-β/Smad/Snail signaling pathway in Hep3B hepatocellular carcinoma cells. Int J Oncol 47: 1845-1853.
81. de Visser KE, Eichten A, Coussens LM (2006) Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 6: 24-37.
82. Hussain SP, Harris CC (2007) Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 121: 2373-2380.
83. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 30: 1073-1081.

84. Liu WB, Wu JF, Du Y, Cao GW (2015) Cancer Evolution-Development: experience on hepatitis B virus-induced hepatocarcinogenesis. Current Oncology.

85. Chen L, Zhang Q, Chang W, Du Y, Zhang H, et al. (2012) Viral and host inflammation-related factors that can predict the prognosis of hepatocellular carcinoma. Eur J Cancer 48: 1977-1987.

86. Yin J, Li N, Han Y, Xue J, Deng Y, et al. (2013) Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. J Clin Oncol 31: 3647-3655.

87. Morisawa T, Marusawa H, Ueda Y, Iwai A, Okazaki IM, et al. (2008) Organ-specific profiles of genetic changes in cancers caused by activation-induced cytidine deaminase expression. Int J Cancer 123: 2735-2740.

88. Fleisher AS, Esteller M, Harpaz N, Leytin A, Rashid A, et al. (2000) Microsatellite instability in inflammatory bowel disease-associated neoplastic lesions is associated with hypermethylation and diminished expression of the DNA mismatch repair gene, hMLH1. Cancer Res 60: 4864-4868.

89. Das PM, Singal R (2004) DNA methylation and cancer. J Clin Oncol 22: 4632-4642.

90. Dong CX, Deng DJ, Pan KF, Zhang L, Zhang Y, et al. (2009) Promoter methylation of p16 associated with Helicobacter pylori infection in precancerous gastric lesions: a population-based study. Int J Cancer 124: 434-439.

91. Kaise M, Yamasaki T, Yonezawa J, Miwa J, Ohta Y, et al. (2008) CpG island hypermethylation of tumor-suppressor genes in H. pylori-infected non-neoplastic gastric mucosa is linked with gastric cancer risk. Helicobacter 13: 35-41.

92. Stratton MR, Campbell PJ, Futreal PA (2009) The cancer genome. Nature 458: 719-724.

93. Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, et al. (2012) Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. Nat Genet 44: 694-698.

94. Han YF, Zhao J, Ma LY, Yin JH, Chang WJ, et al. (2011) Factors predicting occurrence and prognosis of hepatitis-B-virus-related hepatocellular carcinoma. World J Gastroenterol 17: 4258-4270.

95. Xie J, Zhang Y, Zhang Q, Han Y, Yin J, et al. (2013) Interaction of signal transducer and activator of transcription 3 polymorphisms with hepatitis B virus mutations in hepatocellular carcinoma. Hepatology 57: 2369-2377.

96. Zhang Q, Ji XW, Hou XM, Lu FM, Du Y, et al. (2014) Effect of functional nuclear factor-kappaB genetic polymorphisms on hepatitis B virus persistence and their interactions with viral mutations on the risk of hepatocellular carcinoma. Ann Oncol 25: 2413-2419.

97. Xu XW, Chang WJ, Yuan J, Han X, Tan X J, et al. (2015) Periostin expression in intra-tumoral stromal cells is prognostic and predictive for colorectal carcinoma via creating a cancer-supportive niche. Oncotarget.

98. Souma Y, Nishida T, Serada S, Iwahori K, Takahashi T, et al. (2012) Antiproliferative effect of SOCS-1 through the suppression of STAT3 and p38 MAPK activation in gastric cancer cells. Int J Cancer 131: 1287-1296.

99. Yamaguchi T, Mukai H, Yamashita S, Fujii S, Ushijima T (2015) Comprehensive DNA Methylation and Extensive Mutation Analyses of HER2-Positive Breast Cancer. Oncology 88: 377-384.

100. Creixell P, Schoof EM, Simpson CD, Longden J, Miller CJ, et al. (2015) Kinome-wide Decoding of Network-Attacking Mutations Rewiring Cancer Signaling. Cell 163: 202-217.

101. Creixell P, Palmeri A, Miller CJ, Lou HJ, Santini CC, et al. (2015) Unmasking Determinants of Specificity in the Human Kinome. Cell 163: 187-201.

102. Zheng Z, He X, Xie C, Hua S, Li J, et al. (2014) Targeting cytosolic phospholipase A2α in colorectal cancer cells inhibits constitutively activated protein kinase B (AKT) and cell proliferation. Oncotarget 5: 12304-12316.

103. Ogino S, Lochhead P, Giovannucci E, Meyerhardt J A, Fuchs CS, et al. (2014) Discovery of colorectal cancer PIK3CA mutation as potential predictive biomarker: power and promise of molecular pathological epidemiology. Oncogene 33: 2949-2955.

104. Pesu M, Laurence A, Kishore N, Zwillich SH, Chan G, et al. (2008) Therapeutic targeting of Janus kinases. Immunol Rev 223: 132-142.

105. Sanchez-Lopez E, Flashner-Abramson E, Shalapour S, Zhong Z, Taniguchi K, et al. (2015) Targeting colorectal cancer via its microenvironment by inhibiting IGF-1 receptor-insulin receptor substrate and STAT3 signaling. Oncogene.

106. Huang HL, Chiang CH, Hung WC, Hou MF (2015) Targeting of TGF-beta-activated protein kinase 1 inhibits chemokine (C-C motif) receptor 7 expression, tumor growth and metastasis in breast cancer. Oncotarget 6: 995-1007.

107. Yin N, Qi X, Tsai S, Lu Y, Basir Z, et al. (2015) p38γ MAPK is required for inflammation-associated colon tumorigenesis. Oncogene .

108. Coffey G, Betz A, DeGuzman F, Pak Y, Inagaki M, et al. (2014) The novel kinase inhibitor PRT062070 (Cerdulatinib) demonstrates efficacy in models of autoimmunity and B-cell cancer. J Pharmacol Exp Ther 351: 538-548.

109. Chen H, Guan Y, Yuan G, Zhang Q, Jing N (2014) A perylene derivative regulates HIF-1alpha and Stat3 signaling pathways. Bioorg Med Chem 22: 1496-1505.

110. Sehnert B, Burkhardt H, Wessels JT, Schröder A, May MJ, et al. (2013) NF-κB inhibitor targeted to activated endothelium demonstrates a critical role of endothelial NF-κB in immune-mediated diseases. Proc Natl Acad Sci U S A 110: 16556-16561.