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Review Article

Mitogen-activated Protein Kinase Signaling in Inflammation-related Carcinogenesis

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The role of mitogen-activated protein kinases (MAPKs) in regulation of inflammation is well known. MAPK family is activated by various stimuli and involved in transmitting extracellular signals to nucleus leading to gene regulation. Inflammation is primary defensive response of host against microbes. Controlled inflammation is helpful and indispensable for host defense. However, uncontrolled inflammatory response leads to various inflammatory diseases and cancer. Persistent inflammation leads to cell proliferation and survival that plays crucial role in tumorigenesis. In this review, we recapitulate the recent knowledge of MAPK signaling and its roles in inflammation-associated carcinogenesis.

Key Words: Cancer, Inflammation, Mitogen-activated protein kinase

INTRODUCTION

The innate immune system of mammals recognizes microbial infection and plays its role in elimination of microbes. Inflammation is primary protective response of host to eradicate destructive stimuli and repair injured tissue (1). Inflammation is characterized by five fundamental symptoms: heat, redness, pain, swelling, and loss of tissue function (2). Dendritic cells (DCs) and macrophages are the key player in innate immunity. In addition, endothelial cells, epithelial cells, and fibroblasts also take part in innate immunity. Controlled inflammatory response is indispensable and protects against destructive stimuli. However, deregulated inflammation is injurious because it leads to different diseases such as rheumatoid arthritis, atopic dermatitis, septic shock and cancer (1). Tissue macrophages and mast cells are implicated in recognition of primary infection. Upon detection of invading microorganisms, these cells produce inflammatory mediators such as pro-inflammatory cytokines and chemokines. The immediate effect of these mediators educes inflammatory exudates containing plasma proteins and neutrophils (1).

The germ line-encoded pattern recognition receptors are responsible for sensing the pathogen associated molecular patterns of the microbes (2, 3). The pattern recognition receptors are divided into four different groups; Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs) and Retinoic acid inducible gene (RIG)-1-like receptors (RLRs) (2~8). Recent reports have highlighted the role of TLRs in the development of inflammation-associated carcinogenesis. Especially, it has been reported

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that endogenous TLR ligands involved in solid tumor progression and leukemic cell growth were released from dying tumor cells (9~11).

TLR activation leads to phosphorylation of mitogen activated protein kinases (MAPKs) and IκB kinases (IKK) complex which ultimately result in activation of activator protein 1 (AP-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), respectively (12). Activated AP-1 and NF-κB is responsible for production of pro-inflammatory cytokines and chemokines (13). The activation of MAPKs and NF-κB is tightly controlled by phosphorylation and ubiquitination and results in production of tumor necrosis factor (TNF)-α and interleukins (ILs) (14). TNF-α is recognized as a pro- or anti-tumorigenic protein. TNF-α also promotes the production of inflammatory mediators including cyclooxygenase-2 (COX-2), IL-6, IL-8, and TNF-α and results in tumorigenesis through MAPK and NF-κB signaling cascade (15, 16).

Inflammation plays important role in pathogenesis of diverse types of malignancies (17, 18). Different stimulators including growth factors, stress, chemokines, cytokines and reactive oxygen species (ROS) result in activation of MAPK signaling pathways (19). MAPK pathways are the key regulator in the activation of various pro-inflammatory cytokines in different cell types, including dendritic cells, macrophages, epithelial cells, and T cells (18).

Cancer is essentially a disease of failure in tissue growth regulation (17). The feature of caner is unregulated proliferation of cells (17). Cancer cells can subvert c-Jun amino-terminal kinases (JNKs), ERKs and p38 MAPK pathways to facilitate proliferation, survival, and invasion (17). Over-activation of ERK1 and ERK2 MAPKs has been associated with tumors (17, 20). In addition, deregulations of JNK and p38 MAPK pathways are also related with cancer developments (17, 20). As MAPKs have key roles in inflammation and cancer, it has been focused and shown by different scientists that targeting MAPK inhibition is beneficial for cancer therapy (17, 21).

Mitogen-activated Protein Kinases

MAPKs were originally termed as extracellular signal-regulated kinases (ERKs). MAPKs are chain of proteins in the cell and regulate communication of signals in the eukaryotic cells. MAPK pathway is evolutionarily conserved in eukaryotic cells. MAPK pathway plays serious role in communication of signal from cell surface to the nucleus and manages cellular functions such as growth, differentiation, proliferation, migration and death (21, 22). Some defects in MAPK signaling are associated with carcinogenesis by increased production of pro-inflammatory cytokines, growth factors, anti-apoptotic factors and cell proliferation (21) (Fig. 1). Generally growth factors are involved in activation of ERK1 and ERK2, whereas stress stimuli activates the JNK and p38 MAPK (23). In mammals ERKs, JNKs, p38, ERK3 and 4, and ERK5 are well characterized (24).

ERK MAPKs and Cancer Development

ERKs are the well characterized members of the MAPK family. The mammalian ERK1 and ERK2 are profusely present in all tissues and share almost 80% amino acid identity (23). ERK1 and ERK2 are controlled by analogous molecular signals and have numerous overlapping roles in various aspects (21). However, ERK1 and ERK2 knockout mice have shown different phenotypes (21). In ERK1 knockout mice, impaired thymocyte maturation and adipocyte differentiation is reported (25). In contrast, ERK2 knockout mice show different phenotype highlighted by lethality at day 6.5~8.5 due to impaired placental development (26). Rapidly accelerated fibrosarcoma (Raf) kinases (A-Raf, B-Raf, and C-Raf) play vital role in the Ras-Raf-MEK-ERK signaling pathway (27). Rat sarcoma (Ras) family function as molecular switches and involved in regulating intracellular signaling networks.

Stimulation of cell surface receptors tyrosine kinases activates Raf/MEK/ERK signaling cascade (28). Activation of Raf results in phosphorylation of MEK1/2 which in turn phosphorylate ERK1 and ERK2 (29). ERK1 and ERK2

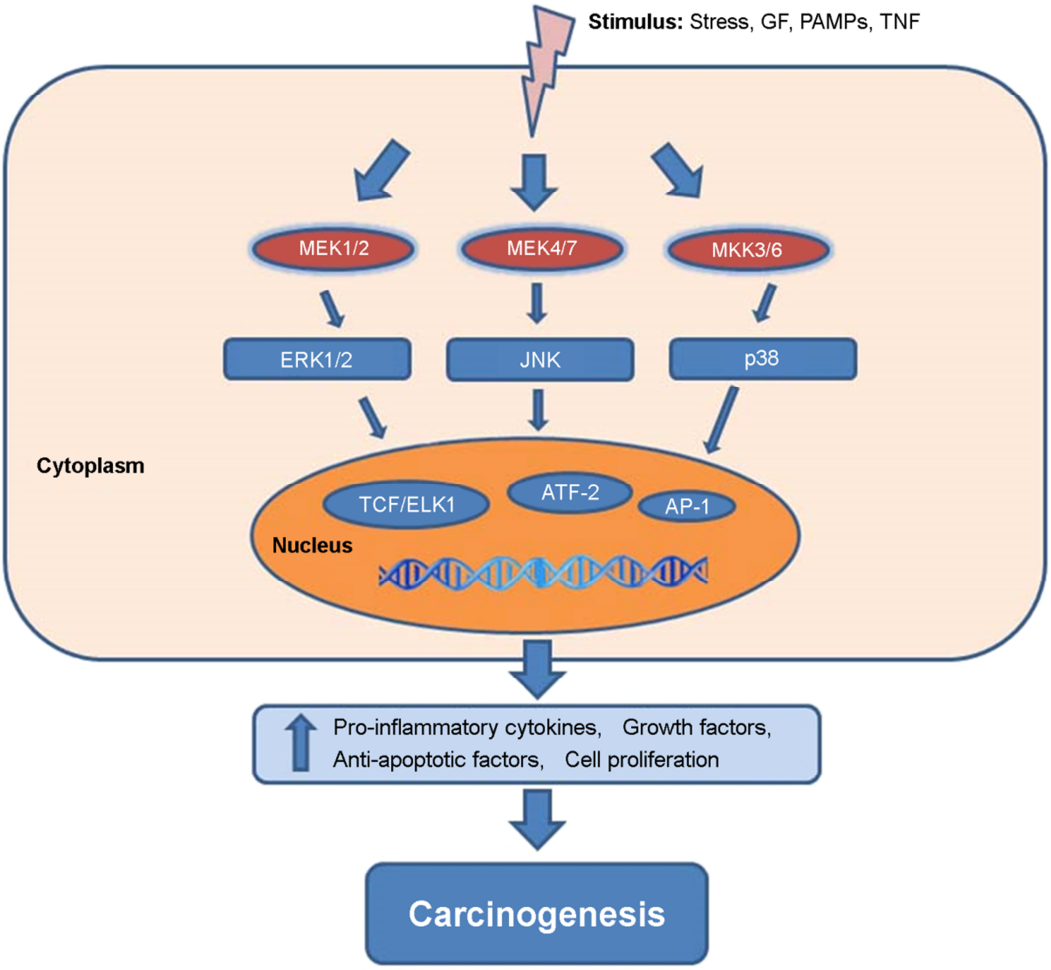

Figure 1. MAPK signaling pathways and cancer development. The MAPK signaling pathways are stimulated by pathogen-associated molecular patterns (PAMPs), growth factors (GF), tumor necrosis factor (TNF), stress, and inflammatory cytokines. Stimulation of MEK1/2 results in activation of MAPK (ERK1/2) activity. Activation of MEK4/7 is responsible for the activation of JNKs. The phosphorylation of p38 is regulated by MKK3/6. ERK1/2, JNK, and p38 activate various transcription factors such as TCF/ELK1, AP-1, ATF-2, and others. Different transcription factors including these result in expression of genes encoding pro-inflammatory cytokines, cell proliferation related proteins, growth factors, and anti-apoptotic factors. These factors are related with cancer development.

signaling are involved in regulation of cell proliferation, motility and shape. In addition ERK1/2 activates cyclin-dependent kinase (CDK) proteins which play role in regulating cell cycle (30). Activation of ERK1/2 leads to phosphorylation of various substrates including some cytoskeletal proteins, nuclear substrates, membrane proteins and numerous MKs (24).

Sustained activation of Ras-ERK signaling pathway is associated with various cancers (31). B-Raf is critical component in Ras-Raf signaling pathway and involved in cell growth. Mutation of B-Raf, which results in excessive signaling in the pathway, has been linked to cancer development in humans. B-Raf shows high incidence of activating mutations and frequently associated with cancers (31). More than 50% melanoma harbors B-Raf mutations and selective B-Raf inhibitors have been shown effective for the treatment of tumors harboring B-Raf mutations (32, 33). Vemurafenib has been approved for the treatment of B-Raf V600 mutation positive metastatic melanoma (32). B-Raf mutations are also linked to papillary thyroid carcinoma

and colorectal cancer (34, 35).

Pancreatic ductal adenocarcinoma is the most prevalent pancreatic carcinoma and deadliest human cancer (36). Pancreatic ductal adenocarcinoma is associated with chronic pancreatitis (36). Both K-Ras oncogenes and chronic pancreatitis are associated for development of pancreatic ductal adenocarcinoma in adult mice (36). During embryonic development, if K-Ras oncogenes are expressed, chronic pancreatitis facilitates the multistep transformation process in adult mice. Recently, one research group showed that IL-22 has very important role in breast carcinogenesis through increase activation of ERK, JNK-c-Jun, and STAT3 signaling pathways (37).

JNK MAPKs and Cancer Development

JNKs were initially known as stress-activated kinases (SAPKs) (38, 39). JNK1, JNK2, and JNK3 are commonly referred as SAPK γ, SAPK α, and SAPK β, respectively (23, 38). The JNKs are activated by growth factor deprivation, UV irradiation and DNA-damaging agents. The JNKs regulate the phosphorylation of various transcription factors including activating transcription factor-2 (ATF-2), Signal transducer and activator of transcription 3 (STAT3) and heat shock factor protein 1 (HSF-1) (24, 38, 40). JNKs can enhance the expression of AP-1 controlled specific genes (41). JNKs are involved in regulating various cellular processes including proliferation, survival and apoptosis (42).

Pro or anti-apoptotic functions of JNK are dependent upon duration of JNK activation (43). JNK regulate the expression and activation of inflammatory mediators such as TNF-α and IL-2 (44). Hyperactivation of JNK is linked with inflammatory bowel disease and its inhibition by SP600125 has been shown to significantly reduce clinical and pathological condition in rats (45). Inflammatory bowel disease is also associated with colorectal cancer development (46). Many researchers have shown the role of JNKs in cancer development (44). Hepatocellular carcinoma (HCC) is commonly observed in human population and major cause of cancer death worldwide (47). Mice lacking JNK1 showed decreased tumor cell proliferation in liver carcinogenesis (47). JNK1 regulates the proliferation of HCC cells by controlling the expression of p21 (47). Increased activity of JNK has been associated with enhanced liver cancer development in mice lacking p38α in hepatocytes (47, 48).

JNK deficient mice showed reduced liver damage in response to concanavalin-A treatment revealing the role of JNK in hepatitis (49, 50). JNK1 activation correlates with up-regulation of histone H3 methylation in HCC tissue, which augment the expression of genes involved in cell growth (51). JNK1/2 deficient mice showed reduced hepatitis which is linked with reduced TNF-α expression in hematopoietic cells (52). Carcinoma of the prostate is a common neoplasm in ageing males and severe health problem. JNKs play critical role in its development (17). In human prostate cancer, c-Jun proteins are up-regulated in advance disease (53). Phosphatase and tensin homolog (PTEN) is tumor suppressor and frequently mutated in prostate cancer. Loss of PTEN is attributed to AKT activation and higher JNK activity (54).

p38 MAPKs and Cancer Development

Four p38 isoforms are identified in mammals: p38α, p38β, p38γ, and p38δ. Generally most of the tissues express p38α and p38β isoforms, however, p38γ and p38δ isoforms are expressed by skin, kidney and muscle cells (55). The stress and inflammatory cytokines activate the p38 isoforms in mammalian cells (56). Upon stimulation, p38 is phosphorylated by MKK3 and MKK6, which are controlled by MTK1 and ASK1 (57, 58). Activated p38 results in phosphorylation of various cellular targets including cytosolic phospholipase A2, the microtubule-associated protein Tau, and the transcription factors MEF2A, Sap-1, Elk-1, ATF1, ATF2, NF-κB, p53, and Ets-1. The p38 is also responsible for activation of some MKs, which includes MSK1, MSK2 and MNK1 (38). The p38 is a critical regulator in inflammatory responses and cell proliferation (59). The specific function of p38 MAPK is dependent on the cell type and also on the external stimulus (60). The p38 MAPK play a key role in breast, liver, prostate, bladder and lung cancer (60). The p38 MAPK has been reported to

regulate TNF-α expression in macrophages and rheumatoid synovial cells (61). The p38α is involved in transcriptional activation of TNF in macrophages by lipopolysaccharide-stimulation (59). TNF-α is a pleiotropic cytokine and involved in variety of inflammatory diseases (61). TNF can induce diverse effects such as immune cell activation, angiogenesis and cell differentiation. Such processes are relevant to tumor immune surveillance and play critical roles in tumorigenesis (62). Neutralization of TNF-α has been reported to inhibit tumor formation during early tumorigenesis (63). In addition, neutralization of TNF-α result in inhibition of murine breast carcinoma development, so TNF-α antagonist may be useful in treating cancer (63).

The p38α is also involved in up-regulation of heat shock protein 25 expression, which inhibits ROS accumulation (64, 65). p21 is also called as cyclin-dependent kinase inhibitor 1 which binds to and inhibits the activity of cyclin and results in cell growth arrest. Inhibition of p38 results in enhanced p21 gene transcription in rat chondrosarcoma (66). Pharmacological inhibition of p38 MAPK has been shown to reduce cell proliferation in rat chondrosarcoma (66). In addition, in prostate cancer patients, the percentages of cells that were immunoreactive for p-ATF-2 or p-Elk-1 (downstream components of p38) were higher than in normal. It has been shown that inhibition of p38 might be helpful in the treatment of prostate cancer (67).

Inflammation and Caner Development

Various epidemiological studies have shown that chronic inflammation, triggered by microbial infection and autoimmune diseases, is involved in the increased risk of tumorigenesis (21, 68). In human chronic *Salmonella typhi* infection is allied with gallbladder cancer (69). Chronic inflammation by *Helicobacter pylori* infection is associated with development of gastric cancer (70). *Streptococcus bovis* has been linked to promote intestinal carcinogenesis by increasing the production of IL-8, which is promoter of angiogenesis (71). Inflammatory bowel diseases come under the class of autoimmune diseases and associated with colorectal cancer development (46).

The hallmark of cancer-related inflammation is the presence of inflammatory mediators such as cytokines and chemokines in tumor microenvironment (68). During chronic inflammation, ineffective clearance of destructive stimuli leads to accumulation of ROS which results in DNA damage and mutation (21, 72). If this mutation is in critical genes such as tumor suppressors, then it leads to initiation or progression of cancer (72).

To maintain tissue homeostasis, cells are continuously proliferating under inflammatory conditions, which is the driving force for transformation of initial tumor cells (21, 68). The chronic inflammation is responsible for persistent undue production of inflammatory cytokines including TNF-α and IL-6 which are important triggers for endorsing malignant tumor (21, 68). IL-6, TNF and IL-1 have been reported to promote colitis-associated tumor development (73). Up-regulation of ERK1 and ERK2 MAPKs has been associated with human tumors (17, 73). The JNK and p38 MAPK pathways are also often deregulated in cancers (17, 20). MAPK activates transcription factors such as AP-1 and C/EBP which results in up-regulation of COX-2 (74). Activation of AP-1 in tumoral microenvironment cells directly regulates the pro-angiogenic genes, including IL-8, CXCL1 and CXCL8 (68). COX-2 has critical role in pathogenesis of carcinogenesis because it's over expression results in dysplasia, metaplasia, hyperplasia, proliferation, immune surveillance, angiogenesis and metastasis (75). Elevated level of COX2 expression has been reported in different type of cancers including breast, colorectal, cervical, lung and prostate cancer (74).

Conclusion and Perspective

Roles of MAPKs in inflammation and host protection against microbial infection have been well characterized. MAPK signaling regulates key cellular functions including gene expression, cell proliferation, cell motility and cell survival. However, uncontrolled MAPK signaling is linked with cancer development. Currently, various MAPK signaling pathway inhibitors are available and many scientists have focused on identification of natural MAPK inhibitors which

will help in the treatment of inflammatory diseases and cancer. MAPK inhibitors might be combined with conventional therapies of cancer to improve their efficacy.

REFERENCES

1) Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454:428-35.
2) Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell 2010;140:805-20.
3) O'Neill LA, Bowie AG. The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. Nat Rev Immunol 2007;7:353-64.
4) Trinchieri G, Sher A. Cooperation of Toll-like receptor signals in innate immune defence. Nat Rev Immunol 2007;7:179-90.
5) Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A, *et al*. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol 2010;11:1136-42.
6) Yuk JM, Jo EK. Host immune responses to mycobacterial antigens and their implications for the development of a vaccine to control tuberculosis. Clin Exp Vaccine Res 2014;3:155-67.
7) Hong S, Park S, Yu JW. Pyrin domain (PYD)-containing inflammasome in innate immunity. J Bacteriol Virol 2011;41:133-46.
8) Manzoor Z, Koh YS. Caspase-11, the main executioner in non-canonical inflammasome. J Bacteriol Virol 2012; 42:169-71.
9) Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature 2007;449: 819-26.
10) Ishii KJ, Koyama S, Nakagawa A, Coban C, Akira S. Host innate immune receptors and beyond: making sense of microbial infections. Cell Host Microbe 2008; 3:352-63.
11) Koh YS. Nucleic acid recognition and signaling by Toll-like receptor 9: compartment-dependent regulation. J Bacteriol Virol 2011;41:131-2.
12) Kawai T, Akira S. Signaling to NF-kappaB by Toll-like receptors. Trends Mol Med 2007;13:460-9.
13) Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 2010;11:373-84.
14) Sun SC, Ley SC. New insights into NF-kappaB regulation and function. Trends Immunol 2008;29:469-78.
15) Clevers H. At the crossroads of inflammation and cancer. Cell 2004;118:671-4.
16) Balkwill F, Joffroy C. TNF: a tumor-suppressing factor or a tumor-promoting factor? Future Oncol 2010;6: 1833-6.
17) Wagner EF, Nebreda AR. Signal integration by JNK and p38 MAPK pathways in cancer development. Nat Rev Cancer 2009;9:537-49.
18) Bromberg J, Wang TC. Inflammation and cancer: IL-6 and STAT3 complete the link. Cancer Cell 2009;15:79 -80.
19) Manzoor Z, Koh YS. Mitogen-activated protein kinases in inflammation. J Bacteriol Virol 2012;42:189-95.
20) Sebolt-Leopold JS, Herrera R. Targeting the mitogen-activated protein kinase cascade to treat cancer. Nat Rev Cancer 2004;4:937-47.
21) Huang P, Han J, Hui L. MAPK signaling in inflammation -associated cancer development. Protein Cell 2010;1: 218-26.
22) Martinez E. Multi-protein complexes in eukaryotic gene transcription. Plant Mol Biol 2002;50:925-47.
23) Pearson G, Robinson F, Beers Gibson T, Xu BE, Karandikar M, Berman K, *et al*. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev 2001;22:153-83.
24) Chen Z, Gibson TB, Robinson F, Silvestro L, Pearson G, Xu B, *et al*. MAP kinases. Chem Rev 2001;101: 2449-76.
25) Pagès G, Guérin S, Grall D, Bonino F, Smith A, Anjuere F, *et al*. Defective thymocyte maturation in p44 MAP kinase (Erk 1) knockout mice. Science 1999;286:1374 -7.
26) Hatano N, Mori Y, Oh-hora M, Kosugi A, Fujikawa T, Nakai N, *et al*. Essential role for ERK2 mitogen-activated protein kinase in placental development. Genes Cells 2003;8:847-56.
27) Zebisch A, Troppmair J. Back to the roots: the remarkable RAF oncogene story. Cell Mol Life Sci 2006;63: 1314-30.
28) Campbell SL, Khosravi-Far R, Rossman KL, Clark GJ,

Der CJ. Increasing complexity of Ras signaling. Oncogene 1998;17:1395-413.
29) Hallberg B, Rayter SI, Downward J. Interaction of Ras and Raf in intact mammalian cells upon extracellular stimulation. J Biol Chem 1994;269:3913-6.
30) Chambard JC, Lefloch R, Pouysségur J, Lenormand P. ERK implication in cell cycle regulation. Biochim Biophys Acta 2007;1773:1299-310.
31) Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, *et al*. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116:855-67.
32) Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, *et al*. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85.
33) Sullivan RJ, Flaherty K. MAP kinase signaling and inhibition in melanoma. Oncogene 2013;32:2373-9.
34) Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003;63:1454-7.
35) Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, *et al*. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-12.
36) Guerra C, Schuhmacher AJ, Cañamero M, Grippo PJ, Verdaguer L, Pérez-Gallego L, *et al*. Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell 2007;11:291-302.
37) Kim K, Kim G, Kim JY, Yun HJ, Lim SC, Choi HS. Interleukin-22 promotes epithelial cell transformation and breast tumorigenesis via MAP3K8 activation. Carcinogenesis 2014;35:1352-61.
38) Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev 2001;81:807-69.
39) Johnson GL, Nakamura K. The c-jun kinase/stress-activated pathway: regulation, function and role in human disease. Biochim Biophys Acta 2007;1773:1341-8.
40) Akira S, Nishio Y, Inoue M, Wang XJ, Wei S, Matsusaka T, *et al*. Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. Cell 1994;77:63-71.
41) Shaulian E, Karin M. AP-1 in cell proliferation and survival. Oncogene 2001;20:2390-400.
42) Nishina H, Wada T, Katada T. Physiological roles of SAPK/JNK signaling pathway. J Biochem 2004;136:123-6.
43) Ventura JJ, Hübner A, Zhang C, Flavell RA, Shokat KM, Davis RJ. Chemical genetic analysis of the time course of signal transduction by JNK. Mol Cell 2006;21:701-10.
44) Rincón M, Davis RJ. Regulation of the immune response by stress-activated protein kinases. Immunol Rev 2009;228:212-24.
45) Mitsuyama K, Suzuki A, Tomiyasu N, Tsuruta O, Kitazaki S, Takeda T, *et al*. Pro-inflammatory signaling by Jun-N-terminal kinase in inflammatory bowel disease. Int J Mol Med 2006;17:449-55.
46) Triantafillidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. Anticancer Res 2009;29:2727-37.
47) Hui L, Zatloukal K, Scheuch H, Stepniak E, Wagner EF. Proliferation of human HCC cells and chemically induced mouse liver cancers requires JNK1-dependent p21 downregulation. J Clin Invest 2008;118:3943-53.
48) Hui L, Bakiri L, Mairhorfer A, Schweifer N, Haslinger C, Kenner L, *et al*. p38alpha suppresses normal and cancer cell proliferation by antagonizing the JNK-c-Jun pathway. Nat Genet 2007;39:741-9.
49) Maeda S, Chang L, Li ZW, Luo JL, Leffert H, Karin M. IKKbeta is required for prevention of apoptosis mediated by cell-bound but not by circulating TNFalpha. Immunity 2003;19:725-37.
50) Hasselblatt P, Rath M, Komnenovic V, Zatloukal K, Wagner EF. Hepatocyte survival in acute hepatitis is due to c-Jun/AP-1-dependent expression of inducible nitric oxide synthase. Proc Natl Acad Sci U S A 2007;104:17105-10.
51) Chang Q, Zhang Y, Beezhold KJ, Bhatia D, Zhao H,

Chen J, *et al*. Sustained JNK1 activation is associated with altered histone H3 methylations in human liver cancer. J Hepatol 2009;50:323-33.
52) Das M, Sabio G, Jiang F, Rincón M, Flavell RA, Davis RJ. Induction of hepatitis by JNK-mediated expression of TNF-alpha. Cell 2009;136:249-60.
53) Ouyang X, Jessen WJ, Al-Ahmadie H, Serio AM, Lin Y, Shih WJ, *et al*. Activator protein-1 transcription factors are associated with progression and recurrence of prostate cancer. Cancer Res 2008;68:2132-44.
54) Wang X, McGowan CH, Zhao M, He L, Downey JS, Fearns C, *et al*. Involvement of the MKK6-p38gamma cascade in gamma-radiation-induced cell cycle arrest. Mol Cell Biol 2000;20:4543-52.
55) Hui L, Bakiri L, Stepniak E, Wagner EF. p38alpha: a suppressor of cell proliferation and tumorigenesis. Cell Cycle 2007;6:2429-33.
56) Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, Green D, *et al*. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. Nature 1994;372:739-46.
57) Roux PP, Blenis J. ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiol Mol Biol Rev 2004;68: 320-44.
58) Han J, Sun P. The pathways to tumor suppression via route p38. Trends Biochem Sci 2007;32:364-71.
59) Kang YJ, Chen J, Otsuka M, Mols J, Ren S, Wang Y, *et al*. Macrophage deletion of p38alpha partially impairs lipopolysaccharide-induced cellular activation. J Immunol 2008;180:5075-82.
60) Koul HK, Pal M, Koul S. Role of p38 MAP Kinase Signal Transduction in Solid Tumors. Genes Cancer 2013;4:342-59.
61) Campbell J, Ciesielski CJ, Hunt AE, Horwood NJ, Beech JT, Hayes LA, *et al*. A novel mechanism for TNF-alpha regulation by p38 MAPK: involvement of NF-kappa B with implications for therapy in rheumatoid arthritis. J Immunol 2004;173:6928-37.
62) Wajant H. The role of TNF in cancer. Results Probl Cell Differ 2009;49:1-15.
63) Scott KA, Moore RJ, Arnott CH, East N, Thompson RG, Scallon BJ, *et al*. An anti-tumor necrosis factor-alpha antibody inhibits the development of experimental skin tumors. Mol Cancer Ther 2003;2:445-51.
64) Lee YJ, Lee DH, Cho CK, Chung HY, Bae S, Jhon GJ, *et al*. HSP25 inhibits radiation-induced apoptosis through reduction of PKCdelta-mediated ROS production. Oncogene 2005;24:3715-25.
65) Sakurai T, He G, Matsuzawa A, Yu GY, Maeda S, Hardiman G, *et al*. Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. Cancer Cell 2008;14:156-65.
66) Halawani D, Mondeh R, Stanton LA, Beier F. p38 MAP kinase signaling is necessary for rat chondrosarcoma cell proliferation. Oncogene 2004;23:3726-31.
67) Ricote M, García-Tuñón I, Bethencourt F, Fraile B, Onsurbe P, Paniagua R, *et al*. The p38 transduction pathway in prostatic neoplasia. J Pathol 2006;208:401 -7.
68) Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.
69) Mager DL. Bacteria and cancer: cause, coincidence or cure? A review. J Transl Med 2006;4:14.
70) Parsonnet J. Bacterial infection as a cause of cancer. Environ Health Perspect 1995;103 Suppl 8:263-8.
71) Ellmerich S, Schöller M, Duranton B, Gossé F, Galluser M, Klein JP, *et al*. Promotion of intestinal carcinogenesis by *Streptococcus bovis*. Carcinogenesis 2000; 21:753-6.
72) Waris G, Ahsan H. Reactive oxygen species: role in the development of cancer and various chronic conditions. J Carcinog 2006;5:14.
73) Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010;138: 2101-14.
74) Chun KS, Surh YJ. Signal transduction pathways regulating cyclooxygenase-2 expression: potential molecular targets for chemoprevention. Biochem Pharmacol 2004; 68:1089-100.
75) Liu CH, Chang SH, Narko K, Trifan OC, Wu MT, Smith E, *et al.* Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. J Biol Chem 2001;276:18563-9.