REVIEW

Mitogen-Activated Protein Kinase Signal Transduction in Solid Tumors

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Abstract

　　Mitogen-activated protein kinase (MAPK) is an important signaling pathway in living beings in response to extracellular stimuli. There are 5 main subgroups manipulating by a set of sequential actions: ERK(ERK1/ERK2), c-Jun N(JNK/SAPK), p38 MAPK(p38α, p38β, p38γ and p38δ), and ERK3/ ERK4/ ERK5. When stimulated, factors of upstream or downstream change, and by interacting with each other, these groups have long been recognized to be related to multiple biologic processes such as cell proliferation, differentiation, death, migration, invasion and inflammation. However, once abnormally activated, cancer may occur. Several components of the MAPK network have already been proposed as targets in cancer therapy, such as p38, JNK, ERK, MEK, RAF, RAS, and DUSP1. Among them, alteration of the RAS-RAF-MEK-ERK-MAPK(RAS-MAPK) pathway has frequently been reported in human cancer as a result of abnormal activation of receptor tyrosine kinases or gain-of-function mutations in genes. The reported roles of MAPK signaling in apoptotic cell death are controversial, so that further in-depth investigations are needed to address these controversies. Based on an extensive analysis of published data, the goal of this review is to provide an overview on recent studies about the mechanism of MAP kinases, and how it generates certain tumors, as well as related treatments.

Keywords: MAPK - mechanisms of action - tumor development - treatment

MAPK Signaling Pathway

　　The mitogen-activated protein kinase (MAPK) signal transduction pathways are evolutionarily conserved among eukaryotes. Normally, the signaling cascades are stimulated by the binding of mitogens, hormones, or neurotransmitters to receptor tyrosinekinases, the transduction of exogenous signals are achieved through sequential phosphorylation (Evans et al., 2013). They are typically organized in 3-tiered architecture consisting of a MAPK, a MAPK activator (MAPK kinase), and a MAPKK activator (MAPKK kinase) (Bagley et al., 2010; Cargnello et al., 2011), leading to the activation of NF-κB, and are relative to cell growth or survival .The kinases MAPK kinase kinases (MAPKKKs) can be phosphorylated by mall G-proteins leading to double phosphorylation and activation of downstream MAPK kinases (MAPKKs) (Bagley et al., 2010). The MAPKs' acting on their target substrates is said to be initially identified as amediator of inflammation. In clinical medicine, targeting inflammatory responses in tumors is now a promising trend (Demaria et al., 2010).

　　Luca Grieco.et.al has ever used a resulting reaction map to design aqualitative dynamical model with GINsim software, further addressed the roles of cross-talks between the different MAPK cascades (considered as a module for the assembly of more comprehensive cancer-related network) (Grieco et al., 2013; Liu et al., 2013). Usually, Many factors affect these signaling pathways, in a recent study, Luciana R Gomes.et.al used transwell assays clarified that the TGF-b1-enhanced migration and invasion capacities were blocked by inhibitors of p38MAPK, ERK1/2 and MMP, indicating TGF-b1 could be a common regulator for MMPs (Matrix metalloproteinases) (Gomes et al., 2012), an important factor in downstream of the MAPK signaling pathway. Also, Isoflavone genistein has been found to inhibit the molecules in the MAPK pathway, leading to the induction of apoptosis perhaps by blocking the activation of p38 MAPK (Li et al., 2011).

　　Generally, there are 5 main subgroups of the MAPKs: ERK (ERK1/ERK2), c-Jun N (JNK/SAPK), p38MAPK (p38α, p38β, p38γ and p38δ), ERK3/ERK4 and ERK5: (Figure 1)

The JNK Pathway

　　The JNKs are encoded by three genes, JNK1, JNK2, and JNK3. the JNK1/2 subtypes are ubiquitously expressed, whereas the JNK3s are restricted mainly to testis and brain. It is an important mediator of apoptosis and cell proliferation. Induction in response to different chemotherapeutic agents and cellular stresses including

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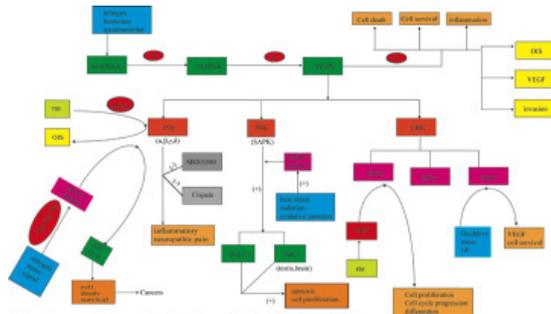
Figure 1. Compositions and Mechanisms of MAPK Signal Pathway. The MAPK pathway is organized in 3-tiered architecture :MAPKKKs, MAPKK, and MAPK ,mainly activated by the mitogens and some other physical or chemical factors, during which phosphorylation matter the most. 5 main subgroups compose the MAPK family, that is, ERK (ERK1/ ERK2), c-Jun (JNK/SAPK), p38 MAPK (p38α, p38β, p38γ and p38δ), ERK3/ERK4, ERK5. And through different way, they mediate cell growth, proliferation,apoptosis,as well as invasion of cancer cells and inflammation and so on.

heat shock, ionizing radiation, oxidative stress. JNK is normally activated by MKK7 and MKK4. Studies show JNK1 and JNK2 are involved in the sensitization to cisplatin-induced cell death upon p38 MAPK inhibition and increased ROS levels mediate JNK activation upon p38 MAPK inhibition (Pereira et al., 2013). Actually, there are some interactions between the JNK and the MAPK pathway (Cargnello et al., 2011), JNK isoforms may stimulate the p38 MAPKs, while many MAPKKKs in the p38 module are shared by the JNK module.

The P38MAPK pathway

As is referred above, the p38 MAPK and JNK pathways can cross talk at several levels, mainly in non-transformed cells. But it was not long before the interplay is shown to be mediated by ROST. There are four isoforms of p38 (p38α, p38β, p38γ and p38δ) (Bagley et al., 2010); also known as stress activated protein kinase (SAPK)2a, 2b, 3 and 4 respectively, which differ in their tissue distributions. the p38 MAP kinase is selectively activated by MAPK kinases (MKK3/6) (Cargnello et al., 2011) and the mechanism is mediated by dual phosphorylation at the Thr-Gly-Tyr motif .They mediate cell survival or cell death depending not only on the type of stimulus but also in a cell type specific manner. SAPKs/JNKs and p38 are poorly activated by mitogens but strongly activated in cells in response to stress signals.

Generally, the p38MAPK may play an important role in prostate cancer, breast cancer, bladder cancer, liver cancer, lung cancer, transformed follicular lymphoma, and leukemia. Decreasing p38 activity has much to do with cancer since continuous cell proliferation requires the activity of p38 in most of the cancers studied, which is carried out by the activation of downstream targets like ATF-2 and Elk-1.

In other ways, studies have revealed the p38 pathway can result in OIS induced by oncogenic ras or its downstream factor raf-1 through upstream kinases MAPK/

ERK kinase (MEK)-ERK MAPK pathway, but isoforms played different roles in OIS (Xu et al., 2014). What's more, the tumor suppressive effects of the p38MAPK are involved in both the activation of p53 and in p53-induced apoptosis. A recent study by Lorena Pereira .et. al shows that p38MAPK can also help tumor cells to survive chemotherapeutic drug treatments. Traditionally, one potential mediator of tumor-induced bone pain is the p38MAPK.

Further, the p38MAPK signaling pathway has been implicated in mediating inflammatory and neuropathic pain, combination of the p38MAPK inhibitors with cisplatin may be exploited for cancer therapy (Pereira et al., 2013). Devki Sukhtankar.et.al used a mouse model of breast cancer showed inhibition of p38 MAPK with SB203580 significantly reduced tumor burden (Sukhtankar et al., 2011).

The ERK Pathway

ERK1 and ERK2 are key transducers of proliferation, differentiation and survival signals. It was originally found to be phosphorylated on Tyr and Thr residues, and almost expressed in all tissues, mainly affecting the growth of cells by G1-to S-phase progression.Generally, growth factors are the most well known activators (Cargnello et al., 2011), which then cause the activation of upstream kinases MEK1/2 MAPK kinases and Raf MAPK kinases (Bagley et al., 2010). Normally, the ERK3/4 are considered atypical because their activation loop lacks a phosphoacceptor Tyr resi-due and contains the Ser-Glu-Gly motif, ERK3 is responsible for cell proliferation, cell cycle progression, and cell differentiation, while the function of ERK4 remains unknown (Cargnello et al., 2011); ERK5 (also known as BMK) is activated by various stimuli such as oxidative stress and growth factors and is essential for early embryonic development, it is required for normal development of the vascular system as well as cell survival.

MAPK and Cancer

MAPK and Prostate Cancer

Prostate cancer is the most common non-skin malignancy among men worldwide. its metastasis to the bone is the main cause of death (Jin et al., 2011). Heredity is one of the strongest risk factors and numerous studies support gene variants, imbalance of SOS (which leads to cumulative damage to lipids), proteins, and DNA (Shen et al., 2010) may potentially contribute to the risks of tumors (Amankwah et al., 2012). But Lifestyle and dietary factors (smoking, antioxidant intake, vitamin D and calcium, and coffee intake)also matter much (Wilson et al., 2012). A number of biomarkers in prostate cancer have facilitated development of targeted treatments (Detchokul et al., 2011). Normally, total serum PSA is a common Marker for detection of prostate cancer (Clarke et al., 2010). Now, MYC act as a therapeutic target in prostate cancer (Koh et al., 2010). Importantly, the recent cell-based immunotherapy in prostate sets a example for tumor immunotherapy (Drake, 2010).

When referring to the mechanism, we might think of the fashionable notion of chronic inflammatory in which large amounts of reactive oxygen/nitrogen species (ROS/RNS) and cytokines are produced, which then act as a well-recognized cause of cancer. In prostate cancer tissues, people found up-regulation of human epidermal growth factor receptor 2 (HER2) (Sfanos et al., 2012), indicating that the MAPK pathway may play an important role. Also, inflammation-related molecule COX-2 may be over-expressed in prostate cancer, COX-2 can be a transcription factor involved in inflammation-mediated stem cell proliferation (Park et al., 2013) (mainly via prostaglandin E2 (PGE2) (Thanan et al., 2012; Dixon et al., 2013), while in turn, inhibition of COX-2 by lasiodin could down-regulate the MAPK signaling pathways (Lin et al., 2014), which finally reduced bladder carcinogenesis (Thanan et al., 2012). The p38 MAPK signaling is proved to be essential in inflammation, perhaps by regulating the function of macrophages (Yang et al., 2014), in some of these cancers, cytokine IL-6 and IL6-R which function in activation of inflammatory and androgen receptor (AR) are up-regulated (Sfanos et al., 2012). In other conditions, IL-6 also activates JAK family tyrosine kinases, which in turn activate multiple pathways through signaling molecules MAPK (Ara et al., 2010; Larsen et al., 2011). These mechanisms may conform with our previous knowledge that IL-6 promotes angiogenesis (Ara et al., 2010), invasion (Ara et al., 2010), and attachment (Obata et al., 1997), and the generation of tumor-associated macrophages (Jeannin et al., 2011).

The structure and function of the MAPK pathways in prostate are far from being clearly understood (Jeannin et al., 2011). But at least, we know for sure that, the p38MAPK protein play an important role in the prostate progress. Normally, in human prostate tissue, the p38MAPK protein is present in the basal cells and epithelial cells of the prostate gland (Mulholland et al., 2012). and it can become active in situations of neoplasia and benign hypertrophy of the prostate gland .MR Milone.et.al demonstrated by using zoledronic acid (ZOL) inhibits and a resistant subline of prostate cancer cells, that the p38MAPK pathway had something to do with drug resistance and invasion of cancers (Milone et al., 2013), the latter is said to be mediated by the down-steam compositions MMP-2 and MMP-9 (Bourboulia et al., 2010; Mao et al., 2010; Kessenbrock et al., 2010; Milone et al., 2013;).

In prostate cancer, hormone may be an important factor. Hari K. Koul1.et.al have observed in immunoprecipitation that the p38MAPK which results in decrease in AR levels and activity in prostate cancer cells in culture (Koul et al., 2013)can associate AR assays while amplification of the AR gene allows the receptor to respond to lower levels of androgens (Kohli et al., 2010). Aiming at this mechanism, there came out a new treatment-androgen deprivation therapy (ADT), referring to any intervention which results in the androgen receptor of target cells not being activated (Connolly et al., 2012). As we know, FGF-1 and KGF -2, IL-6, HB-EGF, TP, vitamin D, carbachol, osmotic shock, and UV light can act as stress response to cause p38 activation (Koul et al., 2013), while in another

way, over-expression of α-PAK, MEK-6, p38, *p*-Elk-1, and *p*-ATF-2 occur in benign prostate hyperplasia and more intensely in prostate cancer patients, enhancing cell proliferation and survival, What's more, Mol Cancer Ther.et.al claimed activating of the p38MAPK pathway might lead to stabilization of p75NTRmRNA and therefore increased levels of p75NTR protein which said treatment with R-flurbiprofen or ibuprofen induced p75NTR expression acted as a sensitive factor in Prostate cancer cells (Khwaja et al., 2008). In another event, to further clarify the signaling pathway in prostate cancer, David J Mulholland1.et.al crossed conditional activatable K-rasG12D/WT mice with the prostate conditional Pten deletion model and found that Ptenloss and RAS/MAPK activation cooperated to promote EMT and metastasis. Inhibition called PD325901 and MEK inhibitor significantly reduced the metastatic progression, and they reported the important collaborative effects of RAS/MAPK and PTEN/PI3K pathways in promoting prostate cancer metastasi. Interestingly, in prostate cells, oncogenic ETS proteins (linking to prostate cell migration behavior) were found to be able to replace RAS/MAPK pathway activation by a specific binding pattern while aberrant expression of oncogenic ETS transcription factors are implicated in the majority of prostate cancers (Hollenhorst et al., 2011). While for the ras family, there are other active ways, in a mouse model of advanced prostate cancer, Jingqiang Wang found inducible expression of a BRAFV600E could activate the ERK1/2 MAPK, leading to up-regulation of the c-Myc oncogene (Wang et al., 2012).

MAPK and Breast Cancer

Breast cancer is the leading cancer diagnosis in women aged 20-45 .Risk Factors of breast cancer include breast density (a highly heritable quantitative trait) (Boyd et al., 2010), age, family history, parity, and so on (Westbrook et al., 2013). To be more accurate, estrogen receptor (ER), progesterone receptor (PR) and HER2 expression are of great importance (Liu et al., 2013). For example, cell proliferation inhibitor Emodin is justly proved to function in a MAPK way, targeting at ERα (Jia-Qi et al., 2014). But endocrine therapy targeting at ER or HER don't receive much effect as imaged, now, researches have showed that the ERK is closely connected to hormone resistance by the oncogenic RAS-MEK-ERK pathway (Polo et al., 2010). So, specific inhibitors of ERK kinase (MEK) should be of help. In modern medical science, there are more targeted therapies, multidisciplinary including the macroscopic and microscopic way can result in prolonged disease control (Cheng and Ueno, 2012).

In breast cancer the p38MAPK also matters much, it acts as a central kinase in a common pathway that plays an important role in breast cancer invasion and metastasis by modulating the expression and activity of molecules involved in the degradation of extracellular matrix (mainly MMP-2 and MMP-9) (Slattery et al., 2013). Normally, it can be activated by TGF-β signals through transmembrane receptor kinases by a Smad-dependent and Smad-independent mechanisms as well as the MAPK4 pathway (Koul et al., 2013). But the TGF-β relative mechanism has

been revealed recently to be blocked by a medicine called Curcumin (Mo et al., 2012).

Recently, Lorena Pereira.et.al used MMTV-PyMT mouse model of breast cancer proved a p38 MAPK chemical inhibition cooperated with cisplatin to reduce breast tumor size (Pereira et al., 2013), and melatonin is proved to play an inhibitory role in breast cancer cell invasion in the p38 pathway (Bourboulia et al., 2010; Mao et al., 2010; Kessenbrock et al., 2010; Milone et al., 2013). Fanyan Meng.et.al also invested biologic function of p38γ MAPK in breast cancer. Through gene expression, knockdown, chemotherapeutic agents, observation of biologic effect, they identified that over-expression of the p38γMAPK led to marked cell cycle arrest in G2/M phase. What's more, they said the main function of p38γ MAPK in breast cancer was to maintain the oncogenic properties rather than to promote cancer progression (Mimura et al., 2013). All these indicate that p38γ MAPK is a promising target for the design of targeted therapies for basal-like breast cancer.

Not long ago, the MAPK-ERK was found to be the predominant pathway promoting notch activation in MDA-MB231 cells referring to breast cancer, the study was carried mainly by a kinase inhibitor library that contained 240 kinase inhibitors. And during the process, TRB3 act as a master regulator (Izrailit et al., 2013). Apart from these, a mutant form of H-Ras can strongly activated p38 MAPK, and actually, activation of the RAS-RAF-MEK-ERK-MAPK pathway is commonly observed in human breast cancers (Cerne et al., 2012). but Yashaswi Shrestha.et.al found other genetic alterations, a breast cancer oncogene PAK1 (amplified in 30-33% of human breast tumors) coordinately activates MAPK signaling (Shrestha et al., 2012). Interestingly, as PTKs and their downstream signaling pathways contribute to critical biological functions relevant to the cancerous phenotype, Brk should be over-expressed in invasive breast carcinomas (Lofgren et al., 2011). From reports of Kristopher A Lofgren.et.al., we know that p38MAPK may contribute to progression in human breast tumors as a downstream signaling mediator of Brk (Lofgren et al., 2011).

As for other mechanisms, we may know from previous reports, that programmed cell death was significantly increased in the cells with low IGF-IR expression and this increased cell death might be mediated through activation of the p38 MAPK (Mendoza et al., 2010).

With these, Rhone A Mendoza.et.al further cloned cell lines with significantly reduced expression of the p38 MAPK. And concluded that the effects of p38 MAPK in regulating growth of breast cancer depended on whether the tumors expressed intact or mutated form of p53 (Shrestha et al., 2012), an important tumor suppressor gene whose inactivation can cause many human cancers. As for triple-negative breast cancers (TNBCs), one of the most aggressive forms of breast cancer with poor clinical outcomes owing to a lack of targeted therapies, activation of the MAPK pathway should be responsible for resistance to conventional chemotherapy, revealing that down-regulating of the MAPK pathway is crucial in the novel targeted therapy for TNBC. Wondrously, S

Gholamit.et.al demonstrated that oncolytic viral therapies were of great promise, and at present, viral therapy with NV1066 can cause a significant decrease in the *p*-MEK and *p*-MAPK (Gholami et al., 2014).

MAPK and Bladder cancer

Generally, age, gender, race, environmental agents, chemicals, cigarette smoking, radiation, infection, and hereditary are thought to be of significance in bladder cancer (Tanaka et al., 2011). But genetic variation matters the most (Dudek et al., 2013). Nowadays, genome-wide association studies (GWAS) which based on the case-control design can predict underlying cancers (Dudek et al., 2013). And as the epidermal growth factor receptor (EGFR) is frequently over-expressed in bladder cancer (Kompier et al., 2010), it can be an important therapeutic target.

Activation of MAPK is a frequent event in tumor progression and metastasis. In bladder cancer, for the ras family, a regular activator, their mutation can cooperate with b-catenin activation to drive bladder tumourigenesi (Ahmad et al., 2011). To be more specific, the KRAS and HRAS mutations occurred with equal frequency. While NRAS mutations were less (Kompier et al., 2010). Still, Lan Mo.et.al claimed over-activation of Ha-ras occurred in human urothelial tumors and hyper-activation of the ras signaling pathway was responsible for the low-grade, non-invasive papillary bladder tumors (Mo et al., 2007).

Then, for the p38MAPK, Hari K.et.al found that it was activated during the log phase growth of bladder cancer cells and it could modulate MMP-2 and MMP-9 expression (Koul et al., 2013), which composed the usual inflammatory mechanism, while cancer itself could cause inflammation through the production of pro-inflammatory factor MMPs (Matrix metalloproteinases) (Thanan et al., 2012), linked to cancer metastasis and tumor suppression (Walia et al., 2012; Mohammad et al., 2013). Then, a considerable vicious circle comes into being (Mohammad et al., 2013). Studies have revealed that TNF-α could regulate MMP-9 expression through NF-ϰB, AP-1, while p38 MAP kinase mediates TNF-α-induced MMP-9 expression (Koul et al., 2013). It has also been shown that the p38 MAPK is essential for the down-regulation of COX-2 expression (responsible for cell proliferation, metastasis, and angiogenesis), and during the process, sulforaphane (SFN), a dietary isothiocyanate in human bladder T24 cells matters much.

MAPK and Liver Cancer

Hepatocellular carcinoma (HCC) is a deadly cancer, with high mortality and poor prognosis, whose incidence is increasing worldwide. Normally, hepatitis B (Philbin et al., 2012) and hepatitis C virus infection are said to be an usual way of obtaining the liver cancer (Chang et al., 2010), and alcohol abuse can add to the risks. In some cases, the stem cells have the potential for therapy of liver diseases, but may also be involved in the formation of liver cancer (Rountree et al., 2012). Not long ago, Zhigang Lv.et.al concluded that TGF-β1could persistently activate ERK and p38MAPK signaling in HSCs (Lv and Xu, 2012). Now, deregulation of TGF-β signaling is

acting as a molecular pathway to TISC-based malignancy (Rountree et al., 2012).

Normally, p38 MAPK activities in human HCCs are significantly lower, while attenuation in the p38MAPK and MKK6 activities in human HCC tissue specimens may cause the resistance to apoptosis, leading to unrestricted cell growth of human HCCs (Lamy et al., 2013). Previous research also shows TNF-α and IL-1 are elevated in liver cell injury and may activate the p38 MAPK pathway (Lamy et al., 2013).

Further, as we all know that telomerase provides a promising target for a selective therapeutic approach of malignancies. Taking telomerase positive HCC cell lines for example, activation of all three MAPK (JNK, ERK1/2 and P38) can be observed, while activated ERK1/2 and P38, but not JNK, is related to telomerase abrogation and consequent apoptosis induction (Lamy et al., 2013). Consistently, blockade of JNK activation promotes cell survival and stimulates p38 MAPK mediated by MKK3/6 and MKK4/7 in human hepatoma cell lines (Lamy et al., 2013).

And like many other cancers, the RAS cascade (RAS-RAF-MEK-MAPK pathway) can also be found in liver cancer, resulting in proliferative and anti-apoptotic signals (Zender et al., 2010). Strangely, Chunmei Wang, et.al noted that AKT/mTOR and Ras/MAPK interacted with each other in hepatocarcinogenesis in a mouse model characterized by the co-expression of activated forms of AKT and Ras in the liver (Wang et al., 2013), which might advanced the targeted treatment for HCC. Apart from these, through series of cell culture and *in vitro* experiments, Margaret A. Park.et.al demonstrated that, in the typical signal way, MEK 1/2 inhibitors could interact with many other pharmaceuticals in killing hepatoma cells (Park et al., 2008).

MAPK and Lung Cancer

Generally, lung cancer is divided into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Tobacco smoking, gender, race and ethnicity, age, diet, obesity, infections, environment, and other Lung diseases or airways obstruction, all contribute much in lung cancer occurring (Egleston et al., 2009; Dela Cruz et al., 2011; Larsen et al., 2011). Also, multiple gene variations shown some roles in lung cancer, which says comprehensive analyses should be necessary (Marshall and Christiani, 2013), and we can notice that 90% of the mutations are located in KRAS, which then activates the RAS/RAF/MEK/MAPK pathway (Larsen and Minna, 2011; Larsen et al., 2011; Kadara et al., 2012), indicating KRAS in lung tumorigenesis may be a significant therapeutic target. And in this way, the MYC (regulator of cell proliferation) acts as main downstream factor (Larsen and Minna 2011). So, based on these mechanisms, K-ras mutations, EGFR (also related to phosphorylation and tyosine kinase) mutations, copy number, and expression, should be better molecular biomarkers for patient selection (Larsen et al., 2011; Hassanein et al., 2012). In clinical medicine, there are also other markers such as COX-2, p53 (de Mello et al., 2011).

As is known for all, the inflammatory cytokines play an important role in airways inflammation and allergic mechanisms (Koul et al., 2013). It is suggested that p38 MAPK would have an impact in these factors mainly mediated by LPS-induced cytokines that mediate chronic lung diseases and consequently leading to cancer. As a rather common factor in the inflammatory progress, IL-6 is also proved to elevate COPD-like inflammation, and lack of IL-6 resulted in a 41% reduction in the visible tumors on the lung surface (Ochoa et al., 2011). Apart from these, Cesar Ochoa Perez.et.al found up-regulation of MMPs (downstream substrates of the MAPK), especially MMP-12, in lung cancers which related to the COPD (Ochoa et al., 2011).

For the NSCLC, in which EGFR exhibits over-expression or aberrant activation in 50-90% of cancer cells (Larsen and Minna, 2011), Eva M. Galan-Moya et al demonstrated by innovatively using transformed cell lines that the interplay between MAPKKs was crucial for p38 MAPK activation in response to cDDP (Cisplatin) and proposed that the imbalance between MKK6 and MKK3 could be a potential biomarker for NSCLL, while MKK3, but not MKK6, was the critical player, although MKK3 controls MKK6 levels in NSCLC derived cell lines through activation of p38 MAPK (Galan-Moya et al., 2011).

When referred to treatments, through control experiment, J Cell Biochem.et.al proved that PBA (an experimental compoun) had some therapeutic effectiveness, mainly by mechanisms such as increasing cell-cell communication, decreasing activation of JNK, up-regulation of p38 MAPK activity (Matesic et al., 2012). And Herbal medicines such as Radix Tetrastigma Hemsleyani Flavone (RTHF) can promote apoptosis via regulation of ERK and p38 phosphorylation (Zhong et al., 2013). In other experiments, by knocking down and over-expression of EAPII in NSCLC, C Li.et.al found that EAPII significantly affected Raf1 and ERK1/2 (important composition of the MAPK signal pathway) and during the process, the MAPK-ERK pathway which elevates levels of MYC and cyclin D1 was activated. In their hypothesis, EAPII has an oncogenic role in lung cancer development (Li et al., 2011a), As for the Ras/MAPK pathway, EGFR protein activates both K-Ras 4B and H-Ras in different ways, and affects nuclear transcription of several downstream genes in a GTP-dependent way (de Mello et al., 2011).

MAPK and Gastric Cancer

Gastric cancer is said to have some things to do with age, sex, geography, dietary, occupation, lifestyle and heredity (Nagini, 2012). Previous research have claimed, that the whole progress is associated with multiple genetic and epigenetic alterations of oncogenes, tumor suppressor genes, DNA repair genes, and other molecule mechanisims (Nagini, 2012). In the modern society, PET, PET/CT imaging (Wu and Zhu, 2014) and availability of gastrointestinal endoscopy have significantly improved the diagnosis of gastric cancer.

Actually, the protein tyrosine kinases (PTKs), EGF-like domains 1 (TIE-1) and mitogen-activated protein kinase kinase 4 (MKK4), can be detected as new molecular biomarkers for gastric cancer prognosis (Wu et al., 2014).

Now, minimally invasive surgery is regarded as one of the standard treatments for early gastric cancer (Son et al., 2014), and acid suppressive drugs such as H2R blocker or PPI may act as a stimulator for gastric cancer (Ahn et al., 2013).

For the pathogenesis, on-cogenes such as K-ras and c-erbB2 (both act as important roles in the MAPK signal pathway) may mutate in gastric cancer (Nagini, 2012), causing abnormal growth cycle in gastric cells, and at the same time, vascular endothelial growth factor (VEGF), related to invasion and angiogenesis by reducing cell-cell adhesion is found over-expressed in the cancer cells (Nagini, 2012; Chao et al., 2013). Experiments showed that once the P38MAPK was inhibited. So was the express of VEGF. And phosphorylation of the JNK may also be positively relative to cell proliferation and the VEGF expression. But activation of the ERK1/2 and PI3K/Aktpathways were thought to be the vital one in tumor progression (Chao et al., 2013). In some case, VEGF-dependent tumor angiogenesis is resulted by interaction of VEGFR1 and VEGFR2 (Zhang et al., 2010), while it is also believed that VEGFR1 signaling is responsible for endothelial cell survival, but VEGFR2 regulates capillary tuber formation (Zhang et al., 2010).

In other ways, Kousaku Mimura.et.al proclaimed the MAPK pathway regulated HLA-A expression in gastric cancer (Mimura et al., 2013), while reduced expression of HLA class I on tumors is often associated with disease progression and poor prognosis in diverse human tumors.

And except from above, the matrix metalloproteinases (MMP) family (downstream molecules of the MAPKs) can alter cancer microenvironment and may function in in cancer invasion through over-expression. Sanjib Deyet. al have revealed that MMP-1.3, MMP-1.4 and MMP-1.5 polymorphisms in the MMP-1 promoter enhances the risk of lower stomach tumor formation in an eastern Indian population (Dey et al., 2014).

MAPK and Melanoma

Melanoma is a malignancy of melanocytes, as well as the fastest growing and most fatal form of skin tumor. Over-exposure to ultraviolet radiation and sunbed exposure may add the risk (Curiel-Lewandrowski et al., 2012), which can be more susceptible in younger people (Cust et al., 2011). Usually, melanoma is recognizable and highly curable when detected early, some studies show that timely skin self-examination may be of great help (Curiel-Lewandrowski et al., 2012; Korner et al., 2013). Reducing rates of sun-burnt, Early Detection, Melanoma is recently considered to be a heterogeneous group of cancers with distinct mutational profiles (Rebecca et al., 2012). Cancer stem cells and nanotechnology may be one of the future direction of melanoma targeted therapy (Evans et al., 2013).

The mitogen activated protein kinase (MAPK) pathway (consist of RAS, RAF, MEK1/2 and ERK1/2), has been identified as a key player in melanoma development making this cascade an important therapeutic target (Tsao et al., 2012; Falchook et al., 2012; Ades and Metzger-Filho, 2012). In melanoma, the RAS family, a monomeric guanosine triphosphatases that are normally activated by mutation or cell surface receptors (related to extracellular signals), function as molecular switches to control cell proliferation and survival, Activated RAS (GTP-bound) triggers the formation of the "MAPK complex" with downstream RAF, MEK1/2, ERK1/2 and several scaffolding proteins to initiate the MAPK cascade, and during the processing, phosphorylation regulates the expression of several downstream genes (Inamdar et al., 2010; Evans et al., 2013).

Through researching the previous studies, MA Davies. et.al concluded that activated NRAS activated both the RAF-MEK-ERK pathway and thePI3K-AKT pathway (Davies and Samuels, 2010; Rebecca et al., 2012; Tsao et al., 2012; Evans et al., 2013), which is frequently implicated in oncogenesis, he also found that, the BRAF (coding a serine/threonine kinase protein), a component of the RAS-RAF-MEK-MAPK pathway, once found mutated, can also activate the RAS-RAF-MEK-MAPK pathway (Rebecca et al., 2012; Walia et al., 2012; Tsao et al., 2012; Ades and Metzger-Filho, 2012; Evans et al., 2013), similar to mutant RAS (Davies and Samuels, 2010; Tsao et al., 2012), which lacks GTPase activity and remains active leading to uncontrolled cell proliferation (Evans et al., 2013). Further, the BRAF can collaborates with the PI3K/AKT pathway in hyper activating the MAPK pathway (Lin et al., 2010). usually, when RAF becomes activated by tyrosine kinases .It activates the MAP kinases MEK 1 and 2, which are then phosphorylated and translocated into the nucleus to bind promoters of genes involved in the induction of cell growth and proliferation. All these shows inhibitor of BRAF such as V600E BRAF should be an effective treatment (Rebecca et al., 2012; Ades and Metzger-Filho, 2012). The MEK inhibitor selumetinib can also help (Falchook et al., 2012). However, drug resistance limits their clinical application, but strangely, MA Davies.et.al knew from other documents that all the durg resistance mechanisms seemed to share continued activation of the RAS-RAF-MEK-ERK signaling pathway (Davies and Samuels, 2010; Rebecca et al., 2012).

when concerning other treatments of Melanoma, Gajanan S.et.al summarized several methods including targeting RAS, B-RAF, MEK, ERK, nanotechnology, cross-talk between AKT3 and MAPK pathway, phosphatase-deregulation and said that combined targeting of the members of MAPK cascade or oncogenic proteins from different signaling pathways will be required to achieve better clinical efficacy (Inamdar et al., 2010). Silymarin, a polyphenolic flavonoid isolated from Silybum marianum, is said to inhibit COX-2 activities and suppress invasion by inactivating PI3K-Aktas and MAPK pathways, and therefore reducing MMP-2 as well as MMP-9 protein levels (Madhunapantula and Robertson, 2012). Berberine, a COX-2 inhibitor, functions in inhibiting melanoma cell proliferation and metastasis by targeting COX-2 and ERK pathways (Madhunapantula and Robertson, 2012). To conclude, in clinical medicine, there are drugs targeting MEK 1/2, MEK, RAF, RAS, and some other Pathways (Evans et al., 2013).

MAPK and Ovarian Cancer

100.0

6.3

75.0

56.3

50.0

25.0

31.3

0

Newly diagnosed without treatment

Ovarian cancer is a common disease among women, and is said to be connected to reproductive disorders, age, and hormone) (Merritt and Cramer, 2010; Modugno et al., 2012). There are three major types: epithelial, germ-cell and stromal cancer. Recently, there are many antiangiogenic therapies are under clinical application, such as anti-VEGF therapies, tyrosine kinase inhibitors [TKIs], Poly-ADP-Ribose Polymerase (PARP) Inhibition, PI3K inhibitors AKT inhibitors, and MEK inhibitor (Westin et al., 2013; Coleman et al., 2013).

In a newly publicated result, KA Bauckman.et.al elucidated iron (rich in the cyst fluid of endometriosis-associated ovarian cancers) levels were essential for cell (especially ovarian cancer cells) survival, for it induced an increase in lysosome numbers in a ras-independent manner (Bauckman et al., 2013). While as introduced above, ras is closely associated with the MAPK pathway in the casacade RAS-RAF-MEK-ERK-MAPK. Also, studies have showed that mutations in KRAS (MEK1/2) could not only activate MAP Kinase (MAPK or ERK), which induce the over-activation of NF-κB (related to anti-apoptotic mechanisms) (Saldanha and Tollefsbol, 2014), but also the PI3K/ AKT pathway (Merritt and Cramer, 2010; Saldanha and Tollefsbol, 2014)which is commonly considered to result in many cancers (Merritt and Cramer, 2010; Saldanha and Tollefsbol, 2014). Further, Charles et al showed that progesterone elevated cAMP levels, then resulted in activation of JNK1/2 and p38 MAPK activity and subsequently leading to induction of pro-apoptotic genes like Bax (Charles et al., 2010). So, we may conclude inhibition of the MAPK pathway could reverse cell death in malignant ovarian cells.

Surprisingly, Melissa A. Merritt.et.al concluded from previous research that alterations in the MAPK signaling cascade, acted as the most important factor that distinguished serous low grade from serous high grade ovarian tumors (Merritt and Cramer, 2010). And except from the above MAPK pathway, hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) may also function much through MAPKs leading to over-growth of cells (Saldanha and Tollefsbol, 2014). So, hormonal therapies may be a nice choice (Jelovac and Armstrong, 2011).

Finally, as an important target protien of the MAPK signal pathway, the AR is expressed in both normal ovary and ovarian cancer. The ovarian cancer cells express AR and respond to androgen with increased proliferation and attenuated apoptosis. Over-expression of AR has been found in ovarian cancer, and once activated, it can stimulate ovarian cancer cell invasion (Gogoi et al., 2008; Ligr et al., 2011), indicating targeting AR is also a promising treatment strategy.

Conclusions and Future Directions

Cancer has long been a vital cause leading to death. the cancer-related fatigue can bring about not only additional economic burden, but also exhaustion and lack of energy.

In the cancer process, genetic and epigenetic modification are thought to cause a variety of abnormal phenotypes including increased proliferation and survival of somatic cells. Normally, enhanced telomere attrition, oxidative stress, ultraviolet radiation exposure, severe DNA damages and oncogenic events can all act as activators to regenerate all kinds of signal ways related to mutations in genes or some other molecules. During the course, various gene products or factors, such as growth factors, protein kinases, and inflammatory mediators contribute to tumor progression. And actually, all the changes may be linked to some certain signal ways, which can cross-talk with each other. So treatments to certain cancers would be obtained by targeting several pathways. Although we have known that the MAPK pathway which related to cell proliferation, growth, transport, death, and many vital factors matters much in many human tumors .

Actually, in today's world, many mechanisms about the signal pathway have been revealed, for advances in our understanding of the genetic composition of cancers make some analyses potentially feasible but how it functions in certain cancers still remains unclear, methodology allowing for robust and cost-efficient analyses are far from enough. So further or comprehensive researches such as genome-wide association studies in cancer may find its way in current and future directions which would easy our way toward finding more targeting treatments or significant markers in the tumor field.

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References

Ades F, Metzger-Filho O (2012). Targeting the cellular signaling: BRAF inhibition and beyond for the treatment of metastatic malignant melanoma. *Dermatol Res Pract*, **2012**, 259170.

Ahmad I, Patel Y, Liu L. B, et al (2011). Ras mutation cooperates with beta-catenin activation to drive bladder tumourigenesis. *Cell Death Dis*, **2**, 124.

Ahn J, Eom C, Jeon S (2013). Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies. *World J Gastroenterol*, **19**, 2560-8.

Amankwah E, Sellers T, Park Y (2012). Gene variants in the angiogenesis pathway and prostate cancer. *Carcinogenesis*, **33**, 1259-69.

Ara T, Declerck Y (2010). Interleukin-6 in bone metastasis and cancer progression. *Eur J Cancer*, **46**, 1223-31.

Bagley M, Davis P, Murziani S, et al (2010). Use of p38 MAPK inhibitors for the treatment of Werner Syndrome. *Pharmaceuticals*, **3**, 1842-72.

Bauckman K, Haller E, Flores I, et al (2013). Iron modulates cell survival in a Ras- and MAPK-dependent manner in ovarian cells. *Cell Death Dis*, **4**, 592.

Bourboulia D, Stetler-Stevenson W (2010). Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs): Positive and negative regulators in tumor cell adhesion. *Semin Cancer Biol*, **20**, 161-8.

Boyd F, Martin L, Bronskill M, et al (2010). Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst*, **102**, 1224-37.

Cargnello M, Roux P (2011). Activation and function of the

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MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev*, **75**, 50-83.

Cerne J, Stegel V, Gersak K, et al (2012). KRAS rs61764370 is associated with HER2-overexpressed and poorly-differentiated breast cancer in hormone replacement therapy users: a case control study. *BMC Cancer*, **12**, 105.

Chang E, Yang J, Alfaro-Velcamp T, et al (2010). Disparities in liver cancer incidence by nativity, acculturation, and socioeconomic status in California Hispanics and Asians. *Cancer Epidemiol Biomarkers Prev*, **19**, 3106-18.

Chao S, Huang S, et al (2013). Subtoxic Levels of Apigenin Inhibit Expression and Secretion of VEGF by Uveal Melanoma Cells via Suppression of ERK1/2 and PI3K/Akt Pathways. *Evid Based Complement Alternat Med*, **2013**, 817674.

Charles N, Thomas P, Lange C (2010). Expression of membrane progesterone receptors (mPR/PAQR) in ovarian cancer cells: implications for progesterone-induced signaling events. *Horm Cancer*, **1**, 167-76.

Cheng Y, Ueno N (2012). Improvement of survival and prospect of cure in patients with metastatic breast cancer. *Breast Cancer*, **19**, 191-9.

Clarke R, Schirra H, Catto J, et al (2010). Markers for detection of prostate cancer. *Cancers*, **2**, 1125-54.

Coleman R, Monk B, Sood A, et al (2013). Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol*, **10**, 211-4.

Connolly R, Carducci M, et al (2012). Use of androgen deprivation therapy in prostate cancer: indications and prevalence. *Asian J Androl*, **14**, 177-86.

Curiel-Lewandrowski C, Chen C, Swetter S, et al (2012). Screening and prevention measures for melanoma: is there a survival advantage? *Curr Oncol Rep*, **14**, 458-67.

Cust A, Armstrong B, Goumas C, et al (2011). Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. *Int J Cancer*, **128**, 2425-35.

Davies M, Samuels Y (2010). Analysis of the genome to personalize therapy for melanoma. *Oncogene*, **29**, 5545-55.

Mello R, Marques D, Medeiros R, et al (2011). Epidermal growth factor receptor and K-Ras in non-small cell lung cancer-molecular pathways involved and targeted therapies. *World J Clin Oncol*, **2**, 367-76.

Dela Cruz C, Tanoue L, et al (2011). Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*, **32**, 605-44.

Demaria S, Pikarsky E, Karin M, et al (2010). Cancer and inflammation: promise for biologic therapy. *J Immunother*, **33**, 335-51.

Detchokul S, Frauman A (2011). Recent developments in prostate cancer biomarker research: therapeutic implications. *Br J Clin Pharmacol*, **71**, 157-74.

Dey S, Ghosh N, Saha D, et al (2014). Matrix metalloproteinase-1 (MMP-1) Promoter polymorphisms are well linked with lower stomach tumor formation in eastern Indian population. *PLoS One*, **9**, 88040.

Dixon D, Blanco F, Bruno A, et al (2013). Mechanistic aspects of COX-2 expression in colorectal neoplasia. *Rec Res Cancer Res*, **91**, 7-37.

Drake G (2010). Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol*, **10**, 580-93.

Dudek A, Grotenhuis A, Vermeulen S, et al (2013). Urinary bladder cancer susceptibility markers. what do we know about functional mechanisms? *Int J Mol Sci*, **14**, 12346-66.

Egleston B, Meireles S, Flieder D, et al (2009). Population-based trends in lung cancer incidence in women. *Semin Oncol*, **36**, 506-15.

Evans M, Madhunapantula S, Robertson G, et al (2013). Current and future trials of targeted therapies in cutaneous melanoma.

Adv Exp Med Biol, **779**, 223-55.

Falchook G, Lewis K, Infante J, et al (2012). Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. *Lancet Oncology*, **13**, 782-89.

Galan-Moya E, Cruz-Morcillo M, Llanos Valero M, et al (2011). Balance between MKK6 and MKK3 mediates p38 MAPK associated resistance to cisplatin in NSCLC. *PLoS One*, **6**, 28406.

Gholami S, Chen C, Gao S, Lou E, et al (2014). Role of MAPK in oncolytic herpes viral therapy in triple-negative breast cancer. *Cancer Gene Ther*, **21**, 283-9.

Gogoi R., Kudla M, Gil O, et al (2008). The activity of medroxyprogesterone acetate, an androgenic ligand, in ovarian cancer cell invasion. *Reprod Sci*, **15**, 846-52.

Gomes L, Terra L, Wailemann R, et al (2012). TGF-beta1 modulates the homeostasis between MMPs and MMP inhibitors through p38 MAPK and ERK1/2 in highly invasive breast cancer cells. *BMC Cancer*, **12**, 26.

Grieco L, Calzone L, Bernard-Pierrot I, et al (2013). Integrative modelling of the influence of MAPK network on cancer cell fate decision. *PLoS Comput Biol*, **9**, 1003286.

Hassanein M, Callison J, Callaway-Lane C, et al (2012). The state of molecular biomarkers for the early detection of lung cancer. *Cancer Prev Res*, **5**, 992-1006.

Hollenhorst P, Ferris M, Hull M, et al (2011). Oncogenic ETS proteins mimic activated RAS/MAPK signaling in prostate cells. *Genes Dev*, **25**, 2147-57.

Inamdar G, Madhunapantula S, et al (2010). Targeting the MAPK pathway in melanoma: why some approaches succeed and other fail. *Biochem Pharmacol*, **80**, 624-37.

Izrailit J, Berman H, Datti K, et al (2013). High throughput kinase inhibitor screens reveal TRB3 and MAPK-ERK/TGFbeta pathways as fundamental Notch regulators in breast cancer. *Proc Natl Acad Sci U S A*, **110**, 1714-9.

Jeannin P, Duluc D, Delneste Y (2011). IL-6 and leukemia-inhibitory factor are involved in the generation of tumor-associated macrophage: regulation by IFN-gamma. *Immunotherapy*, **3**, 23-26.

Jelovac D, Armstrong D (2011). Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*, **61**, 183-203.

Jia-Qi S, Kun-Peng X, Wei Z (2014). Emodin inhibits breast cancer cell proliferation through the ERα-MAPK/Akt-Cyclin D1/Bcl-2 signaling pathway. *Asian Pac J Cancer Prev*, **15**, 6247-51.

Jin J, Dayyani F, Gallick G (2011). Steps in prostate cancer progression that lead to bone metastasis. *Int J Cancer*, **128**, 2545-61.

Kadara H, Kabbout M, Wistuba M (2012). Pulmonary adenocarcinoma: a renewed entity in 2011. *Respirology*, **17**, 50-65.

Kessenbrock K, Plaks V, Werb Z (2010). Matrix metalloproteinases: regulators of the tumor microenvironment. *Cel*, **141**, 52-67.

Khwaja F, Quann E, Pattabiraman N, et al (2008). Carprofen induction of p75NTR-dependent apoptosis via the p38 mitogen-activated protein kinase pathway in prostate cancer cells. *Mol Cancer Ther*, **7**, 3539-45.

Koh C, Bieberich C, Dang C, et al (2010). MYC and prostate cancer. *Genes Cancer*, **1**, 617-28.

Kohli M, Tindall D (2010). New developments in the medical management of prostate cancer. *Mayo Clin Proc*, **85**, 77-86.

Kompier L, Lurkin I, Aa M, et al (2010). FGFR3, HRAS, KRAS, NRAS and PIK3CA mutations in bladder cancer and their potential as biomarkers for surveillance and therapy. *PLoS One*, **5**, 13821.

Korner A, Drapeau M, Thombs B, et al (2013). Barriers and

facilitators of adherence to medical advice on skin self-examination during melanoma follow-up care. *BMC Dermatol*, **13**, 3.

Koul H, Pal M, Koul S (2013). Role of p38 MAP Kinase Signal Transduction in Solid Tumors. *Genes Cancer*, 342-59.

Lamy E, Herz C, Lutz-Bonengel S, et al (2013). The MAPK pathway signals telomerase modulation in response to isothiocyanate-induced DNA damage of human liver cancer cells. *PLoS One*, **8**, 53240.

Larsen J, Cascone T, Gerber D, et al (2011). Targeted therapies for lung cancer: clinical experience and novel agents. *Cancer J*, **17**, 512-27.

Larsen J, Minna J (2011). Molecular biology of lung cancer: clinical implications. *Clin Chest Med*, **32**, 703-40.

Li C, Fan S, Owonikoko T, et al (2011). Oncogenic role of EAPII in lung cancer development and its activation of the MAPK-ERK pathway. *Oncogene*, **30**, 3802-12.

Li Y, Kong D, Bao B, et al (2011). Induction of cancer cell death by isoflavone: the role of multiple signaling pathways. *Nutrients*, **3**, 877-96.

Ligr M, Patwa R, Daniels G, et al (2011). Expression and function of androgen receptor coactivator p44/Mep50/WDR77 in ovarian cancer. *PLoS One*, **6**, 26250.

Lin K, Baritaki S, Militello L, et al (2010). The role of B-RAF mutations in melanoma and the induction of emt via dysregulation of the NF-kappaB/Snail/RKIP/PTEN circuit. *Genes Cancer*, **1**, 409-20.

Lin L, Deng W, Tian Y, et al (2014). Lasiodin inhibits proliferation of human nasopharyngeal carcinoma cells by simultaneous modulation of the Apaf-1/caspase, AKT/MAPK and COX-2/NF-kappaB signaling pathways. *PLoS One*, **9**, 97799.

Liu H, Wang L, Liu Z, et al (2013). Association between functional polymorphisms in genes involved in the MAPK signaling pathways and cutaneous melanoma risk. *Carcinogenesis*, **34**, 885-92.

Lofgren K, Ostrander J, et al (2011). Mammary gland specific expression of Brk/PTK6 promotes delayed involution and tumor formation associated with activation of p38 MAPK. *Breast Cancer Res*, **13**, 89.

Lv Z, Xu L (2012). Salvianolic Acid B Inhibits ERK and p38 MAPK Signaling in TGF-beta1-Stimulated Human Hepatic Stellate Cell Line (LX-2) via Distinct Pathways. *Evid Based Complement Alternat Med*, **2012**, 960128.

Madhunapantula S, Robertson G (2012). Chemoprevention of melanoma. *Adv Pharmacol*, **65**, 361-98.

Mao L, Yuan L, Slakey L, et al (2010). Inhibition of breast cancer cell invasion by melatonin is mediated through regulation of the p38 mitogen-activated protein kinase signaling pathway. *Breast Cancer Res*, 12107.

Marshall A, Christiani D (2013). Genetic susceptibility to lung cancer--light at the end of the tunnel? *Carcinogenesis*, **34**, 487-502.

Matesic D, Sidorova T (2012). p38 MAPK activation, JNK inhibition, neoplastic growth inhibition, and increased gap junction communication in human lung carcinoma and Ras-transformed cells by 4-phenyl-3-butenoic acid. *J Cell Biochem*, **113**, 269-81.

Mendoza M, Er E, et al (2010). ERK-MAP Kinase signaling in the cytoplasm. *Methods Mol Biol*, **661**, 185-203.

Merritt M, Cramer D (2010). Molecular pathogenesis of endometrial and ovarian cancer. *Cancer Biomark*, **9**, 287-305.

Milone M, Pucci B, et al (2013). Acquired resistance to zoledronic acid and the parallel acquisition of an aggressive phenotype are mediated by p38-MAP kinase activation in prostate cancer cells. *Cell Death Dis*, **4**, 641.

Mimura K, Shiraishi K, Mueller A, et al (2013). The MAPK pathway is a predominant regulator of HLA-A expression in esophageal and gastric cancer. *J Immunol*, **191**, 6261-72.

Mo L, Zheng X, Huang H, et al (2007). Hyperactivation of Ha-ras oncogene, but not Ink4a/Arf deficiency, triggers bladder tumorigenesis. *J Clin Invest*, **117**, 314-25.

Mo N, Li Z, Cao Y (2012). Curcumin inhibits TGF-β1-induced MMP-9 and invasion through ERK and Smad signaling in breast cancer MDA-MB-231 Cells. *Asian Pac J Cancer Prev*, **13**, 5709-14.

Modugno F, Laskey R, Smith A, et al (2012). Hormone response in ovarian cancer: time to reconsider as a clinical target? *Endocr Relat Cancer*, **19**, 255-79.

Mohammad G, Mairaj Siddiquei M, Imtiaz Nawaz M, et al (2013). The ERK1/2 inhibitor U0126 attenuates diabetes-induced upregulation of MMP-9 and biomarkers of inflammation in the retina. *J Diabetes Res*, **2013**, 658548.

Mulholland D, Kobayashi N, et al (2012). Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. *Cancer Res*, **72**, 1878-89.

Nagini S (2012). Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol*, **4**, 156-69.

Obata N, Tamakoshi K, et al (1997). Effects of interleukin-6 on *in vitro* cell attachment, migration and invasion of human ovarian carcinoma. *Anticancer Res*, **17**, 337-42.

Ochoa C, Mirabolfathinejad S, et al (2011). Interleukin 6, but not T helper 2 cytokines, promotes lung carcinogenesis. *Cancer Prev Res (Phila)*, **4**, 51-64.

Park M, Zhang G, et al (2008). Mitogen-activated protein kinase kinase 1/2 inhibitors and 17-allylamino-17-demethoxygeldanamycin synergize to kill human gastrointestinal tumor cells *in vitro* via suppression of c-FLIP-s levels and activation of CD95. *Mol Cancer Ther*, **7**, 2633-48.

Park W, Amin A, Chen Z, et al (2013). New perspectives of curcumin in cancer prevention. *Cancer Prev Res*, **6**, 387-400.

Pereira L, Igea A, Canovas B, et al (2013). Inhibition of p38 MAPK sensitizes tumour cells to cisplatin-induced apoptosis mediated by reactive oxygen species and JNK. *EMBO Mol Med*, **5**, 1759-74.

Philbin M, Erby L, Lee S, et al (2012) Hepatitis B and liver cancer among three Asian American sub-groups: a focus group inquiry. *J Immigr Minor Health*, **14**, 858-68.

Polo M, Arnoni M, et al (2010). Responsiveness to PI3K and MEK inhibitors in breast cancer. Use of a 3D culture system to study pathways related to hormone independence in mice. *PLoS One*, **5**, 10786.

Rebecca V, Sondak V, et al (2012). A brief history of melanoma: from mummies to mutations. *Melanoma Res*, **22**, 114-22.

Rountree C, Mishra L, et al (2012). Stem cells in liver diseases and cancer: recent advances on the path to new therapies. *Hepatology*, **55**, 298-306.

Saldanha S, Tollefsbol T (2014). Pathway modulations and epigenetic alterations in ovarian tumorbiogenesis. *J Cell Physiol*, **229**, 393-406.

Sfanos K, Marzo A (2012). Prostate cancer and inflammation: the evidence.Histopathology, 60, 199-215.

Shen M, Abate-Shen C (2010). Molecular genetics of prostate cancer: new prospects for old challenges. *Genes Dev*, **24**, 1967-2000.

Shrestha Y, Schafer E, Boehm J, et al (2012). PAK1 is a breast cancer oncogene that coordinately activates MAPK and MET signaling. *Oncogene*, **31**, 3397-408.

Slattery M, John E, et al (2013). Matrix metalloproteinase genes are associated with breast cancer risk and survival: the Breast

Cancer Health Disparities Study. *PLoS One*, **8**, 63165.

Son T, Kwon I, Hyung W (2014). Minimally invasive surgery for gastric cancer treatment: current status and future perspectives. *Gut Liver*, **8**, 229-36.

Sukhtankar D, Okun A, Chandramouli A, et al (2011). Inhibition of p38-MAPK signaling pathway attenuates breast cancer induced bone pain and disease progression in a murine model of cancer-induced bone pain. *Mol Pain*, **7**, 81.

Tanaka T, Miyazawa K, Tsukamoto T, et al (2011). Pathobiology and chemoprevention of bladder cancer. *J Oncol*, **2011**, 528353.

Thanan R, Murata M, Ma N, et al (2012). Nuclear localization of COX-2 in relation to the expression of stemness markers in urinary bladder cancer. *Mediators Inflamm*, **2012**, 165879.

Tsao H, Chin L, Garraway L, et al (2012). Melanoma: from mutations to medicine. *Genes Dev,* **26,** 1131-55.

Walia V, Mu W, Lin J, et al (2012). Delving into somatic variation in sporadic melanoma. *Pigment Cell Melanoma Res*, **25**, 155-70.

Wang C, Cigliano A, Delogu S, et al (2013). Functional crosstalk between AKT/mTOR and Ras/MAPK pathways in hepatocarcinogenesis: implications for the treatment of human liver cancer. *Cell Cycle*, **12**, 1999-2010.

Wang J, Kobayashi T, Floc'h N, et al (2012). B-Raf activation cooperates with PTEN loss to drive c-Myc expression in advanced prostate cancer. *Cancer Res*, **72**, 4765-76.

Westbrook K, Stearns V (2013). Pharmacogenomics of breast cancer therapy: an update. *Pharmacol Ther*, **139**, 1-11.

Westin S, Herzog T, et al (2013). Investigational agents in development for the treatment of ovarian cancer. *Invest New Drugs*, **31**, 213-29.

Wilson K, Giovannucci E, et al (2012). Lifestyle and dietary factors in the prevention of lethal prostate cancer. *Asian J Androl*, **14**, 365-74.

Wu C, Zhu Z (2014). Diagnosis and evaluation of gastric cancer by positron emission tomography. *World J Gastroenterol*, **20**, 4574-85.

Wu H, Lin W, Tsai K (2014). Advances in molecular biomarkers for gastric cancer: miRNAs as emerging novel cancer markers. *Expert Rev Mol Med*, **16**, 1.

Xu Y, Li N, Xiang R, (2014). Emerging roles of the p38 MAPK and PI3K/AKT/mTOR pathways in oncogene-induced senescence. *Trends Biochem Sci*, **39**, 268-76.

Yang Y, Kim S, Yu T, et al (2014). Functional roles of p38 mitogen-activated protein kinase in macrophage-mediated inflammatory responses. *Mediators Inflamm*, **2014**, 352371.

Zender L, Villanueva A, Tovar V, et al (2010). Cancer gene discovery in hepatocellular carcinoma. *J Hepatol*, **52**, 921-9.

Zhang Z, Neiva K, Lingen M, et al (2010). VEGF-dependent tumor angiogenesis requires inverse and reciprocal regulation of VEGFR1 and VEGFR2. *Cell Death Differ*, **17**, 499-512.

Liang-Rui Z, Xian C, Ke-Min W (2013). *Radix tetrastigma* Hemsleyani flavone induces apoptosis in human lung carcinoma A549 cells by modulating the MAPK pathway. *Asian Pac J Cancer Prev*, **14**, 5983-87.