We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

MAP Kinases and Prostate Cancer

Gonzalo Rodríguez-Berriguete, Benito Fraile, Laura Galvis,
Ricardo Paniagua and Mar Royuela
Department of Cell Biology and Genetics. University of Alcalá, Madrid
Spain

1. Introduction

One of the most relevant aspects in cell death regulation is the signaling of apoptosis by serine/threonine kinases, a broad category of kinases that includes, among others, the mitogen-activated protein kinases (MAPKs) (Cross et al., 2000; Khlodenko & Birtwistle, 2009). The three main members that integrate the MAPK family in mammalian cells are: the stress-activated protein kinase c-Jun NH$_2$-terminal kinases (JNK), the stress-activated protein kinase 2 (SAPK2, p38), and the extracellular signal-regulated protein kinases (ERK1/2, p44/p42) (Fig. 1). In addition, other less well-characterized MAPK pathways exist, such as the extracellular regulated kinase 5 (ERK5) pathway (Hayashi &Lee, 2004; Junttila & Li, 2008) (Fig. 1). Albeit with multiple exceptions, JNK and ERK5 are generally associated with apoptosis induction; while ERK1/2 are generally associated to mitogenesis, and therefore inversely related to apoptosis (Hayashi &Lee, 2004; Junttila & Li, 2008); and contradictory effects on cell death have been described to p38 (Chang et al., 2008; Joo & Yoo, 2009; Khwaja et al., 2008; Ricote et al., 2006a; Shimada et al., 2006; Vayalil et al., 2004; Zhang &Kong, 2008).

ERK is a threonine-glutamic acid-tyrosine (Thr-Glu-Tyr) motif (Hunter, 2000; Liu et al., 2010) that play a central role in stimulation of cell proliferation (Marais & Marshall, 1990; Peng et al., 2010). Two isoforms of ERK, referred as ERK1 (or p44) and ERK2 (or p42), are ubiquitously expressed and represent a convergence point for mitogenic signaling from a diverse array of pathways (Cullen &Lockyer, 2002; Eisinger &Ammer, 2008; Gao et al., 2010). Both are ubiquitously expressed, although their relative abundance in tissues is variable. For example, in many immune cells ERK2 is the predominant species, while in several cells of neuroendocrine origin they may be equally expressed (Zebisch et al., 2007). ERK 1/2 is activated by MEK1/2 specifically by phosphorylating a tyrosine and a threonine residue, separated by a glutamate residue (TEY) (Zebisch et al., 2007). Activated ERK1 and ERK2 can translocate to the nucleus, where it activates several transcription factors such as ATF-2, Elk-1, c-Fos, c-myc or Ets-1 (Junttila & Li, 2008). At the same time, it can also phosphorylate cytoplasmic and nuclear kinases, such as MNK1, MNK2, MPKAP-2, RSK or MSK1 (Zebisch et al., 2007). The ERK1/2 cascade is triggered by growth factors and cytokines acting through receptor tyrosine kinases, G-protein-coupled receptors, and non-nuclear activated steroid hormone receptors. The biological consequences of ERK1/2 substrate phosphorylation include pro-proliferative (Pearson et al., 2001), pro-differentiation (Pearson et al., 2001), pro-survival (Pearson et al., 2001), pro-angiogenic (Pàges et al., 2000), pro-motility (Joslin et al., 2007) and pro-invasive effects (Price et al., 2002).

P38 plays roles in cell differentiation, growth inhibition and apoptosis, proliferation and cell survival (Hui et al., 2007; Raingeaud et al., 1995; Thornton & Rincon, 2009). p38 is activated in cells in response to stress signals, growth factors, inflammatory cytokines, UV, heat and osmotic shock (Raingeaud et al., 1995; Whyte et al., 2009). Four isoforms of p38 exist (p38α, β, γ and δ), although p38α is the most widely expressed. MKK3/6 (MAPKKK) and SEK (MAPKK) activate p38. A great number MAPKKs and MAPKKKs (e.g. Mlk1-3, MEKK1-4, TAK, ASK1/2) upstream of p38 have been identified. Both MAPKKs and MAPKKKs are generally activated by G small proteins as Rac1, Cdc42, RhoA and RhoB (Fenf et al., 2009). Activated p38 phosphorylates and regulates many transcription factors (including activating transcription factor-2, NF-kB, Elk-1, Max, myocyte enhancer factor-2, Mac, p53 or Stat1) (Royuela et al., 2008; Whyte et al., 2009; Zhao et al., 1999), and other cell cycle and apoptosis mediators (e.g. Cdc25A, Bcl-2) (Thornton & Rincon, 2009). p38 has been defined as tumor suppressor and generally exert a pro-apoptotic role. However, it has been also shown to enhance cell survival in response to stress stimuli, for instance, in response to DNA damage (Thornton& Rincon., 2009; Whyte et al., 2009; Jiang et al., 1997; Wang XS et al., 1997; Feng et al., 2009; Zhao et al., 1999; Royuela et al., 2008; Wood et al., 2009). Triggering of pro- or anti-apoptotic p38-mediated response seems to depend on the stimuli, the cell system and the involved p38 isoform (Feng et al., 2009).
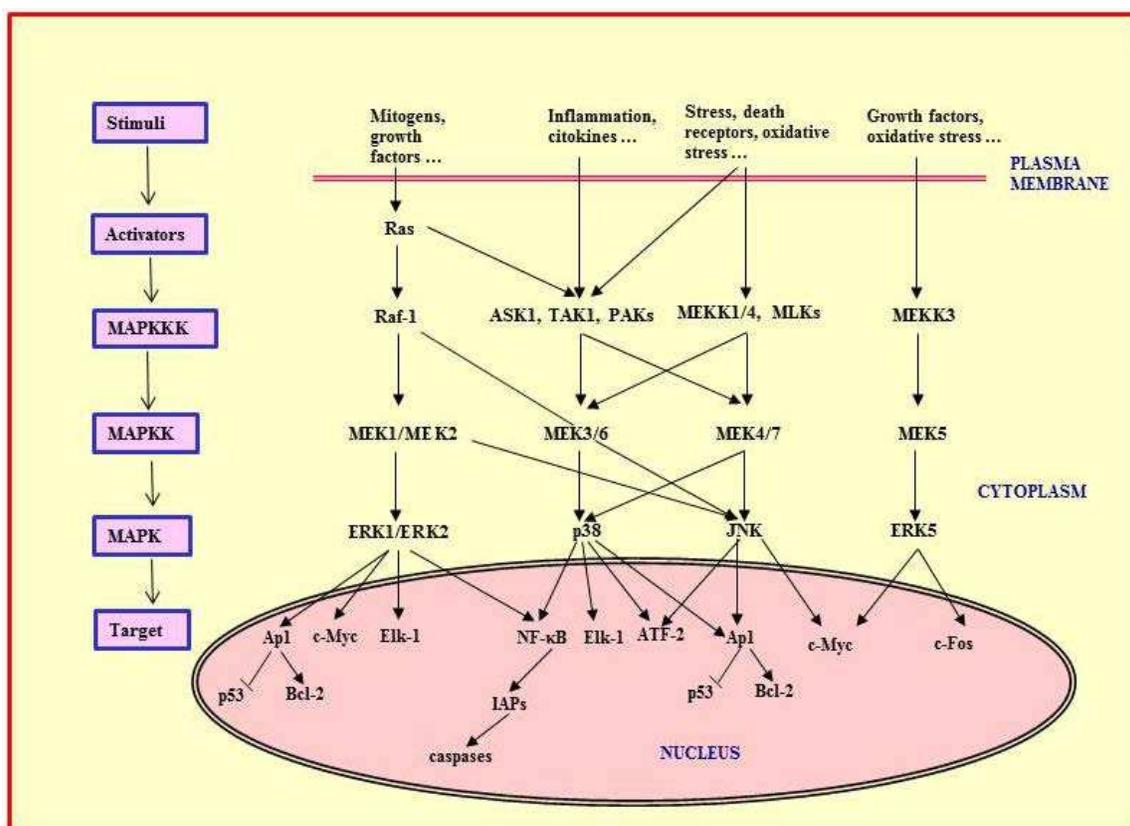

Fig. 1. Mitogen activated protein kinase (MAPK) signaling. MAP kinases are activated by upstream kinases such as MAP kinase kinase (MAPKK), that include MEKs 1, 2, 3, 4, 5, 6 and 7. In turn, MAPKKs are activated by several different MAP kinase kinase kinases (MAPKKKs). Numerous stimulatory factors such as cytokines, mitogens or death receptors, can activate MAPKKKs. Each MAPK, depending on the stimulus and cell type, can phosphorylate different transcription factors.

JNK proteins, also called stress activated protein kinases (SAPKs), are activated in response to a variety of extracellular stimuli, including UV irradiation, mitogens and cytokines (De Graeve et al., 1999). Notably, the earliest discoveries included the identification of the three mammalian JNK genes called JNK1, JNK2, and JNK3 (also termed stress-activated protein kinase (SAPK)-γ, SAPK-α and SAPK-β, respectively) which can be subdivided into 10 isoforms by alternative splicing (Bogoyevitch et al., 2010; Dérijard et al., 1994). Alternative splicing further increases the diversity of JNK proteins, however apart from early biochemical studies on these splice forms (Gupta et al., 1996) their functional significance *in vivo* has remained largely unexplored (Bogoyevitch et al., 2010). The products of JNK1 and JNK2 are ubiquitously expressed in every cells and tissues, whereas JNK3 is localized primarily in brain, heart and testis. Due to the specificity of tissue, JNK3 presents different functions than JNK1 and JNK2. In addition, several authors believe that JNK1 and JNK2 present redundant functions. Several studies suggest that JNK are involved in regulation of the cell cycle (Bode & Dong, 2007.). JNK signaling contributes to the ability of p53 to mediate apoptosis through stabilization and activation of p53 (Bode & Dong, 2007; Fuchs et al., 1998). The fourth MAPK of interest in this review is ERK5. ERK5 is a large molecular size kinase (Lee et al., 1995) identified independently by two groups. One used a two hybrid screen with an upstream activator MEK5 as the bait; the other used a degenerate PCR strategy to clone novel MAPK (Lee et al., 1995; Zhou et al., 2005). ERK5 is activated by growth factors (Kato et al., 1998), integrin engagement (Sawhney et al., 2009) and cell stress (Pi et al., 2004), and its important molecular targets would seem to include the induction of transcription of components of the transcription factor Ap1 (cJun (Kayahama et al., 2005) and Fos (Kamakura et al., 1999) and activation of transcription factors of the myocyte enhancer family group (for example, MEF2C, a well characterized target (Kato et al., 1997)), and cMyc (English et al., 1998).

In an *in vitro* study directed using androgen-dependent PC3 cells, McCracken et al. (2008) described ERK5-overexpresion related with proliferative, migrative and invasive capabilities, establishing the potential importance of ERK5 in aggressive prostate cancer. In similar studies Sawhney et al. (Sawhney et al., 2009) hypothesized that ERK5 activation could promote cancer metastasis.

In mammalian cells, ERK, p38 and JNK activities are respectively regulated by three different MAPK cascades, which provide a link between transmembrane signaling and changes in transcription and are activated in response to different environmental or developmental signals (Junttila & Li, 2008) (Fig. 1). Depending on the cell type, a particular MAPK cascade may be involved in different cellular responses. The JNK and p38 signaling pathways are activated by pro-inflammatory (TNFα, IL-6 or IL-1) or anti-inflammatory (EGF, TGF-β) cytokines, but also in response to cellular stresses such as genotoxic, osmotic, hypoxic, or oxidative stress. The JNK pathway consists of JNK, a MAPKK such as SEK1 (also known as MEK4) or MEK7, and a MAPKKK such as ASK1, MEKK1, mixed-lineage kinase (MLK), or transforming growth factor-β-activated kinase 1 (TAK1) (Davis, 2000; Kim & Choi, 2010). In the p38 signaling pathway, distinct MAPKKs such as MEK3 and MEK6 activate p38 and these are activated by the same MAPKKKs (such as ASK1 and TAK1) that function in the JNK pathway. In the ERK signaling pathway, ERK1 or ERK2 (ERK1/2) is activated by MEK1/2, which in turn is activated by a Raf isoform such as A-Raf, B-Raf, or Raf-1 (also known as C-Raf) but also by TRAF-2 and TRAF-6. The kinase Raf-1 is activated by the small Ras-like GTPase, whose activation is mediated by the receptor tyrosine kinase

(RTK)-Grb2-SOS signaling axis (Dhillon et al., 2007). Members of the Ras family of proteins, including K-Ras, H-Ras, and N-Ras, play a key role in transmission of extracellular signals into cells (Ancrile et al., 2008) (Fig. 1).

The aim of this review was to focus on the possible involvement of MAPKs in several transduction pathways related with prostate cancer development as well as the possible functional role of MAPKs in cell death/ survival/ proliferation decisions depending on the cell type, stage and cell stimulus. We also discuss the possible use of some members of this pathway as a potential therapeutic target.

2. IL-6/TNF/JNK pathway

Depending on the stimulus and cell type, JNKs can phosphorylate different substrates such as Ap1, ATF-2, Elk-1, c-Myc, p53, MLK2 and several members of the Bcl-2 family. JNKs are implicated in development, morphogenesis and cell differentiation (Heasley & Han, 2006). Several studies suggest that in apoptosis JNKs have opposite functions depending on the cellular stimulus. In this way, JNKs can induce apoptosis, but also can enhance cell survival and proliferation. JNKs are also involved in regulation of the cell cycle (Bode & Dong, 2007). JNK signaling contributes to the ability of p53 to mediate apoptosis through stabilization and activation of p53 (Bode & Dong, 2007; Fuchs et al., 1998). Several authors suggest that JNK activity is chronically altered in various cancer types such as prostate (Meshki et al., 2010; Royuela et al., 2002), breast (Wang HY et al., 2003; Wang J et al., 2010), pancreatic or lung (Lee et al., 2010; Su et al., 1998) carcinomas.

Investigations of JNKs have focused on their activation in response to diverse stresses including ultraviolet and gamma radiation, inflammatory cytokines and cytotoxic drugs. In this way, pro inflammatory cytokines such as IL-6 or TNF activate different transduction pathway (Khalaf et al., 2010).

IL-6 exerts its effects through a membrane receptor complex composed by IL-6 receptor a (IL-6Ra) and glycoprotein 130 (gp130). Silver and Hunter (Silver & Hunter, 2010) described the role of gp130 in promoting or preventing the development of autoimmunity and cancer, two processes that are associated with aberrant inflammatory responses. In addition to an immunological role, IL-6 is involved in cell proliferation in other tissues such as bone (Kurihara et al., 1990), testis (spermatogenesis) (Huleihel & Lunenfeld, 2004), skin (Krueguer et al., 1990) or nervous system (Hama et al., 1989). It has been shown that IL-6 also stimulates the development of many tumors, including melanoma, renal cell carcinoma, Kaposi's sarcoma, ovarian carcinoma, lymphoma and leukemia, multiple myeloma, prostate carcinoma and breast carcinoma (García-Tuñon et al., 2005; Hong et al., 2007; Rabinovich et al., 2007; Royuela et al., 2004).

First, IL-6 binds to IL-6Ra, which is unable to initiate signal transduction, and this complex attracts gp130 molecules, which dimerize leading to the intracellular signal by the activation of constituvely-associated gp130 Jak proteins (Heinrich et al., 1998; Hong et al., 2007; Silver & Hunter, 2010). In PC (prostate cancer) immunoreaction to IL-6 and gp-130 were increased. IL-6 signalling could be enhanced not only due to increased autocrine production but also increasing levels of this receptor (Rodriguez-Berriguete et al., 2010a; Royuela et al., 2004). Jak proteins can simultaneously trigger functionally distinct and even contradictory signaling pathways. One of them leads to the recruitment at the complex receptor of SHP2, Sos and Grb2, which in turn activates Ras by stimulating the exchange of GDP bound to Ras for GTP. Then, Ras initiates a MAPK cascade by phosphorylation of Raf-1 (Ancrile &

O'Hayer, 2008). Raf-1 activation might stimulate two different pathways. One pathway is initiated by MEK1/2 and the other with the activation of JNK. In prostate cancer expression of to Raf-1, MEK-1 and p-MEK were increased with Gleason grade (Rodruguez et al., 2010a). TNF-α is a 17 kDa polypeptide that has been implicated in skin carcinogenesis and in metastatic tumor spread of a variety of carcinomas and sarcomas. The action of TNF- α is mediated by two distinct receptors named TNF-receptor I (55 kDa, TNFRI) and receptor II (75 kDa, TNFRII) with similar affinity for TNF- α in human tissues (Loetscher et al., 1990; Smith et al., 1990). The domains of these receptors are different (Tartaglia et al., 1991). TNFRI is the major mediator of most TNF-α activity (Wiegmann et al., 1992). The expression and action of TNF- α and its receptors has been reported in several tumors such as esophageal (Hubel et al., 2000), prostate (De Miguel et al., 2000; Meshki et al., 2010), follicular thyroid (Zubelewicz et al., 2002), skin (Arnott et al., 2004), ovarian (Qiu et al., 2010; Rzymski et al., 2005) and breast (García-Tuñon et al., 2006) cancers.

In human prostate cancer, TNFα cascade seems to be over-stimulated since TNFα receptors (TNFRI and TNFRII) present high immunoexpression (Ricote et al., 2003). Binding of TNF-α/TNFRI complex to TNF receptor associated death domain proteins (TRADD) activates TRAF-2 (1 of the 6 members of the TNF receptor associated factor), which represents an integration point for pro-apoptotic and antiapoptotic signals (Wajant & Scheurich, 2001). TRAF-2 activation might stimulate two different pathways. One pathway is initiated by the interaction of TRAF-2 with the activation of NF-kB inducing kinase termed NIK, which is a MAP3K-related kinase that activates the IKK complex composed of IKK-α and IKK-β (Wu & Kral, 2005). In prostate cancer, NIK seems to be triggered by TNF/TRAF-2 or IL-1/IRAK/TRAF-6, since the presence of TNF, TNFRI and TRAF-2 has been described (De Miguel et al., 2000; Ricote et al., 2003), but also the presence of IL-1 family members (Nuñez et al., 2008; Ricote et al., 2004). NIK stimulate IKK-β, which induces IKK-α degradation. IKK complex phosphorylates IkB, following its ubiquitination and rapid degradation causing the nuclear translocation of NF-kB, which in turn, activates target genes involved in carcinogenesis: tumor initiation, malignant transformation and metastasis (Wu & Kral., 2005; Chengedza & Benbrook, 2010). In PC, TRAF-2 might be involved in the NIK activation pathway, although immunoexpression to TRAF-2 was detected in a low number of cases (decrease with Gleason grade), at the same time that the most of these patients were positives to NF-kB/p50 and NF-kB/p65 (Nuñez et al., 2008). These data, in addition with the elevated immunoexpressions to IL-1, IRAK, TRAF-6 and NIK observed in the same samples, suggest that NIK is stimulated by IL-1. Using the prostate carcinoma cell lines LNCaP, DU45 and PC3, Gasparian et al. (2009) found that increased IKK activation leads to the activation of NF-kB. A potential role of NF-kB in the development of different tumors as breast (Miller et al., 2000; Wu & Kral, 2005), colon (Dejardin et al., 1999; Wang S et al., 2009), pancreas (Wang W et al 1999; Eldor et al., 2009), thyroid (Visconti et al., 1997) or prostate (Nuñez et al., 2008; Domingo-Domenech et al., 2005) have been reported.

The other pathway activates the cascade ASK-1 (signal regulating kinase), MEK-4 (mitogen activated protein kinase-kinase 4) and Jun N-terminal kinase (JNK) (Royuela et al., 2008). When JNK is translocated to the nucleus is phosphorylated and activates transcription factors such as AP-1 or ATF-2. In all normal human prostates, positive immunoreactions to TRAF-2 and ASK1 (cytoplasm localization) MEK-4 (cytoplasm and nucleus localization) and JNK were found. Although in prostate cancer the transduction pathway from TRAF-2 to AP-1 seems to be inactive, since immunoreaction to TRAF-2, ASK-1 And MEK-4 decreased and

no immunoreaction to AP-1 was even found (Ricote et al., 2003; Royuela et al., 2008). The mechanism that accounts for the nuclear location MEK-4 is unclear, since this protein is activated by a cytoplasmic protein and phosphorylates JNK in the cytoplasm. However, MEK-4 function may not be restricted to the JNK signal transduction pathway because MEK-4 also phosphorylate and activates p38, and this latter is prelocalized in the nucleus and is rapidly exported to the cytoplasm upon activation (Taylor et al., 2008).
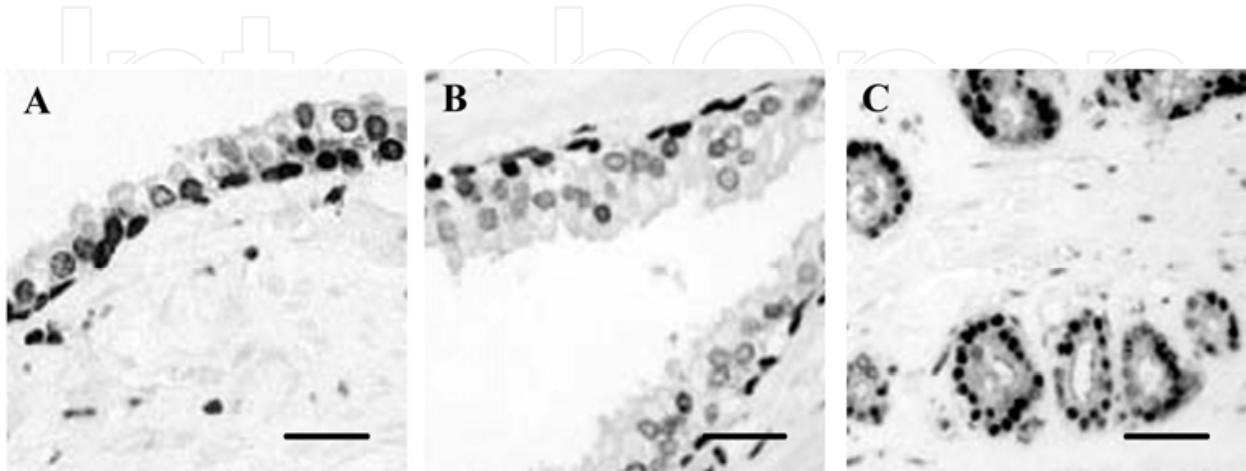
Fig. 2. JNK immunostaining appeared in normal (A), BPH (B) and PC (B) samples. Scale bars: 20 μm (A-B) and 30 μm (C).

JNK immunoreactiveness is increased in the glandular epithelium of PC specimens (Royuela et al., 2002; Shimada et al., 2006). With these data, Ricote et al. (2003) suggest that MEK-4 is not involved in JNK/AP-1 pathway, although it might be involved in p38 activation pathway. This hypothesis agrees with the high p38 levels found in normal prostate in our laboratory (Royuela et al., 2002). In this pathology there must be several extracellular or intracellular factors that are blocking the activation of this transduction pathway in different steps. ASK1 might be a critical blockage point of this transduction pathway. P21 has been reported as an ASK1 inhibitor and has been found significantly associated with a high Gleason score (Aaltomaa et al., 1999; Royuela et al., 2001). Bcl-2 has been postulated as a potential modulator of JNK activation in fibroblasts. Since an increase of bcl-2 has been reported in prostate cancer specimens, bcl-2 might be another potential inhibitor of JNK in prostate cancer (Haeusgen et al., 2010; Royuela et al., 2000). Ricote et al. (2006) reported in an *in vitro* study that JNK phosphorylation was found to be increased by TNF-α dose-dependent manner in LNCaP cells (but not in PC3 cells), and the rate of apoptosis was reduced by the administration of a specific JNK inhibitor, suggesting that JNK positively regulates apoptosis induction by TNF-α in this cell model.

Two opposite roles in the cell cycle control have been reported for JNK: cell proliferation and apoptosis. In contrast, JNK activation by some cytokines, such as TNF-α and IL-6, stimulates apoptosis. Since these two cytokines have been found increased in the prostatic epithelium of PC patients (Rodriguez-Berriguete et al., 2010a; Royuela et al., 2008), it might be that the increased apoptotic indexes in PC are related to the elevated levels of TNF-α, IL-6 and JNK. Nevertheless, the apoptotic mechanism stimulated by JNK is via p53 (Fuchs et al., 1998), but the p53 present in PC patients (Lee y cols., 2008), as occurs in most cancers is a mutant form with deletions or mutations which obstruct its association to JNK (Fuchs et al., 1998). Therefore, the elevated apoptotic rates in PC does not seem to be related to the high

levels of cytokines and JNK in these patients but to other factors including the increased p38 levels mentioned above. Therefore, the most probable action of JNK in PC would be cell proliferation stimulation rather than apoptosis.

3. IL-1/ TNF/ p38

Several studies suggested that p38 play an important role in leukemia (Feng et al., 2009); lymphomas (Zheng et al., 2003) or tumor such as breast (Ancrile et al., 2008), prostate (Ricote et al., 2006a), gastrical (Guo et al., 2008) or lung (Zhang et al., 2010).
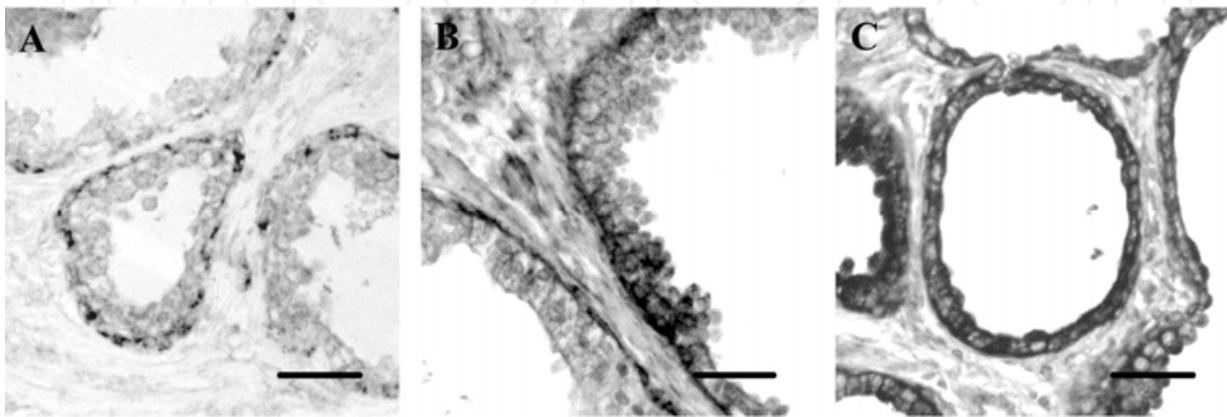
Fig. 3. p38 immunostaining appeared in normal (A), BPH (B) and PC (B) samples. Scale bars: 25 μm (B) 30 μm (A, C).

In addition to TNFα/AP1 pathway (by ASK-1 or MEK-4), Interleukin-1 (IL-1) is another physiological regulator of p38. IL-1 activates PAK-1 through its binding to two GTPases, called Cdc42 and Rac. These ones activate PAK-1, which induces MEK-6 activation that in turns activates p38 (Raingeaud et al., 1995).

Several reports about IL-1 family in cancer have been reported. IL-1α, IL-1β and IL-1Ra have been detected in human breast cancer, and have been related to protumorigenic activity (Miller et al., 2010). The number of men showing IL-1β immunoexpression is lower in prostate cancer group than in normal prostate group but most cancer patients studied presented immunoreaction to IL-1α, IL-1RI, IL-1RII and IL-1Ra [60]. The interaction between IL-1α and IL-RI would be involved in the high proliferation degree of these tumors. No association between IL-1 and IL-1Ra has also been reported in premalignant gastric conditions (Kupcinskas et al., 2010).

In human prostate cancer, intense immnoreaction to PAK-1, MEK-6 and p38 were found but also to p-Elk-1 and p-ATF-2 whose location change from the nucleus to the cytoplasm (Ricote et al., 2006a; Rodriguez-Berriguete et al., 2010b). This fact may be related with its biological function. In mammalian cells, endogenous p38 is present in the nucleus but it can be exported to the cytoplasm upon activation (Ricote et al., 2006). Recently, Wood et al. (2009) described nuclear localization of p38 in response to DNA damage. In the nucleus, p38 phosphorylates Elk-1, ATF-2 and also NF-kB (Junttila et al., 2008; Raingeaud et al., 1995; Royuela et al., 2008). ATF-2 (Li & Wicks, 2001) and Elk-1 (Amorino & Parsons, 2004) are not only a target of p38 but also a target for JNK. Since immunoreaction to JNK was found in normal human prostate, but not in prostate cancer, is reasonable to suggest that the activation of ATF-2 and Elk-1 are the consequence of p38 pathway activation (Ricote et al.,
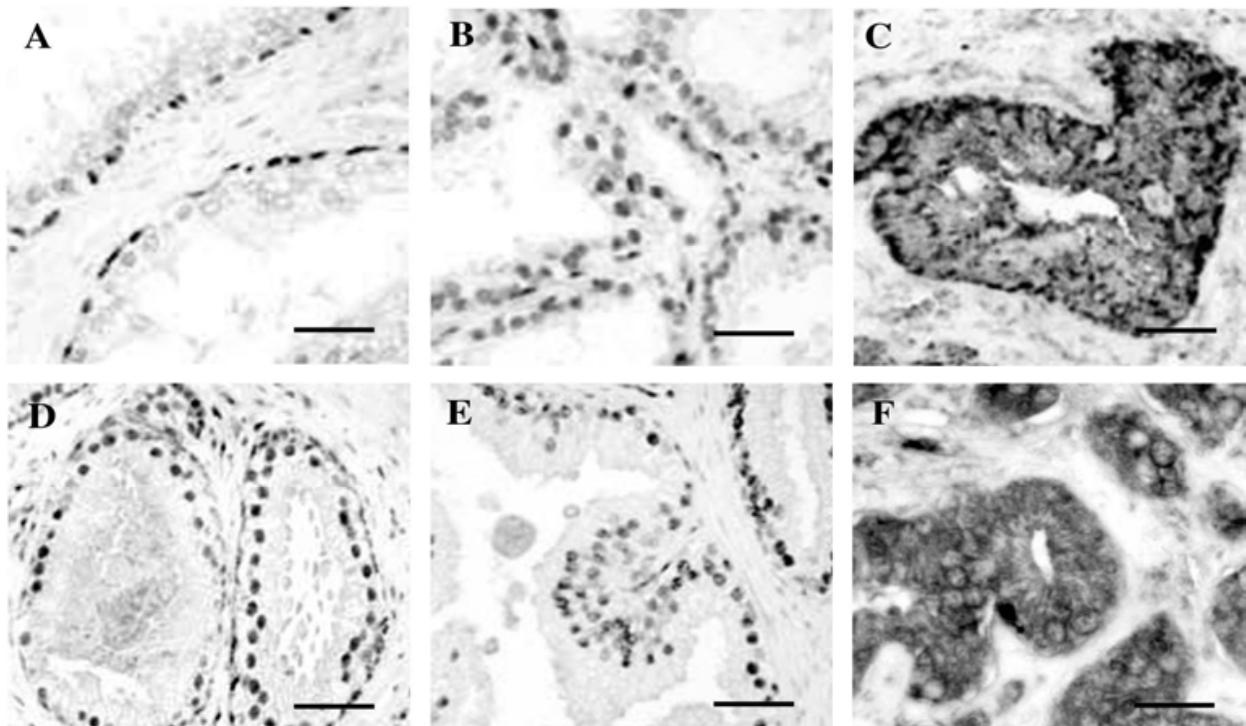
Fig. 4. Nuclear immunoreaction to p-Elk-1 appeared in the epithelial basal cells of normal prostate (A) or all epithelial cells in BPH (B). In PC samples p-Elk-1 (C) was observed in the cytoplasm. p-ATF-2 immunostaining was localised in the nuclei of epithelial cells in normal prostate (D) but more intense in BPH (E) and PC (F). Scale bar: 20 μm (B, E) and 25 μm (A, C-D, F).

2006a). However, the TNF-α signal may be diverted from the Ap-1 pathway towards the p38 pathway, because MEK-4 may also phosphorylate and activate p38 and ASK-1 may activate MEK-6, which, in turn, phosphorylates p38 (Stein et al., 1996). Proapoptotic effects of TNFα/AP-1 pathway decrease, because this pathway is inhibited by p21 at ASK1 step (Ricote et al., 2003). Cell proliferation stimulation triggered by TNFα via p38 occurs, since intense immunoreaction to PAK-1 and MEK-6 was found (Ricote et al., 2006a), but previous studies have shown elevated levels of IL-1 (Ricote et al., 2004) and p38 (Royuela et al., 2002). Ricote et al. (2006)b using LNCaP cells suggest that p38 plays an important role in prostatic tumor promotion by TNFα stimulation, and hence may represent a target for the treatment of prostatic cancer. Treatment with the p38 inhibitor SB203580 caused a notable increase in the frequency of apoptosis in LNCaP cell cultures, indicating that p38 exerts an anti-apoptotic action in this cell line (Ricote et al., 2006). Noted that LNCaP cells represent a good model of well-differentiated tumor and as such its behavior is more comparable to the in vivo tumor condition. In this way, Thornton and Rincon (2009) considered the potential use of pharmacological inhibitors of p38 in therapeutic treatment for several diseases.

4. TNF/IL-1/IL-6/ERK

When IL-6 and IL-6Rα induces dimerization of gp130, and subsequently the activation of constituvely-associated gp130 Jak proteins, simultaneously trigger functionally distinct and even contradictory signaling pathways. One of them leads to the recruitment at the complex receptor of SHP2, Sos and Grb2, which in turn activates Ras by stimulating the exchange of

GDP bound to Ras for GTP (Silver & Hunter, 2010). Then, Ras phosphorylate of Raf-1. In this way is iniciate a MAPK cascade when Raf-1 (via IL-6 pathway), TRAF-2 (via TNF pathway) or TRAF-6 (via Il-6 pathway) phosphorylate sequentially MEK1/2 and ERK1/2, in a process that culminates in modulation of gene transcription through the activation of several transcription factors such as c-Myc, Elk-1 (Werlen et al., 2003) or NF-kB (Turjanski et al., 2007).
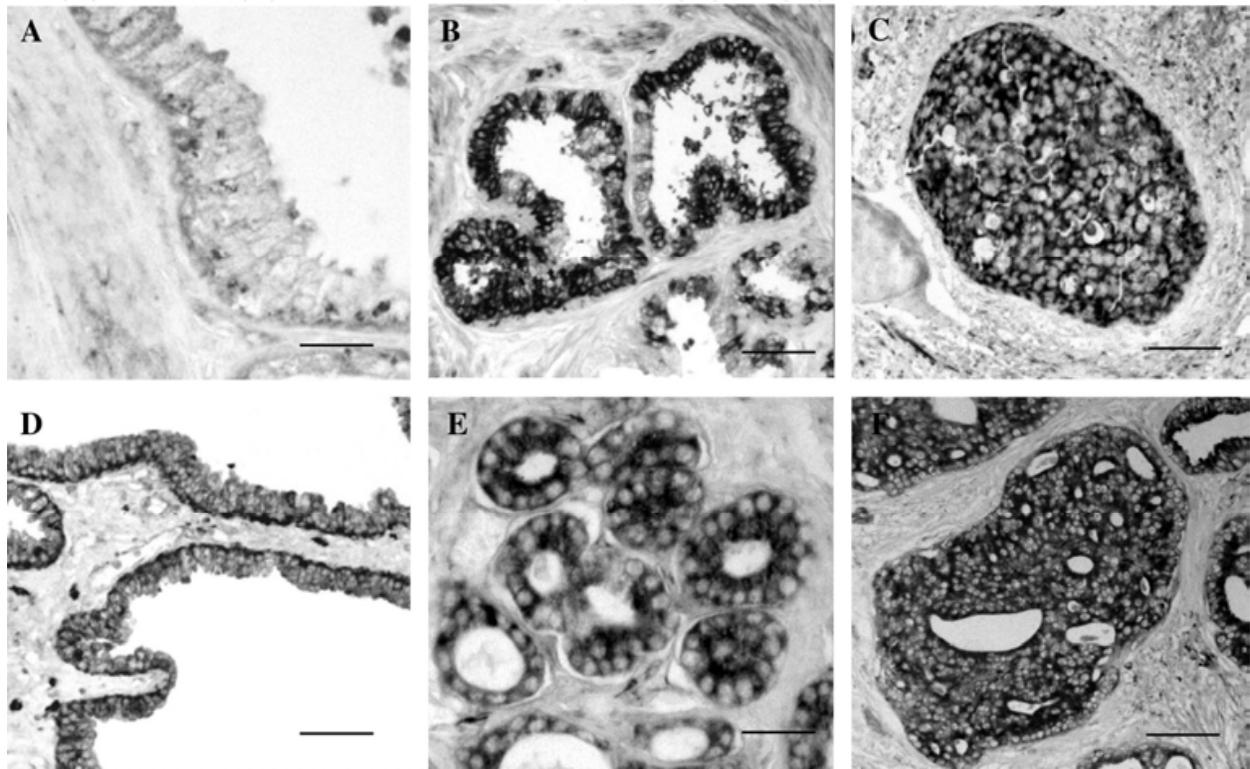

Fig. 5. P50 was scantly in the cytoplasm epithelial cells of normal (A) but in PC immunostaining also was nuclear, increasing the expression in medium (B) and after, in high (C) Gleason. No immunoreaction was found to p65 in normal prostate but was localized in the cytoplasm of epithelial cells in BPH (D) and PC (E-F) samples; but in PC was also localized in the nuclei of epithelial increasing nuclear localization with Gleason grade. Scale bars: 20 μm (A), 25 μm (B-C, E-F) and 30 μm (D).

Some components of the Raf-MEK-ERK pathway are activated in solid tumors and hematological malignaces (Grant, 2008; McCubrey et al., 2007).

In approximately 30% of human breast cancers, mutations are found in the ERK1/2 MAPK pathway (Whyte et al., 2009). ERK1/2 and downstream ERK1/2 targets are hyper-phosphorylated in a large subset of mammary tumors (Mueller et al., 2000). Increased expressions of Raf pathway has been associated with advance prostate cancer, hormonal independence, metastasis and a poor prognosis (Keller et al., 2004). Moreover, prostate cancer cell lines isolated from advanced cancer patients (LNCaP, PC3, DU145) expressed low levels of active Raf kinase inhibitors (McCubrey et al., 2007). TNFα acts as an ERK activator in some cases related to inflammation and cell proliferation. In this way, Ricote et al. (2006b) showed that ERK phosphorylation was notably increased by TNFα dose dependent manner in LNCaP cells. In prostate cancer, presence of Raf-1 and MEK-1 in

conjunction with elevated ERK-1 and ERK-2 suggest that stimulation of cell proliferation could be triggered by IL-6 via the ERK pathway (Rodriguez-Berriguete et al., 2010a). In this way, Ricote et al. (2006b) in *in vitro* studies with LNCaP cells, showed that the use of specific ERK inhibitor minimally affected apoptosis, suggesting that ERK activation does not play a significant role in apoptosis regulation.

Moreover, ERK may also induce the phosphorilation of apoptotic regulatory molecules including bcl-2 family members (e.g. Bad, Bim and controversially Bcl-2) and caspase 9 (McCubrey et al., 2007). There are evidences suggesting a protective effect in cells by NF-kB activation via ERK (Chu et al., 2008; Zhu et al., 2004). This transcription factor in a basal state is retained in the cytoplasm by binding to specific inhibitors, the inhibitors of NF-kB (IkBs). Upon cell stimulation IkBs are degradated and consequently NF-kB is translocated into the nucleus (Karin, 2006), where it promotes the expression of several anti-apoptotic genes such as inhibitors of apoptosis proteins (IAPs) (Rodriguez-Berriguete et al., 2010) and bcl-2 family members (Aggarwal, 2000).

5. New perspectives

In summary, it is reasonable to speculate that MAPK could be involved in prostate cancer development, maintenance and/or progression, since are involucrate in several transduction pathway related with prostate cancer development. These transduction pathways were interrelated and activated by pro-inflammatory (IL-6, IL-1 and TNF). At the end are activated several transcription factor such as NF-kB, Elk-1, ATF-2, p53, or mcl-1. Translocation of NF-kB to the nucleus in PC might be due to the overactivation of several transduction pathways triggered by pro-inflammatory cytokines (IL-1, IL-6 and TNF-α). NF-kB has been considered a marker of predicting PC since nuclear localization was only observed in PC, but another transcription factor activate by these pro-inflammatory cytokines relate with cell proliferation such as Elk-1, ATF-2 or c-myc were also increased in PC. For this, might be that overexpression of MAPKs might be secondary to overexpression of these cytokines and, subsequently, MAPKs also might be involved in the development of prostatic hyperplasia and neoplasia. Therefore, since PC is a heterogeneous disease in which multiple transduction pathways may contribute to uncontrolled apoptosis/cell proliferation balance, we concluded that significant attention would be focused to the rational combination of novel agents directed toward the inactivation of pro-inflammatory cytokines, because could be disrupt complementary tumor cell proliferation pathways.

6. Acknowledgements

7. References

Aaltomaa, S.; Lipponen, P.; Eskelinen, M.; Ala-Opas, M.; Kosma, V.M. (1999). Prognostic value and expression of p21 (waf1/cip1) protein in prostate cancer. *The Prostate*, Vol. 39, No. 1 (Apr 1), pp. 8-15, ISSN: 0270-4137.

Aggarwal, B.B. (2000). Tumour necrosis factors receptor associated signalling molecules and their role in activation of apoptosis, JNK and NF-kappaB. *Annals of the Rheumatic Diseases*, Vol. 59, Supp l (Nov), pp.i6-16., ISSN: 1468-2060.

Amorino, G.P. & Parsons, S.J. (2004). Neuroendocrine cells in prostate cancer. *Critical Reviews in Eukaryotic Gene Expression,* Vol. 14, No. 4, pp. 287-300. ISSN: 1045-4403.

Ancrile, B.B.; O'Hayer, K.M.; Counter, C.M. (2008). Oncogenic ras-induced expression of cytokines: a new target of anti-cancer therapeutics. *Molecular Interventions*, Vol. 8, No. 1 (Feb), pp: 22-27, ISSN: 1534-0384.

Arnott, C.H.; Scott, K.A.; Moore, R.J.; Robinson, S.C.; Thompson, R.G.; Balkwill, F.R. (2004). Expression of both TNF-alpha receptor subtypes is essential for optimal skin tumour development. *Oncogene,* Vol. 23, No. 10 (Mar 11), pp. 1902-1910, ISSN: 0950-9232.

Bode, A.M. & Dong, Z. (2007). The functional contrariety of JNK. *Molecular Carcinogenesis*, Vol. 46, No. 8 (Aug), pp. 591-598, ISSN: 0899-1987.

Bogoyevitch, M.A.; Ngoei, K.R.; Zhao, T.T.; Yeap, Y.Y.; Ng, D.C. (2010). c-Jun N-terminal kinase (JNK) signaling: recent advances and challenges. *Biochimica et Biophysica Acta*, Vol. 1804, No.3 (Mar), pp. 463-475, ISSN: 0006-3002.

Chang, H.L.; Wu, Y.C.; Su, J.H.; Yeh, Y.T.; Yuan, S.S. (2008). Protoapigenone, a novel flavonoid, induces apoptosis in human prostate cancer cells through activation of p38 mitogen-activated protein kinase and c-Jun NH2-terminal kinase 1/2. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 325, No. 3 (Jun), pp. 841-849, ISSN: 0022-3565.

Chengedza, S. & Benbrook, D.M. (2010). NF-kappaB is involved in SHetA2 circumvention of TNF-alpha resistance, but not induction of intrinsic apoptosis. *Anticancer Drugs*, Vol. 21, No. 3 (Mar), pp. 297-305, ISSN: 0959-4973.

Chu, L.F.; Wang, W.T.; Ghanta, V.K.; Lin, C.H.; Chiang, Y.Y.; Hsueh, C,M. (2008). Ischemic brain cell-derived conditioned medium protects astrocytes against ischemia through GDNF/ERK/NF-kB signaling pathway. *Brain Research*, Vol. 1239 (Nov 6), pp. 24-35, ISSN: 0006-8993.

Cross, T.G.; Scheel-Toellner, D.; Henriquez, N.V.; Deacon, E.; Salmon, M.; Lord, J.M. (2000). Serine/threonine protein kinases and apoptosis. *Experimental Cell Research*, Vol. 256, No. 1 (Apr 10), 34-41, ISSN: 0014-4827.

Cullen, P.J. & Lockyer, P.J. (2002). Intergration of calcium and Ras signaling. *Nature Reviews Molecular Cell Biology*, Vol. 3, No. 5 (May), pp. 339-348. ISSN: 1471-0072.

Dejardin, E.; Deregowski, V.; Chapelier, M.; Jacobs, N.; Gielen, J.; Merville, M.; Bours, V. (1999). Regulation of NF-iB activity by IiBrelated proteins in adenocarcinoma cells. *Oncogene*, Vol. 18, No. 16 (Apr 22), pp. 2567-2577, ISSN: 0950-9232.

De Graeve, F.; Bahr, A.; Sabapathy, K.T.; Hauss, C.; Wagner, E.F.; Kedinger, C.; Chatton, B. (1999). Role of the ATFa/JNK2 complex in Jun activation. *Oncogene*, Vol. 18, No. 23 (Jun 10), pp. 3491-3500, ISSN: 0950-9232.

De Miguel, M.P.; Royuela, M.; Bethencourt, F.R.; Santamaria, L.; Fraile, B.; Paniagua, R. (2000). Immuno-expression of tumor necrosis factor-a and its receptors 1 and 2 correlates with proliferation/apoptosis equilibrium in normal, hyperplasic and carcinomatous human prostate. *Cytokine*, Vol. 12, No. 5, (May), pp. 535-538, ISSN: 1043-4666.

Dérijard, B.; Hibi, M.; Wu, I-H.; Barrett, T.; Su, B.; Deng, T.; Karin, M.; Davis, R.J. (1994). JNK1: a protein kinase stimulated by UV light and Ha-Ras that binds and phosphorylates the c-Jun activation domain. *Cell*, Vol. 76, No. 6 (Mar 25), pp. 1025-1037, ISSN: 0092-8674.

Dhillon, A.S.; Hagan, S.; Rath, O.; Kolch, W. (2007). MAP kinase signalling pathways in cancer. *Oncogene*, Vol. 26, No. 22 (May 14) pp. 3279-3290, ISSN: 0950-9232.

Domingo-Domenech, J.; Mellado, B.; Ferrer, B.; Truan, D.; Codony-Servat, J.; Sauleda, S.; Alcover, J.; Campo, E.; Gascon, P.; Rovira, A.; Ross, J.S.; Fernandez, P.L.; Albanell, J. (2005). Activation of nuclear factor-kappaB in human prostate carcinogenesis and association to biochemical relapse. British Journal of Cancer, Vol. 93, No. 11 (Nov 28), pp. 1285-1294, ISSN: 0007-0920.

English, J.M.; Pearson, G.; Baer, R.; Cobb, M.H. (1998). Identification of substrates and regulators of the mitogen-activated protein kinase ERK5 using chimeric protein kinases. *The Journal of Biological Chemistry*, Vol. 273, No. 7 (Feb 13), pp. 3854-3860, ISSN: 0021-9258.

Eisinger, D.A. & Ammer, H. (2008). Delta-opioid receptors activate ERK/MAP kinase via integrinstimulated receptor tyrosine kinases. *Cellular Signalling*; Vol. 20, No. 12(Dec), pp. 2324-2331, ISSN: 0898-6568.

Davis, R.J. (2000). Signal transduction by the JNK group of MAP kinases. *Cell*, Vol. 103, No. 2 (Oct 13), pp. 239-252, ISSN: 0092-8674.

Eldor, R.; Baum. K.; Abel, R.; Sever, D.; Melloul, D. (2009). The ToI-beta transgenic mouse: a model to study the specific role of NF-kappaB in beta-cells. *Diabetes Research and Clinical Practice*, Vol. 86, Suppl 1 (Dec), pp. S7-14, ISSN: 0168-8227.

Feng, Y.; Wen, J.; Chang, C.C. (2009). p38 Mitogen-activated protein kinase and hematologic malignancies. *Archives of Pathology & Laboratory Medicine*, Vol. 133, No. 11 (Nov), pp. 1850-1856, ISSN: 0003-9985.

Fuchs, S.Y.; Adler, V.; Pincus, M.R.; Ronai, Z. (1998). MEKK1/JNK signaling stabilizes and activates p53. *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 95, No. 18 (Sep 1), pp. 10541-10546, ISSN: 0027-8424.

Gao, L.; Chao, L.; Chao, J. (2010). A novel signaling pathway of tissue kallikrein in promoting keratinocyte migration: Activation of proteinase-activated receptor 1 and epidermal growth factor receptor. *Experimental Cell Research*, Vol. 316, No. 3 (Feb 1), pp. 376-389, ISSN: 0014-4827.

Garcia-Tuñon, I.; Ricote, M.; Ruiz, A.; Fraile, B.; Paniagua, R.; Royuela, M. (2005). IL-6, its receptors and its relationship with bcl-2 and bax proteins in infiltrating and in situ human breast carcinoma. *Histopathology*, Vol. 47, No. 1 (Jul), pp.82-89, ISSN: 1365-2559.

Garcia-Tuñon, I.; Ricote, M.; Ruiz, A.; Fraile, B.; Paniagua, R.; Royuela, M. (2006). Role of tumor necrosis factor-alpha and its receptors in human benign breast lesions and tumors (in situ and infiltrative). *Cancer Science*, Vol. 97, No. 10 (Oct), pp. 1044-1049, ISSN: 1349-7006.

Gasparian, A.V.; Guryanova, O.A.; Chebotaev, D.V.; Shishkin, A.A.; Yemelyanov, A.Y.; Budunova, I.V. (2009). Targeting transcription factor NFkappaB: comparative analysis of proteasome and IKK inhibitors. *Cell Cycle*, Vol. 8, No. 10 (May 15), pp. 1559-1566, ISSN: 1538-4101.

Grant, S. (2008). Cotargeting survival signaling pathways in cancer. *The Journal Of Clinical Investigation*, Vol. 118, No. 9 (Sep), pp. 3003-3006, ISSN:0021-9738.

Guo, X.; Ma, N.; Wang, J.; Song, J.; Bu, X.; Cheng, Y.; Sun, K.; Xiong, H.; Jiang, G.; Zhang, B.; Wu, M.; Wei, L. (2008). Increased p38-MAPK is responsible for chemotherapy resistance in human gastric cancer cells. *BMC Cancer*, Vol. 8 (Dec 18), pp. 375, ISSN 1471-2407.

Gupta, S.; Barrett, T.; Whitmarsh, A.J.; Cavanagh, J.; Sluss, H.K.; Dérijard, B.; Davis, R.J. (1996). Selective interaction of JNK protein kinase isoforms with transcription factors. *The EMBO Journal,* Vol. 15, No. 11 (Jun 3), pp. 2760-2770, ISSN 0261-4189.

Haeusgen, W.; Herdegen, T.; Waetzig, V. (2010). Specific regulation of JNK signalling by the novel rat MKK7gamma1 isoform. *Cellular Signalling* Vol. 22, No. 11 (Nov), pp. 1761-1772, ISSN: 0898-6568.

Hama, T.; Miyamoto, M.; Tsuki, H.; Nishio, C.; Hatanaka, M. (1989). Interleukin-6 is a neurotrophic factor for promoting the survival of cultured basal forebrain cholinergic neurons fron postnatal rats. *Neuroscience Letters*, Vol. 104, No. 3 (Oct 9), 340-344, ISSN: 0304-3940.

Hayashi, M.; Lee, J.D. (2004). Role of the BMK1/ERK5 signaling pathway: lessons from knockout mice. Journal of Molecular Medicine, Vol. 82, No. 12 (Dec), pp. 800-808, ISSN: 0946-2716.

Heasley, L.E. & Han, S.Y. (2006). JNK regulation of oncogenesis. *Molecular Cell*, Vol. 21, No. 2 (Apr 30), pp. 167-173, ISSN 1097-2765.

Heinrich, P.C.; Behrmann, I.; Mueller-Newen, G.; Shaper, F.; Graeve, L. (1998). Interleukin 6-type cytokine signaling throught the gp130/jak/stat pathways. *Biochemical Journal,* Vol. 334, Pt. 2 (Sep 1), pp. 297-314, ISSN: 0264-6021.

Hong, D.S.; Angelo, L.S.; Kurzrock, R. (2007). Interleukin-6 and its receptor in cancer: implications for Translational Therapeutics. *Cancer*, Vol. 110 No. 9 (Nov 1), pp. 1911-1928, ISSN: 1097-0142.

Hubel, K.; Mansmann, G.; Schafer, H.; Oberhauser, F.; Diehl, V.; Engert, A. (2000). Increase of anti-inflammatory cytokines in patients with esophageal cancer after perioperative treatment with G-CSF. *Cytokine*, Vol. 12, No. 12 (Dec), pp. 1797-1800, ISSN: 1043-4666.

Hui, L.; Bakiri, L.; Stepniak, E.; Wagner, E.F. (2007). p38alpha: a suppressor of cell proliferation and tumorigenesis. *Cell Cycle*, Vol. 6, No. 20 (Oct 15), pp. 2429-2433, ISSN: 1551-4005.

Huleihel, M.; Lunenfeld, E. (2004). Regulation of spermatogenesis by paracrine/autocrine testicular factors. *Asian Journal of Andrology*, Vol. 6, No. 3 (Sep), pp. 259-268, ISSN: 1008-682X.

Hunter, T. (2000). Signaling -2000 and beyond. *Cell*, Vol. 100, No. 1 (Jan 7), pp. 113-127, ISSN: 0092-8674.

Jiang, Y.; Li, Z.; Schwarz, E.M.; Lin, A.; Guan, K.; Ulevitch, R.J.; Han, J. (1997). Structure-function studies of p38 mitogen-activated protein kinase. Loop 12 influences substrate specificity and autophosphorylation, but not upstream kinase selection. *The Journal of Biological Chemistry*, Vol. 272, No. 17 (Apr 25), pp. 11096-11102, ISSN: 0021-9258.

Joo, S.S.; Yoo, Y.M. (2009). Melatonin induces apoptotic death in LNCaP cells via p38 and JNK pathways: therapeutic implications for prostate cancer. *Journal of Pineal Research*, Vol. 47, No. 1 (Aug), pp. 8-14, ISSN: 1600-079X.

Joslin, E.J.; Opresko, L.K.; Wells, A.; Wiley, H.S.; Lauffenburger, D.A. (2007). EGF-receptor-mediated mammary epithelial cell migration is driven by sustained ERK signaling from autocrine stimulation. *Journal of Cell Science*, Vol. 120, Pt. 20 (Oct 15), pp. 3688-3699, ISSN: 0370-2952.

Junttila, M.R.; Li, S.P.; Westermarck, J. (2008). Phosphatase-mediated crosstalk between MAPK signaling pathways in the regulation of cell survival. *The FASEB Journal*, Vol. 22, No. 4 (Apr), pp. 954-965, ISSN: 0892-6638.

Karin, M. (2006). Nuclear factor-kappaB in cancer development and progression. *Nature*, Vol. 441, No. 7092 (May 25), pp. 431-436, ISSN : 0028-0836.

Keller, E.T.; Fu, Z.; Yeung, K.; Brennan, M. (2004). Raf kinase inhibitor protein: a prostate cancer metastasis suppressor gene. *Cancer Letters*, Vol. 207, No. 2 (Apr 30), pp. 131-137, ISSN: 0304-3835.

Kato, Y.; Kravchenko, V.V.; Tapping, R.I.; Han, J.; Ulevitch, R.J.; Lee, J.D. (1997). BMK1/ERK5 regulates serum-induced early gene expression through transcription factor MEF2C. *The EMBO Journal*, Vol. 16, No. 23 (Dec 1), pp. 7054-7066, ISSN 0261-4189.

Kato, Y.; Tapping, R.I.; Huang, S.; Watson, M.H.; Ulevitch, R.J.; Lee, J.D. (1998). Bmk1/Erk5 is required for cell proliferation induced by epidermal growth factor. *Nature*, Vol. 395, No. 6703 (Oct 15), pp. 713-716, ISSN : 0028-0836.

Kamakura, S.; Moriguchi, T.; Nishida, E. (1999). Activation of the protein kinase ERK5/BMK1 by receptor tyrosine kinases. Identification and characterization of a signalling pathway to the nucleus. *The Journal of Biological Chemistry*, Vol. 274, No. 37 (Sep 10), pp. 26563-26571, ISSN: 0021-9258

Kayahara, M.; Wang, X.; Tournier, C. (2005). Selective regulation of c-jun gene expression by mitogen-activated protein kinases via the 12-o-tetradecanoylphorbol-13-acetate-responsive element and myocyte enhancer factor 2 binding sites. *Molecular and Cellular Biology*, Vol. 25, No. 9 (May), pp. 3784-3792, ISSN: 0270-7306.

Khalaf, H.; Jass, J.; Olsson, P.E. (2010). Differential cytokine regulation by NF-kappaB and AP-1 in Jurkat T-cells. *BMC Immunology*, Vol. 11 (May 27), pp. 26, ISSN: 1471-2172.

Kholodenko, B.N. & Birtwistle, M.R. (2009). Four-dimensional dynamics of MAPK information processing systems. *Wiley interdisciplinary reviews. Systems biology and medicine*, Vol. 1, No. 1 (Jul-Aug), pp. 28-44, ISSN:1939-5094.

Khwaja, F.S.; Quann, E.J.; Pattabiraman, N.; Wynne, S.; Djakiew, D. (2008). Carprofen induction of p75NTR-dependent apoptosis via the p38 mitogen-activated protein kinase pathway in prostate cancer cells. *Molecular Cancer Therapeutics*, Vol. 7, No. 11 (Nov), pp. 3539-3545, ISSN: 1535-7163.

Kim, E.K. & Choi, E.J. (2010)Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta (BBA)*, Vol. 1802, No. 4 (Apr), 396-405, ISSN 0005-2736.

Kupcinskas, L.; Wex, T.; Kupcinskas, J.; Leja, M.; Ivanauskas, A.; Jonaitis, L.V.; Janciauskas, D.; Kiudelis, G.; Funka, K.; Sudraba, A.; Chiu, H.M.; Lin, J.T.; Malfertheiner, P. (2010). Interleukin-1B and interleukin-1 receptor antagonist gene polymorphisms are not associated with premalignant gastric conditions: a combined haplotype

analysis. *European Journal of Gastroenterology and Hepatology*, Vol. 22, No. 10 (Oct), pp. 1189-1195, ISSN: 0954-691X.

Kurihara, N.; Bertolini, D.; Suda, T.; Akiyama, Y.; Roodman, G.D. (1990). IL-6 stimulates osteoclast-like multinucleated cell formation in long term human marrow cultures by inducing IL-1 release. *The Journal of Immunology*, Vol. 144, No. 11 (Jun 1), pp. 4226-30, ISSN: 0022-1767.

Krueguer, J.; Krane, J.; Carter, D.; Gottlieb, A. (1990). Role of growth factors, cytokines, and their receptors in the pathogenesis of psoriasis. *Journal of Investigative Dermatology*, Vol. 94, No. 6 Suppl (Jun), pp. 135S-140S, ISSN: 0022-202X.

Lee, J.D.; Ulevitch, R.J.; Han, J. (1995). Primary structure of BMK1: a new mammalian map kinase. *Biochemical and Biophysical Research Communications*, Vol. 213, No. 2 (Aug 15), pp. 715-724, ISSN: 0006-291X.

Lee, J.J.; Lee, J.H.; Ko, Y.G.; Hong, S.I.; Lee, J.S. (2010). Prevention of premature senescence requires JNK regulation of Bcl-2 and reactive oxygen species. *Oncogene*, Vol. 29, No. 4 (Jan 28), pp. 561-575, ISSN: 0950-9232.

Lee, J.T.; Lehmann, B.D.; Terrian, D.M.; Chappell, W.H.; Stivala, F.; Libra, M.; Martelli, A.M.; Steelman, L.S.; McCubrey, J.A. (2008). Targeting prostate cancer based on signal transduction and cell cycle pathways. *Cell Cycle*, Vol. 7, No. 12 (Jun 15), pp. 1745-1762, ISSN: 1551-4005.

Li, H. & Wicks, W.D. (2001). Retinoblastoma protein interacts with ATF2 and JNK/p38 in stimulating the transforming growth factor-beta2 promoter. *Archives of Biochemistry and Biophysics*, Vol. 394, No. 1 (Oct 1), pp. 1-12, ISSN: 0003-9861.

Liu, Y.; Formisano, L.; Savtchouk, I.; Takayasu, Y.; Szabó, G.; Zukin, R.S.; Liu, S.J. (2010). A single fear-inducing stimulus induces a transcription-dependent switch in synaptic AMPAR phenotype. *Nature Neuroscience*, Vol. 13, No. 2 (Feb), pp. 223-231, ISSN: 1097-6256.

Loetscher, H.; Pan, Y.C.; Lahm, H.W.; Gentz, R.; Brockhaus, M.; Tabuchi, H.; Lesslauer, W. (1990). Molecular cloning and expression of the human 55 kd tumor necrosis factor receptor. *Cell*, Vol. 61, No. 2 (Apr 20), pp. 351-359, ISSN: 0092-8674.

Marais, R. & Marshall, C.J. (1996). Control of the ERK MAP kinase cascade by ras and raf. Cancer Surveys, Vol. 27, pp. 101-25, ISSN: 0261-2429.

McCracken, S.R.; Ramsay, A.; Heer, R.; Mathers, M.E.; Jenkins, B.L.; Edwards, J.; Robson, C.N.; Marquez, R.; Cohen, P.; Leung, H.Y. (2008). Aberrant expression of extracellular signal-regulated kinase 5 in human prostate cancer. *Oncogene*, Vol. 27, No. 21 (May 8), pp. 2978-2988, ISSN: 0950-9232.

McCubrey, J.A.; Steelman, L.S.; Chappell, W.H.; Abrams, S.L.; Wong, E.W.; Chang, F.; Lehmann, B.; Terrian, D.M.; Milella, M.; Tafuri, A.; Stivala, F.; Libra, M.; Basecke, J.; Evangelisti, C.; Martelli, A.M.; Franklin, R.A. (2007). Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Biochimica et Biophysica Acta (BBA)*, Vol. 1773, No. 8 (Aug), pp. 1263-1284, ISSN: 0005-2736.

Mechergui, Y.B., Ben Jemaa, A.; Mezigh, C.; Fraile, B.; Ben Rais, N.; Paniagua, R.; Royuela, M.; Oueslati, R. (2009). The profile of prostate epithelial cytokines and its impact on sera prostate specific antigen levels. *Inflammation*, Vol. 32, No. 3 (Jun), pp. 202-210, ISSN: 0360-3997.

Meshki, J.; Caino, M.C.; von Burstin, V.A.; Griner, E.M.; Kazanietz, M.G. (2010). Regulation of prostate cancer cell survival by protein kinase C {epsilon} involves Bad

phosphorylation and modulation of the TNF{alpha}/JNK pathway. *The Journal of Biological Chemistry*, Vol. 285, No. 34 (Aug 20), pp. 26033-26040, ISSN: 0021-9258

Miller, L.J.; Kurtzman, S.H.; Anderson, K.; Wang, Y.; Stankus, M.; Renna, M.; Lindquist, R.; Barrows, G.; Kreutzer, D.L. (2000). Interleukin-1 family expre-ssion in human breast cancer: interleukin-1 receptor antagonist. *Cancer Investigation*, Vol. 18, No. 4, pp. 293-302, ISSN: 0735-7907.

Miller, S.C.; Huang, R.; Sakamuru, S.; Shukla, S.J.; Attene-Ramos, M.S.; Shinn, P.; Van Leer, D.; Leister, W.; Austin, C.P.; Xia, M. (2010). Identification of known drugs that act as inhibitors of NF-kappaB signaling and their mechanism of action. *Biochemical Pharmacology*, Vol. 79, No. 9 (May 1), pp. 1272-1280, ISSN: 0006-2952.

Mueller, H.; Flury, N.; Eppenberger-Castori, S.; Kueng, W.; David, F.; Eppenberger, U. (2000). Potential prognostic value of mitogen-activated protein kinase activity for disease-free survival of primary breast cancer patients. *International Journal of Cancer*, Vol. 89, No. 4 (Jul 20), pp. 384-388, ISSN: 0020-7136.

Nuñez, C.; Cansino, J.R.; Bethencourt, F.; Pérez-Utrilla, M.; Fraile, B.; Martínez-Onsurbe, P.; Olmedilla, G.; Paniagua, R.; Royuela, M. (2008). TNF/IL-1/NIK/NF-kappa B transduction pathway: a comparative study in normal and pathological human prostate (benign hyperplasia and carcinoma). *Histopathology*, Vol. 53, No. 2 (Aug), pp. 166-176, ISSN: 0213-3911.

Pagès, G.; Milanini, J.; Richard, D.E.; Berra, E.; Gothié, E.; Viñals, F.; Pouysségur, J. (2000). Signaling angiogenesis via p42/p44 MAP kinase cascade. *Annals of the New York Academy of Sciences*, Vol. 902 (May), pp. 187-200, ISSN: 0077-8923.

Pearson, G.; Robinson, F.; Beers Gibson, T.; Xu, B.E.; Karandikar, M.; Berman, K.; Cobb, M.H. (2001). Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocrine Reviews*, Vol. 22, No. 2 (Apr), pp. 153-183, ISSN: 0163-769X.

Peng, S.; Zhang, Y.; Zhang, J.; Wang, H.; Ren B. (2010). ERK in learning and memory: A review of recent research. *International Journal of Molecular Sciences*, Vol. 11, No. 1 (Jan 13), pp. 222-232, ISSN: 1422-0067.

Pi, X.; Yan, C.; Berk, B.C. (2004). Big mitogen-activated protein kinase (BMK1)/ERK5 protects endothelial cells from apoptosis. *Circulation Research*, Vol. 94, No. 3 (Feb 20), pp. 362-369, ISSN: 0009-7330.

Price, D.J.; Avraham, S.; Feuerstein, J.; Fu, Y.; Avraham, H.K. (2002). The invasive phenotype in HMT-3522 cells requires increased EGF receptor signaling through both PI 3-kinase and ERK 1,2 pathways. *Cell Communication and Adhesion*, Vol. 9, No. 2 (Mar-Apr), pp. 87-102, ISSN: 1543-5180.

Qiu, J.; Xiao, J.; Han, C.; Li, N.; Shen, X.; Jiang, H.; Cao, X. (2010). Potentiation of tumor necrosis factor-alpha-induced tumor cell apoptosis by a small molecule inhibitor for anti-apoptotic protein hPEBP4. *The Journal of Biological Chemistry*, Vol. 285, No. 16 (Apr 16), pp. 12241-12247, ISSN: 0021-9258.

Rabinovich, A.; Medina, L.; Piura, B.; Segal, S.; Huleihel, M. (2007). Regulation of ovarian carcinoma SKOV-3 cell proliferation and secretion of MMPs by autocrine IL-6. *Anticancer Research*, Vol. 27, No. 1A (Jan-Feb;), pp. 267-272, ISSN: 0250-7005.

Raingeaud, J.; Gupta, S.; Rogers, J.S.; Dickens, M.; Han, J.; Ulevitch, R.J.; Davis, R.J. (1995). Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *The*

Journal of Biological Chemistry, Vol. 270, No. 13 (Mar 31), pp. 7420-7426, ISSN: 0021-9258.

Ricote, M.; Royuela, M.; Garcia-Tuñon, I.; Bethencourt, F.R.; Paniagua, R.; and Fraile, B. (2003). Pro-apoptotic tumor necrosis factor-alpha transduction pathway in normal prostate, benign prostatic hyperplasia and prostatic carcinoma. *Journal of Urology*, Vol. 170, No. 3 (Sep), pp. 787-790, ISSN: 0022-5347.

Ricote, M.; Garcia-Tuñon, I.; Bethencourt, F.R.; Fraile, B.; Paniagua, R.; Royuela, M. (2004). Interleukin-1 (IL-1alpha and IL-1beta) and its receptors (IL-1RI, IL-1RII, and IL-1Ra) in prostate carcinoma. *Cancer*, Vol. 100, No. 7 (Apr 1), pp. 1388-1396, ISSN: 1097-0142.

Ricote, M.; García-Tuñón, I.; Bethencourt, F.; Fraile, B.; Onsurbe, P.; Paniagua, R.; Royuela, M. (2006a). The p38 transduction pathway in prostatic neoplasia. *The Journal of Pathology*, Vol. 208, No. 3 (Feb), pp. 401-407, ISSN: 1096-9896.

Ricote, M.; García-Tuñón, I.; Fraile, B.; Fernández, C.; Aller, P.; Paniagua, R.; Royuela, M. (2006b). P38 MAPK protects against TNF-alpha-provoked apoptosis in LNCaP prostatic cancer cells. *Apoptosis*, Vol. 11, No. 11 (Nov), pp. 1969-1975, ISSN: 1360-8185.

Rodriguez-Berriguete, G.; Prieto, A.; Fraile, B.; Bouraoui, Y.; Bethencourt, F.; Martínez-Onsurbe, P.; Olmedilla, G.; Paniagua, R.; Royuela, M. (2010a). IL-6/ERK/NF-kB transduction pathway: a study in normal and pathological human prostate (benign hyperplasia, intraepithelial neoplasia and cancer). *European Cytokine Network*, Vol. 21, No. 4 (Dec 1), pp. 241-250, ISSN: 1148-5493.

Rodriguez-Berriguete, G.; Fraile, B.; de Bethencourt, F.R.; Prieto-Folgado, A.; Bartolome, N.; Nunez, C.; Prati, B.; Martinez-Onsurbe, P.; Olmedilla, G.; Paniagua, R.; Royuela, M. (2010b). Role of IAPs in prostate cancer progression: immunohistochemical study in normal and pathological (benign hyperplastic, prostatic intraepithelial neoplasia and cancer) human prostate. *BMC Cancer*, Vol. 10 (Jan 15), pp. 18, ISSN: 1471-1407.

Royuela, M.; De Miguel, M.P.; Bethencourt, F.; Fraile, B.; Arenas, M.I.; Paniagua, R. (2000). IL-2, Its receptors, and bcl-2 and bax genes in Normal, Hyperplastic and Carcinomatous human prostates: Immunohistochemical Comparative Analysis. Growth Factors; Vol. 18, No. 2, pp. 135-146, ISSN: 0897-7194.

Royuela, M.; Arenas, M.I.; Bethencourt, F.R.; Sanchez-Chapado, M.; Fraile, B.; Paniagua, R. (2001). Immuno expressions of p21, Rb, mcl-1 and bad gene products in normal, hyperplastic and carcinomatous human prostates. *European Cytokine Network*, Vol. 12, No. 4 (Oct-Dec), pp. 654-663, ISSN: 1148-5493.

Royuela, M.; Arenas, M.I.; Bethencourt, F.R.; Sánchez-Chapado, M.; Fraile, B.; Paniagua, R. (2002). Regulation of proliferation/apoptosis equilibrium by mitogen-activated protein kinases in normal, hyperplastic, and carcinomatous human prostate. *Human Pathology*, Vol. 33, No. 3 (Mar), pp. 299-306, ISSN: 0046-8177.

Royuela, M.; Ricote, M.; Parsons, M.S.; Garcia-Tuñon, I.; Paniagua, R.; De Miguel, M.P. (2004). Immunohistochemical analysis of IL-6 family of cytokines and their receptors in benign, hyperplastic and malignant human prostate. *The Journal of Pathology*, Vol. 202, No. 1 (Jan), pp. 41-49, ISSN: 1096-9896.

Royuela, M.; Rodríguez-Berriguete, G.; Fraile, B.; Paniagua, R. (2008). TNF-alpha/IL-1/NF-kappaB transduction pathway in human cancer prostate. *Histology and Histopathology*, Vol. 23, No. 10 (Oct), pp. 1279-1290, ISSN: 0213-3911.

Rzymski, P.; Opala, T.; Wilczak, M.; Wozniak, J.; Sajdak, S. (2005). Serum tumor necrosis factor alpha receptors p55/p75 ratio and ovarian cancer detection. *International Journal of Gynecology & Obstetrics*, Vol. 88, No. 3, (Mar), pp. 292-298, ISSN: 1097-6868.

Sawhney, R.S.; Liu, W.; Brattain, M.G. (2009). A novel role of ERK5 in integrin-mediated cell adhesion and motility in cancer cells via Fak signaling. *Journal of Cellular Physiology*, Vol. 219, No. 1 (Apr), pp. 152-161, ISSN: 0021-9541.

Shimada, K.; Nakamura, M.; Ishida, E.; Konishi, N. (2006). Molecular roles of MAP kinases and FADD phosphorylation in prostate cancer. *Histology and Histopathology*, Vol. 21, No. 4, (Apr), pp. 415-422, ISSN: 0213-3911.

Silver, J.S. & Hunter, C.A. (2010). gp130 at the nexus of inflammation, autoimmunity, and cancer. *Journal of Leukocyte Biology*, Vol. 88, No. 6, (Dec), pp. 1145-1156, ISSN: 0741-5400.

Smith, C.A.; Davis, T.; Anderson, D.; Solam, L.; Beckmann, M.P.; Jerzy, R.; Dower, S.K.; Cosman, D.; Goodwin, R.G. (1990). A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins. *Science,* Vol. 248, No. 4958 (May 25), pp. 1019-1023, ISSN: 1095-9203.

Stein, B.; Brady, H.; Yang, M.X.; Young, D.B.; Barbosa, M.S. (1996). Cloning and characterization of MEK-6, a novel member of the mitogen-activated protein kinase kinase cascade. *The Journal of Biological Chemistry*, Vol. 271, No. 19 (May 10), pp. 11427-11433, ISSN: 0021-9258.

Su, G.H.; Hilgers, W.; Shekher, M.C.; Tang, D.J.; Yeo, C.J.; Hruban, R.H.; Kern, S.E. (1998). Alterations in pancreatic, biliary, and breast carcinomas support MKK4 as a genetically targeted tumor suppressor gene. *Cancer Research*, Vol. 58, No. 11 (Jun 1), pp. 2339-2342, ISSN: 0008-5472.

Tartaglia, L.A.; Weber, R.F.; Figari, I.S.; Reynolds, C.; Palladino Jr, M.A.; Goeddel, D.V. (1991). The two different receptors for tumor necrosis factor mediate distinct cellular responses. *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 88, No. 20(Oct 15), pp. 9292-9296, ISSN: 0027-8424.

Taylor, J.L.; Szmulewitz, R.Z.; Lotan, T.; Hickson, J.; Griend, D.V.; Yamada, S.D.; Macleod, K.; Rinker-Schaeffer, C.W. (2008). New paradigms for the function of JNKK1/MKK4 in controlling growth of disseminated cancer cells. *Cancer Letters*, Vol. 272, No. 1 (Dec 8), pp. 12-22, ISSN: 0304-3835.

Thornton, T.M. & Rincon, M. (2009). Non-classical p38 map kinase functions: cell cycle checkpoints and survival. *International Journal of Biological Sciences,* Vol. 5, No. 1 (), pp. 44-51, ISSN: 1449-2288.

Turjanski, A.G.; Vaqué, J.P.; Gutkind, J.S. (2007). MAP kinases and the control of nuclear events. *Oncogene*, Vol. 26, No. 22 (May 14), pp. 3240-3253, ISSN: 0950-9232.

Vayalil, P.K.; Mittal, A.; Katiyar, S.K. (2004). Proanthocyanidins from grape seeds inhibit expression of matrix metalloproteinases in human prostate carcinoma cells, which is associated with the inhibition of activation of MAPK and NF kappa B. *Carcinogenesis*, Vol. 25, No. 6 (Jun), pp. 987-995, ISSN 0143-3334.

Visconti, R.; Cerutti, J.; Battista, S.; Fedele, M.; Trapasso, F.; Zeki, K.; Miano, M.P.; de Nigris, F.; Casalino, L.; Curcio, F.; Santoro, M.; Fusco, A. (1997). Expression of the neoplastic phenotype by human thyroid carcinoma cell lines requires NF-iB p65

protein expression. *Oncogene*, Vol. 15, No. 16 (Oct 16), pp. 1987-1994, ISSN: 0950-9232.

Wajant, H. & Scheurich, P. (2001). Tumor necrosis factor receptor associated factor (TRAF)2 and its role in TNF signaling. *The International Journal of Biochemistry & Cell Biology*, Vol. 33, No. 1 (Jan), pp. 19-32, ISSN: 1357-2725.

Wang, J.; Kuiatse, I.; Lee, A.V.; Pan, J.; Giuliano, A.; Cui, X. (2010). Sustained c-Jun-NH2-kinase activity promotes epithelial-mesenchymal transition, invasion, and survival of breast cancer cells by regulating extracellular signal-regulated kinase activation. *Molecular Cancer Research*, Vol. 8, No. 2 (Feb), pp. 266-277, ISSN: 1541-7786.

Wang, H.Y.; Cheng, Z.; Malbon, C.C. (2003). Overexpression of mitogen-activated protein kinase phosphatases MKP1, MKP2 in human breast cancer. *Cancer Letters*, Vol. 191, No. 2 (Mar 10), pp.229-237, ISSN: 0304-3835.

Wang, S.; Liu, Z.; Wang, L.; Zhang, X. (2009). NF-kappaB signaling pathway, inflammation and colorectal cancer. *Cellular & Molecular Immunology*, Vol. 6, No. 5 (Oct), pp. 327-334, ISSN: 1672-7681.

Wang, X.S.; Diener, K.; Manthey, C.L.; Wang, S.; Rosenzweig, B.; Bray, J.; Delaney, J.; Cole, C.N.; Chan-Hui, P.Y.; Mantlo, N.; Lichenstein, H.S.; Zukowski, M., Yao, Z. (1997). Molecular cloning and characterization of a novel p38 mitogen-activated protein kinase. *The Journal of Biological Chemistry*, Vol. 272, No. 38 (Sep 19), pp. 23668-23674, ISSN: 0021-9258.

Wang, W.; Abbruzzese, J.L.; Evans, D.B.; Larry, L.; Cleary, K.R.; Chiao, P.J. (1999). The nuclear factor-IB transcription factor is constitutively active in human pancreatic adenocarcinoma cells. *Clinical Cancer Research*, Vol. 5, No. 1 (Jan), pp. 119-127, ISSN: 1078-0432.

Werlen, G.; Hausmann, B.; Naeher, D; Palmer, E. (2003). Signaling life and death in the thymus: timing is everything. *Science,* Vol. 299, No. 5614 (Mar 21), pp. 1859-1863, ISSN: 1095-9203.

Whyte, J.; Bergin, O.; Bianchi, A.; McNally, S.; Martin, F. (2009). Key signalling nodes in mammary gland development and cancer. Mitogen-activated protein kinase signalling in experimental models of breast cancer progression and in mammary gland development. *Breast Cancer Research*, Vol. 11, No. 5 (), pp. 209, ISSN: 1465-5411.

Wiegmann, K.; Schutze, S.; Kampen, E.; Himmler, A.; Machleidt, T.; Kronke, M. (1992). Human 55-kDa receptor for tumor necrosis factor coupled to signal transduction cascades. *The Journal of Biological Chemistry*, Vol. 267, No. 25 (Sep 5), pp. 17997-18001, ISSN: 0021-9258.

Wood, C.D., Thornton, T.M.; Sabio, G.; Davis, R.A.; Rincon, M. (2009). Nuclear localization of p38 MAPK in response to DNA damage. Int J Biol Sci; 5:428-37.

Wu, J.T. & Kral, J.G. (2005). The NF-kappaB/IkappaB signaling system: a molecular target in breast cancer therapy. *Journal of Surgical Research*, Vol. 123, No. 1 (Jan), pp. 158-169, ISSN: 0022-4804.

Zebisch, A.; Czernilofsky, A.P.; Keri, G.; Smigelskaite, J.; Sill, H.; Troppmair, J. (2007). Signaling through RAS-RAF-MEK-ERK: from basics to bedside. *Current Topics in Medicinal Chemistry*, Vol. 14, No. 5 (), pp. 601-623, ISSN: 1568-0266.

Zhang, C.; Zhu, H.; Yang, X.; Lou, J.; Zhu, D.; Lu, W.; He, Q.; Yang, B. (2010). P53 and p38 MAPK pathways are involved in MONCPT-induced cell cycle G2/M arrest in

human non-small cell lung cancer A549. *Journal of Cancer Research and Clinical Oncology*, Vol. 136, No. 3 (Mar), pp. 437-445, ISSN: 0171-5216.

Zhang, Y.X. & Kong, C.Z. (2008). The role of mitogen-activated protein kinase cascades in inhibition of proliferation in human prostate carcinoma cells by raloxifene: an in vitro experiment. *Zhonghua yi xue yi chuan xue za zhi*, Jan 22;Vol. 88, No. 4 (), pp. 271-5, ISSN: 0376-2491.

Zhao, M.; New, L.; Kravchenko, V.V.; Kato, Y.; Gram, H.; di Padova, F.; Olson, E.N.; Ulevitch, R.J.; Han, J. (1999). Regulation of the MEF2 family of transcription factors by p38. *Molecular and Cellular Biology*, Vol. 19, No. 1 (Jan), pp. 21-30.

Zheng, B.; Fiumara, P.; Li, Y.V.; Georgakis, G.; Snell, V.; Younes, M.; Vauthey, J.N.; Carbone, A., Younes, A. (2003). MEK/ERK pathway is aberrantly active in Hodgkin disease: a signaling pathway shared by CD30, CD40, and RANK that regulates cell proliferation and survival. *Blood*, Vol. 102, No. 3 (Aug 1), pp. 1019-1027, ISSN: 0006-4971.

Zhou, G.; Bao, Z.Q.; Dixon, J.E. (1995). Components of a new human protein kinase signal transduction pathway. *The Journal of Biological Chemistry*, Vol. 270, No. 21 (May 26), pp. 12665-12669, ISSN: 0021-9258

Zhu, Y.; Culmsee, C.; Klumpp, S.; Krieglstein, J. (2004). Neuroprotection by transforming growth factor-beta1 involves activation of nuclear factor-kappaB through phosphatidylinositol-3-OH kinase/Akt and mitogen-activated protein kinase-extracellular-signal regulated kinase1,2 signaling pathways. *Neuroscience*, Vol. 123, No. 4, pp. 897-906, ISSN: 0306-4522.

Zubelewicz, B.; Muc-Wierzgon, M.; Wierzgon, J.; Romanowski, W.; Mazurek, U.; Wilczok, T.; Podwinska, E. (2002). Genetic disregulation of gene coding tumor necrosis factor alpha receptors (TNF alpha Rs) in follicular thyroid cancer-preliminary report. *Journal of Biological Regulators & Homeostatic Agents*, Vol.16, No. 2 (Apr-Jun), pp. 98-104, ISSN: 0393-974X.
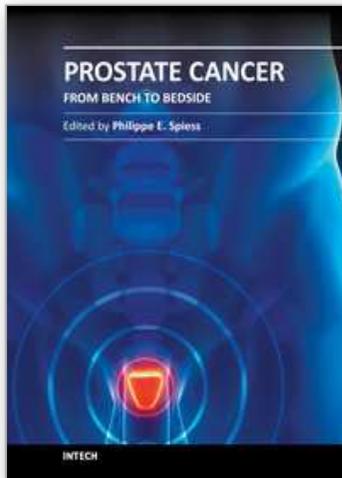
Prostate Cancer - From Bench to Bedside

Edited by Dr. Philippe E. Spiess

The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

INTECH
open science | open minds