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NSAID Induction of p75^{NTR} in the Prostate: A Suppressor of Growth and Cell Migration Via the p38 MAPK Pathway

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1. Introduction

Chronic consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) has been associated with a reduced incidence of prostate cancer (Nelson & Harris, 2000). Pathologic inflammation can induce oxidative stress generating free radicals that can subsequently react with infectious agents and surrounding cells during induction of innate immunity. Different forms of reactive oxygen species can form DNA adducts by halogenation, nitration and oxygenation of bases (Kang & Sowers, 2008). DNA repair of reactive oxygen species damaged bases can seal in mutations that may eventually lead to transformation of cells and carcinogenesis (Burrows, 2009). NSAIDs inhibit inflammation (Masferrer et al., 1995, Tegeder et al., 2001) and therefore may reduce the incidence of carcinogenesis by preventing free radical transformation of cells. NSAID inhibition of the cyclo-oxygenases (COXs) reduces inflammation, however, the mechanism of action of NSAIDs associated with reduced risk of prostate cancer appears independent of COX inhibition (Quann et al., 2007a; Quann et al., 2007b). NSAIDs represent a diverse category of pharmacological compounds with the common biological activity to reduce inflammation, temperature and pain, but with diverse chemical structures that undoubtedly interact with multiple target molecules with multiple mechanisms of action. In the prostate, selected aryl propionic acid NSAIDS such as ibuprofen and r-flurbiprofen (profens) inhibit epithelial cell growth in a COX independent manner (Quann et al., 2007a; Quann et al., 2007b). A mechanism by which these profens inhibit prostate growth appears to be via re-induction of the p75 neurotrophin receptor (p75^{NTR}) which has been shown to exhibit both tumor suppressor and metastasis suppressor activity (Krygier & Djakiew, 2001a; Krygier & Djakiew, 2002). In pathologic human prostate cancer tissues, the p75^{NTR} protein exhibits focal loss of expression which is further lost with malignant progression of tissues (Perez et al., 1997). Significantly, treatment of prostate tumor cells with profen NSAIDs promotes re-expression of the p75^{NTR} protein that inhibits growth (Quann et al., 2007a; Quann et al., 2007b) consistent with p75^{NTR} dependent tumor and metastasis suppressor activity (Krygier & Djakiew, 2001;2002). The COX independent pathway by which profen NSAIDs induce p75^{NTR} re-expression involves rapid phosphorylation of p38 MAPK and down stream effectors leading to re-expression of p75^{NTR} protein and suppressor activity (Quann et al., 2007b). This review discusses the body of evidence for the inhibitory role of the p75^{NTR} in prostate growth; the pathologic loss of

p75NTR expression during progression to prostate cancer, and the ability of profen NSAIDs to re-induce p75NTR protein expression through the p38 MAPK pathway with concomitant tumor and metastasis suppressor activity which provides a basis for NSAID associated reduced risk of prostate cancer.

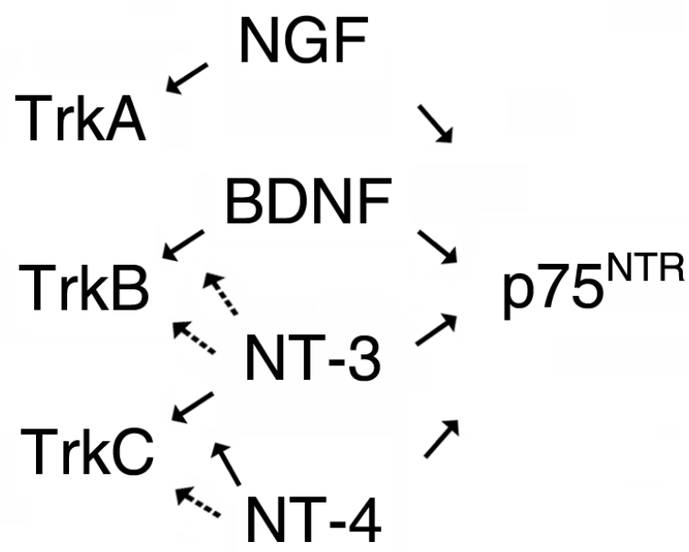

Fig. 1. Affinities of the neurotrophin ligands, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) for the family of tropomyosin receptor kinases (Trks) and the p75 neurotrophin receptor (p75NTR). Solid arrows show primary affinities, while dotted arrows show secondary affinities.

2. Expression of neurotrophins and their receptors ($p75^{NTR}$ and Trks) in the prostate

The progression of prostate cancer is accompanied by modifications in the expression of growth factors and their receptors (Bostwick et al, 2004). Amongst these are nerve growth factor (NGF) and its receptors, p75NTR and the Trk family (Djakiew, 2000). The neurotrophin family of ligands (Leibrock et al., 1989, Maisonpierre et al., 1990, Hallbook et al., 1991) consisting of nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) which is identical to NT-5, all of which can bind with similar affinity to the p75NTR (Bothwell, 1995) and with differential affinities to the Trk family (TrkA, TrkB, TrkC) of high affinity receptors (Figure 1). TrkA preferentially binds with NGF, but also binds BDNF. TrkB preferentially binds BDNF (Soppert et al., 1991), but also binds NT-3 and NT-4 (Berkemeier et al., 1991) and TrkC preferentially binds NT-3 (Lamballe et al., 1991), but also binds NT-4 (Figure 1). NGF immunoreactive protein has been localized to normal epithelium (MacGrogan, 1992; Paul et., 1992) and the stroma of normal, BPH (Djakiew et al., 1991) and cancer tissues of the human prostate (MacGrogan et al., 1992; Djakiew, 1991; Graham et al., 1992). Exogenous NGFβ has been shown to stimulate proliferation *in vitro* (Delsite & Djakiew, 1999; Angelsen et al., 1998; Pflug & Djakiew, 1998), and anchorage independent growth of several prostate tumor cell lines (Chung et al., 1992).

BDNF also is also expressed by human prostate stromal cells (Dalal & Djakiew, 1997). Hence, the two neurotrophins, NGF and BDNF appear to function as paracrine factors for prostate epithelial cell growth (Dalal & Djakiew, (1997).

The p75^{NTR} is expressed by normal human prostate epithelial cells (MacGrogan et al., 1992; Graham et al., 1992). Immunoblot (Pflug et al., 1992), immunofluorescence (Graham et al., 1992), and immunohistochemical (Pflug et al., 1992) studies have shown that p75^{NTR} protein expression progressively declines in human prostate cancer (Perez et al., 1997; Pflug et al., 1995; Djakiew et al., 1996). The p75^{NTR} is expressed in PIN tissue (Perez et al., 1997), and shows a gradual decline in the percentage of cells that retain expression with increasing Gleason score of pathologic prostate tissues (Perez et al., 1997). Hence, loss of p75^{NTR} expression appears to be correlated with cancer grade in organ-confined disease (Perez et al., 1997). The p75^{NTR} is also absent in three human cancer cell lines derived from metastases (Pflug et al., 1992). Loss of p75^{NTR} expression in prostate cancer may be related to its role in the induction of programmed cell death (Pflug & Djakiew, 1998; Djakiew et al., 1996). In this context, the p75 neurotrophin receptor (p75^{NTR}) is a 75 kD cell surface receptor glycoprotein that shares both structural and sequence homology with the tumor necrosis factor receptor super-family of proteins (Chao, 1994; Chapman, 1995). Some of these proteins (e.g. p75^{NTR}, p55^{TNFR}, Fas, DRs3-5) have similar sequence motifs of defined elongated structure (Chao, 1994) designated "death domains" based upon their apoptosis inducing function (Chao, 1994). Hence, re-expression of p75^{NTR} by stable and transient transfection showed that the p75^{NTR} inhibits growth of prostate epithelium *in vitro*, at least in part, by induction of programmed cell death (Pflug & Djakiew, 1998). Hence, loss of p75^{NTR} expression appears to eliminate a potential programmed cell death pathway in prostate cancer cells (Figure 2), thereby facilitating the growth of these cancer cells during carcinogenesis (Perez et al., 1997; Djakiew et al., 1996).

Since expression of the p75^{NTR} is lost during malignant progression and transformation of the prostate (Figure 2), NGF mediated growth of cancer cells has been shown to occur via the family of high affinity Trk receptors (Pflug & Djakiew, 1998; Dalal & Djakiew, 1997; Pflug et al., 1995). Differential expression of TrkA, TrkB and TrkC occurs in normal, organ confined and metastatic prostate cancer tissue (Chapman, 1995) and cell lines (Dalal & Djakiew, 1997) suggesting the presence of a neurotophin mediated proliferative stimulus via the Trk receptors (Figure 2). Expression of the TrkA receptor has been observed in normal prostate epithelial cells, organ confined prostate adenocarcinoma tissues (Djakiew et al., 1996; Pflug et al., 1995; Djakiew et al., 1996; Dionne et al., 1998), in prostate tumors that have metastasized to the bone (Dionne et al., 1998), as well as in several human prostate tumor cell lines derived from metastases (Djakiew et al., 1996). Interestingly, although normal prostate epithelial cells do the not express either TrkB or TrkC (Dionne et al., 1998), these receptors are expressed in metastatic prostate cancer of the bone (Dionne et al., 1998). Hence, it appears that normal prostate epithelial cells express TrkA, and that cancer cells continue to express TrkA within primary tumors and at metastatic foci, while TrkB and TrkC expression is subsequently up-regulated within metastatic prostate tumors (Dionne et al., 1998). Pharmacological inhibition of the Trk family of receptors has provided a basis for their role in mediating a proliferative stimulus is tumor cells. In this context, the indolocarbazole kinase inhibitors selectively antagonize Trk receptors at nanomolar concentrations (Berg et al., 1992) and inhibit NGF-stimulated Trk phosphorylation in cancer cell lines (Delsite & Djakiew, 1996). Concurrently, Trk selective indolocarbazoles inhibit growth of cancer cell lines *in vitro* (Delsite & Djakiew, 1996), and *in vivo* (Dionne et al., 1998).

Interestingly, Trk family mutations within the human prostate have not been identified (George et al., 1998). However, the absence of mutations in otherwise genetically unstable prostate tumor DNA suggests that intact Trk family signaling pathways may be important in prostate cancer development (George et al., 1998) consistent with a role as a proto-oncogene.

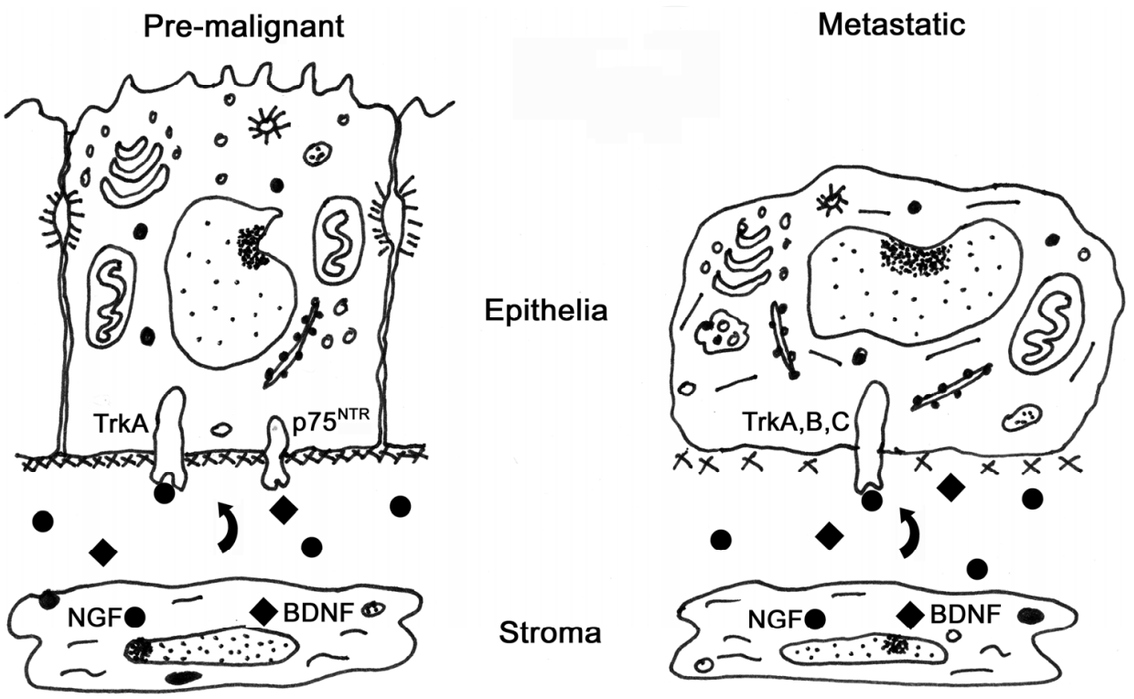

Fig. 2. Schematic diagram showing expression of NGF and BDNF in prostatic stroma for the paracrine regulation of epithelial cell growth. Pre-malignant epithelial cells express both TrkA and the p75NTR, whereas metastatic tumor cells have lost expression of the p75NTR and gained expression of both TrkB and TrkC.

3. Ectopic re-expression of $p75^{NTR}$ induces tumor suppressor, metastasis suppressor and differentiation phenotypes in prostate tumor cells

Whereas the gene encoding $p75^{NTR}$ is intact in prostate cancer cells (Krygier & Djakiew, 2001b), expression of the $p75^{NTR}$ protein is suppressed (Perez et al., 1997; Pflug et al., 1992; Pflug et al., 1995). Moreover, transient transfection of two constructs of $p75^{NTR}$ into prostate cell lines that do not express the protein, one construct containing the full 2-kb 3′ untranslated region and another that contains just a few hundred bases of the 3′ untranslated region, showed that only the truncated construct allowed expression of the $p75^{NTR}$ protein (Krygier & Djakiew, 2001b). This lead to the conclusion that elements of the 3′ untranslated region of $p75^{NTR}$ contribute to mRNA stability and $p75^{NTR}$ protein expression (Krygier & Djakiew, 2001b). Utilizing the truncated $p75^{NTR}$ expression vector that allows protein expression, a series of stable prostate cell lines were developed that express different levels of $p75^{NTR}$ protein (Pflug et al., 1992, Pflug et al., 1995). These cancer cells that

ectopically expressed the p75^{NTR} protein exhibited a retardation of cell cycle progression characterized by accumulation of cells in G1 phase with a corresponding reduction of cells in the S phase of the cell cycle (Krygier & Djakiew, 2001a). In rank order, prostate cancer cells that expressed increased levels of p75^{NTR} protein exhibited increased rates of apoptosis and reduced rates of proliferation (Krygier & Djakiew, 2001a). When the same series of tumor cells were injected into the flanks of SCID mice the growth of prostate tumors was suppressed in proportion to increased p75^{NTR} expression levels (Krygier & Djakiew, 2001a) thereby functionally demonstrating that the p75^{NTR} exhibits tumor suppressor activity (Krygier & Djakiew, 2001a). Further evidence for the tumor suppressor function of p75^{NTR} was show utilizing a gene therapy strategy based upon intra-tumoral injection into xenografts of PC-3 prostate tumor cells of a lipoplex containing the p75^{NTR} gene. Administration of the p75^{NTR} gene into subcutaneous PC-3 xenografts suppressed in a dose-dependent manner the growth of tumors (Allen et al., 2004). Within the gene therapy treated tumors re-expression of the p75^{NTR} gene product was associated with increased apoptosis and reduced proliferation of tumor cells (Allen et al., 2004), the net effect of which was to reduce overall growth and tumor volume. Utilizing the same prostate tumor cells that exhibited a rank order (dose-dependent) increase in p75^{NTR} expression for growth of subcutaneous tumors in SCID mice (Krygier & Djakiew, 2001a), treatment of these tumors with NGF stimulated both proliferation as indicated by PCNA expression, and apoptosis as indicated by TUNEL assay, the net result of which was no change in the overall growth of the tumors (Krygier & Djakiew, 2002). However, NGF was found to increase the formation of smaller secondary satellite tumors, both contiguous and non-contiguous with respect to the primary tumor mass, indicating dose-dependent induction of metastasis (Krygier & Djakiew , 2002). Significantly, the formation of satellite tumors was suppressed by the expression of p75^{NTR} thus showing that p75^{NTR} is a tumor suppressor of growth and a metastasis suppressor of NGF stimulated migration (Djakiew et al, 1993) of human prostate tumor cells (Krygier & Djakiew, 2002). To better understand the molecular mechanism of p75^{NTR} on tumor and metastasis suppression a cDNA microarray composed of approximately 6,000 human cancer-related genes was used to determine the gene expression pattern altered by re-introduction of p75^{NTR} into PC-3 prostate tumor cells (Nalbandian et al., 2005). Comparison of the transcripts in the *neo* control and p75^{NTR}-transfected cells revealed 52 differentially expressed genes, of which 21 were up-regulated and 31 were down-regulated in the presence of p75^{NTR}. The known biological functions of these p75^{NTR} regulated genes suggested a role in the regulation of differentiation as well as cell adhesion, signal transduction, apoptosis, tumor cell invasion and metastasis (Nalbandian et al., 2005). Quantitative real-time polymerase chain reaction and immunoblot analysis confirmed increased CRABPI and IGFBP5 protein levels and decreased level of PLAUR protein with increasing p75^{NTR} protein expression. Indeed, CRABPI was elevated far more than any other genes (Nalbandian et al., 2005). In this context, the retinoids, ATRA and 9-*cis* RA, that bind CRABPI, promoted functional cell differentiation in p75^{NTR} PC-3 cells, but not in *neo* control PC-3 cells. Subsequent examination of the retinoic acid receptors expression levels demonstrated an absence of RAR-β in the *neo* control cells and re-expression in the p75^{NTR} expressing cells, consistent with previous findings where RAR-β is believed to play a critical role as a tumor suppressor gene which is lost during de-differentiation of prostate epithelial cells. Whereas the RAR-α and -γ protein levels remained unchanged, RXR-α and -β also exhibited increasing protein levels with re-expression of the p75^{NTR} protein (Nalbandian et al., 2005). Moreover, the ability of p75^{NTR} siRNA to knockdown levels of RAR-β, RXR-α, and

RXR-β support the specificity of the functional involvement of p75^{NTR} in differentiation. Hence, re-expression of the p75^{NTR} appears to partially reverse de-differentiation of prostate cancer cells by up-regulating expression of CRABPI for localized sequestration of retinoids that are available to newly up-regulated RAR-β, RXR-α, and RXR-β proteins (Nalbandian et al., 2005). Hence, the p75^{NTR} has been shown to exhibit tumor suppressor (Krygier & Djakiew, 2001a), metastasis suppressor (Krygier & Djakiew, 2002) and differentiation (Nalbandian et al., 2005) functions all of which contribute to an anti-cancer phenotype in the prostate.

4. Effectors of signal transduction, cell cycle and apoptosis following constitutive p75^{NTR} expression in the prostate

Ectopic re-expression of p75^{NTR} down regulates the NFκB and JNK pathways leading to reduced survival of tumor cells (Allen et al., 2005). As a member of the TNF receptor super-family the p75^{NTR} has been shown to mediate signal transduction through it's intracellular death domain. Expression of two adaptor proteins, TRAF2 and RIP are down-regulated following restoration of p75^{NTR} protein by stable transfection of prostate tumor cells (Allen et al., 2005). Significantly, TRAF2 has previously been implicated as an upstream signaling molecule of both the NFκB and JNK pathways (MacEwan, 2002), both of which function as potent effectors of transcription. Similarly, RIP has also been shown to interact with death receptors that signal through both the NFκB and JNK pathways (Harper et al, 2003). Moreover, deletion constructs that lack much of the intracellular death domain were shown to rescue p75^{NTR} down-regulation of RIP (Allen et al., 2005). This p75^{NTR}-dependent reduction in RIP protein appeared to be a consequence of caspase-8 cleavage of RIP, since a caspase-8 inhibitor rescued the p75^{NTR}-dependent reduction in the levels of RIP. This observation is consistent with previous reports where caspase-8 cleavage of RIP was shown to prevent activation of the NFκB pathway (Lin et al., 1999; Martinon et al., 2000) and suggests that caspase-8 cleavage of RIP is capable of preventing the previously reported RIP activation of the JNK pathway (Kelliher et al., 1998). Hence, both the NFκB and JNK pathways appear to be regulated by p75^{NTR} expression (Allen et al., 2005). With regard to the NFκB signaling bifurcation, ectopic re-expression of p75^{NTR} reduces levels of IKKs, with consequent reduced phosphorylation levels of IκBα, stabilized levels of unphosphorylated IκBα, and reduced levels of RelA (Allen et al., 2005). Moreover, the activity of the IKKs is regulated through the serine/threonine kinase activity of upstream full length RIP (Hur et al., 2003). Hence, the p75^{NTR}-dependent reduction in the levels of RIP, via caspase-8 cleavage of RIP, leads to an overall reduction in signal transduction components required for activation of NFκB (Allen et al., 2005). Several of these p75^{NTR} dependent changes in signaling components are rescued with dominant negative death domain deletion constructs, thereby further establishing a link between the NFκB pathway downstream of p75^{NTR} (Allen et al., 2005). With regard to the JNK signaling bifurcation, ectopic restoration of p75^{NTR} levels is associated with a reduction in the expression of the MKK4 kinase and a reduction in the phosphorylated (active) form of JNK. Since MKK4 phosphorylation of JNK has been shown to promote nuclear translocation (Cobb, 1999; Gonzalez et al., 2000) where activated JNK may function as an effector of transcription for growth (Gee et al., 2000; Herr & Debatin, 2001), p75^{NTR} associated suppression of JNK phosphorylation and suppression of translocation is consistent with the suppression of the JNK signaling pathway. Moreover,

deletion constructs that lack much of the intracellular death domain were shown to rescue p75^{NTR} down-regulation of MKK4 and phosphorylated JNK (Allen et al., 2005) thereby further establishing a link between the JNK pathway downstream of p75^{NTR} (Allen et al., 2005). At the functional level, ectopic re-expression of p75^{NTR} reduces cell survival (Allen et al., 2005), and dominant negative antagonism of IKKβ or MKK4 partially rescues survival (Allen et al., 2005). Hence, it appears that both the NFκB and JNK pathways promote cell survival and that p75^{NTR} down regulation of these pathways inhibits survival in prostate cancer cells, thereby providing a signal transduction pathway for the observed suppressor activities of the p75^{NTR} protein (Krygier and Djakiew, 2001a; Krygier and Djakiew, 2002). The observation that both signaling pathways bifurcate from the p75^{NTR} suggests a redundancy whereby robust down regulation of either pathway may function independently to promote suppressor activity.

Ectopic re-expression of p75^{NTR} alters the cell cycle kinetics of prostate tumor cells (Krygier & Djakiew, 2001a). Cell cycle initiation and progression is cooperatively regulated by several classes of cyclin-dependent kinases (cdks). The expression of cyclin D1-cdk6 (Boonstra, 2003; Sherr, & Roberts, 1995) complexed with PCNA has been shown to promote hyperphosphorylation of Rb during progression through early to mid-G1 (Satyanarayana & Rudolph, 2004). Conversely, p16^{INK4a} binds and induces an allosteric conformational change in cdk6 that inhibits the binding of ATP thereby disrupting the formation of the cdk6-cyclin D1 complex (Satyanarayana & Rudolph, 2004; Golsteyn, 2005). Prostate cancer cells that express rank-order (dose-dependent) increased levels of p75^{NTR} show suppression of cdk6, PCNA and hypophosphorylated Rb, and up-regulation of p16^{INK4a} levels indicates that p75^{NTR} selectively regulates specific components of the holoenzyme complex (Khwaja et al., 2006) associated with retarded progression through early to mid-G1 of the cell cycle (Meyer et al., 2002). The rescue of cdk6, PCNA and phosphorylated Rb levels, and conversely suppression of p16^{INK4a} levels, by both a death domain deleted dominant–negative antagonist of p75^{NTR} and by NGF ligand, show a p75^{NTR}-dependent regulation of early to mid-G1 in prostate tumor cells (Khwaja, et al., 2006). Beyond mid-G1, near the G1/S restriction point, the expression of cyclin E complexed with cdk2 has been shown to promote hyper-phosphorylation of Rb (Boonstra, 2003; Shintani et al., 2002).

A rank-order increase in p75^{NTR} suppression of cyclin E and cdk2 in prostate tumor cells (Khwaja et al., 2006) indicate that progression through the G1/S restriction point is regulated by p75^{NTR} protein expression. (Figure 3). Since the Rb protein is a major effector of cell proliferation through its ability to regulate entry into the S phase (Sellers & Kaelin, 1996; , Huang et al., 2002), and the cyclin E/cdk2 holoenzyme complex hyper-phosphorylates Rb during the G1/S transition, the observation that p75^{NTR} expression can stabilize hypo-phosphorylated Rb and diminish the phosphorylation of Rb is consistent with a mechanism by which p75^{NTR} retards progression through the G1/S restriction point of the cell cycle (Khwaja et al., 2006). Furthermore, hypophosphorylated Rb has been shown to bind the E2F1 transcription factor (Harbour & Dean, 2000), so that the Rb/E2F1 complex can no longer promote transcription of PCNA preventing progression into the S phase of the cell cycle. Hence, the observation that p75^{NTR} associated hypo-phosphorylation of Rb in conjunction with suppression of E2F1 and PCNA expression (Westwood et al., 2002) further supports a role of p75^{NTR} in G1/S restriction point cytostasis (Khwaja et al., 2006). Beyond the G1/S restriction point, expression of the cyclin A/cdk2 holoenzyme complex has been shown to maintain hyper-phosphorylation of Rb during the S phase of the cell cycle (Sherr, 1996). Hence,

observations that p75NTR-potentiated suppression of cdk2 and cyclin A support a selective effect of p75NTR expression on maintaining hypo-phosphorylation of Rb (Khwaja et al., 2006), thereby retarding progression through the S phase of the cell cycle (Figure 3). Significantly, the rescue of cyclin E, cdk2, PCNA, phosphorylated Rb, E2F1 and PCNA by both a death domain deleted dominant–negative antagonist of p75NTR and also by NGF ligand (Khwaja et al., 2006) show a p75NTR-dependence of the regulation of progression through both the G1/S restriction point and the S phase in prostate tumor cells. Hence, it seems clear that p75NTR expression selectively alters specific cell cycle regulatory molecules that retard progression through early to mid-G1, the G1/S restriction point and the S phase of the cell cycle (Figure 3). Moreover, in the absence of ligand, the ability of p75NTR to retard cell cycle progression is dependent on the intracellular death domain, and that addition of NGF ligand attenuates inhibition of cell cycle progression at the level of the cyclin/cdk holoenzyme complex and related effects on Rb expression and tumor cell proliferation. Hence, p75NTR-dependent regulation of specific cyclin-dependent kinases and associated cell cycle effectors to retard progression of prostate tumors through the G1 phase and entry into S phase of the cell cycle (Figure 3) provides a biochemical basis upon which p75NTR inhibits prostate cell proliferation (Khwaja et al., 2006).

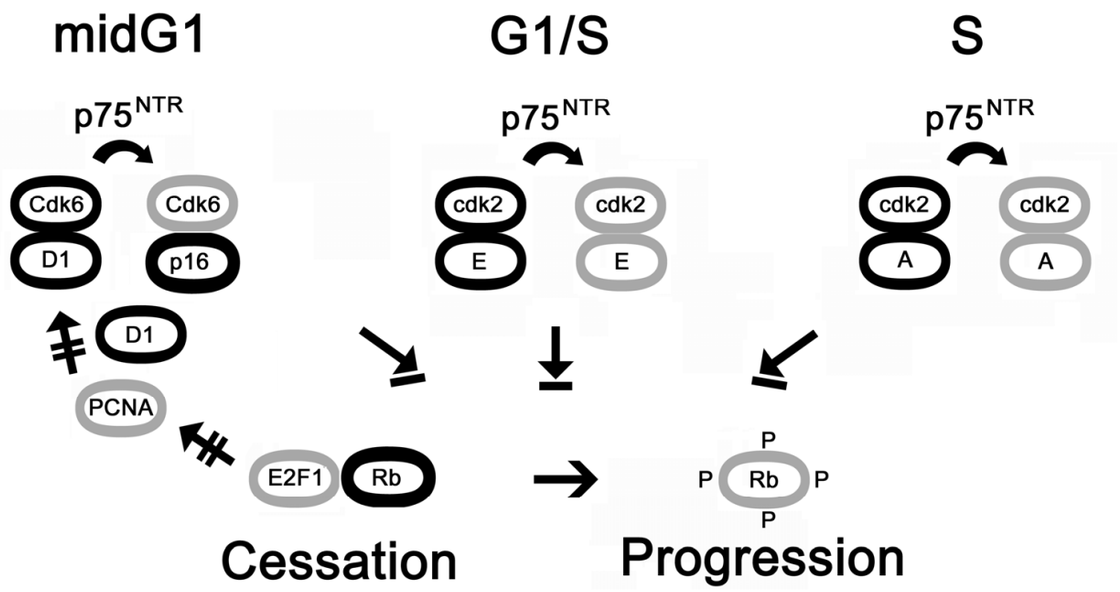

Fig. 3. Effects of p75NTR on regulation of the cell cycle. Re-expression of p75NTR induces midG1 suppression of cdk6 and up-regulation of p16Ink4a. During the G1/S transition re-expression of p75NTR induces suppression of cdk2 and cyclin E. Similarly, during S phase re-expression of p75NTR induces suppression of cdk2 and cyclin A. The net effect of these changes is to diminish phosphorylation of Rb thereby preventing progression of the cell cycle in favor of cessation.

In addition to cell cycle effects, ectopic re-expression of p75NTR has been shown to modify mitochondrial effector proteins that activate the caspase cascade leading to apoptosis (Khwaja, et al., 2006). Mitochondrial mediated apoptosis is facilitated by members of the Bcl-2 homology (Puthalakath & Strasser, 2002) family of proteins (O'Neill et al., 2004) that

include both pro- and anti-apoptotic members (Puthalakath & Strasser, 2002). In this context, a rank-order increase in p75NTR levels (Khwaja et al., 2006) was associated with a decrease in the mitochondrial pro-survival effector, Bcl-xL, and concomitantly, an increase in proapoptotic effectors (Smac, Bax, Bak, Bad). In the absence of NGF ligand the ability of a death domain deleted dominant–negative antagonist of p75NTR to rescue p75NTR-dependent changes in Smac and BH family proteins, and the addition of NGF having a comparable effect, suggest a ligand independent p75NTR-potentiated apoptosis in prostate cells that occurs via a mitochondrial stress pathway (Khwaja et al., 2006). Release of Smac from the intermembranous space of the mitochondria into the cytosol (Shiozaki & Shi, 2004) also initiates apoptosis where it competes with caspases for binding to XIAP. Indeed, to protect against inadvertent activation of apoptosis, the IAP family of proteins (Shiozaki & Shi, 2004) have been shown to bind and prevent activation of caspases. Hence, p75NTR-dependent down-regulation of XIAP in prostate cells allows for activation of the caspase cascade. Significantly, a rank-order increase in p75NTR levels was shown to activate both caspase-9 and caspase-7 (Khwaja et al., 2006). In the intrinsic mitochondrial dependent pathway, the assembly of the apoptosome requires the recruitment of the initiator caspase-9 (Shiozaki & Shi, 2004) which subsequently activates the effector caspase-7. Interestingly, a specific peptide inhibitor of procaspase-9 cleavage was shown to prevent cleavage/activation of procaspase-7. Since the initiator procaspase-9 is a proximate component of the caspase cascade, it is clear that procaspase-7 is downstream from procaspase-9 during mitochondrial mediated p75NTR potentiation of apoptosis (Shiozaki & Shi, 2004). Moreover, in p75NTR expressing prostate cells the activation of caspase-7 appears to facilitate subsequent cleavage of PARP. PARP cleavage has been shown to be a key event in the execution phase of apoptosis leading to cellular demise (Lazebnik et al., 1994). Clearly, the ability of a death domain deleted dominant–negative antagonist of p75NTR and NGF ligand to rescue p75NTR potentiated changes in XIAP, caspase-9, caspase-7, PARP and apoptotic nuclear fragmentation show that mitochondrial mediated apoptosis is dependent, in part, on p75NTR in the prostate. Moreover, the effect of p75NTR-dependent down regulation of NFκB and JNK survival pathways, regulation of cell cycle regulatory molecules of the cyclin/cdk holoenzyme complex that produce stasis in G1 and/or inhibition of progression to S phase of the cell cycle and regulation of mitochondrial effector proteins that activate the caspase cascade leading to apoptosis, in combination, all inhibit growth of prostate cells as a function of it's tumor suppressor activity (Krygier & Djakiew, 2001a; Khwaja et al., 2006).

5. Constitutive p75NTR expression regulates protease activity in the prostate

Ectopic re-expression of p75NTR down regulates protease activities in prostate cancer cells (Nalbandian & Djakiew, 2006). The urokinase plasminogen activator (uPA) and its receptor (uPAR) are associated with tumor malignancy through an extracellular cascade of proteolysis (Andreasen et al., 2000; Reuning et al., 1998) including activation of the type IV collagen matrix metalloproteinases (MMP-2 and MMP-9) during invasion and tumor progression (Mazzier et al., 1997). Ectopic re-expression of p75NTR reduces enzymatic protein levels and activity of uPA, MMP-2 and MMP-9 in prostate tumor cells (Nalbandian & Djakiew, 2006). Conversely, expression of an MMP-9 antagonist, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) exhibits an increase in protein levels with an increase in p75NTR levels. Whereas, levels of TIMP-2 were not detectable (Nalbandian & Djakiew, 2006) transient transfection with an inducible death domain deleted dominant–negative antagonist of p75NTR rescued uPA, MMP-

2, and MMP-9 protein levels and protease activities, and conversely suppressed TIMP-1 levels (Nalbandian & Djakiew, 2006). Since ectopic $p75^{NTR}$ signal transduction has been shown to suppress the NFκB and JNK pathways (Allen et al., 2005), antagonism of signaling intermediaries in these pathways, using dominant negative IKKβ or dominant negative MKK-4, respectively, was shown to further decrease expression of uPA, MMP-2, and MMP-9 protein and enzymatic activity levels, and conversely up-regulate levels of TIMP-1. Hence, expression of uPA, MMP-2, MMP-9, and TIMP-1 are directly regulated by expression of $p75^{NTR}$ and its downstream signal transduction cascade. This suggests that the metastasis suppressor activity of $p75^{NTR}$ (Krygier & Djakiew, 2002) is mediated, in part, by down-regulation of specific proteases (uPA, type IV collagenases) implicated in cell migration and metastasis (Nalbandian & Djakiew, 2006).

6. NSAIDS selectively induce pharmacological re-expression of the $p75^{NTR}$

NSAIDs represent a diverse and often structurally unrelated group of compounds that exhibit a range of anti-inflammatory, anti-pyretic and analgesic activities. NSAIDs can be classified into three broad categories as carboxylic acids, enolic acids, and COX-2 inhibitors, or coxibs (Figure 4). The carboxylic acid group is further divided into salicylic acids and esters, acetic acids, and propionic acids. The enolic acids are divided into pyrazolones and oxicams. Many NSAIDs used to treat inflammation inhibit cyclooxygenase (COX) activity. Two well known isoforms of COX exist, COX-1 and COX-2. COX-1 is considered to be a house keeping gene, and is expressed constitutively and ubiquitously at low levels. COX-2 is highly inducible in response to cytokines, hormones, and growth factors. The COX enzymes catalyze the conversion of arachidonic acid to various prostaglandins, which play a role in biological processes including immune response, blood pressure regulation, angiogenesis, ovulation, pain and inflammatory responses. Nonselective NSAIDs inhibit both COX-1 and COX-2, and are frequently associated with gastrointestinal side effects. Whereas, NSAIDs that selectively inhibit COX-2 have significantly decreased gastrointestinal side effects, they often exhibit enhanced cardiovascular toxicity (Dubois et al., 2004). Overexpression of COX-2 is observed in several cancer types including colon, breast, pancreas, and lung (Sarkar et al., 2007; Mascaux et al., 2006). Increased COX-2 expression is believed to contribute to tumorigenesis through several mechanisms including stimulation of growth, promotion of angiogenesis, increased inflammation, increased invasion and migration, immune suppression, and inhibition of apoptosis (Liao et al., 2007). Hence, NSAID inhibition of COX-2 activity may suppress these mechanisms that contribute to tumorigenesis. Consistently, several reports have linked long term NSAID use to decreased cancer risk for colon (Thun et al., 1991), bladder (Castelao et al., 2000), and prostate (Nelson & Harris, 2000) and possibly other organ specific sites. Although it has been the subject of multiple reports, there is not a consensus concerning the expression and role of COX-2 in prostate cancer. Several studies show that COX-2 is overexpressed, while others found that it is low or absent in most prostate cancers (Madaan et al., 2000; Kirschenbaum et al., 2000; Yoshimura et al., 2000). In addition, expression of COX-2 is absent in the metastatic human prostate cancer cell lines LNCaP, DU145, and PC-3 (Yoshimura et al., 2000). Although reports of COX-2 expression in prostate cancer vary, long term NSAID use is associated with decreased prostate cancer risk (Nelson & Harris, 2000), and several COX

inhibitors consistently induce apoptosis in prostate cancer cells regardless of COX-2 expression (Zha et al., 2001; Jacobs et al., 2007; Roberts et al., 2002; Hsu et al., 2000; Johnson et al., 2001). Indeed, NSAIDS that do not inhibit the cyclo-oxygenases (R-flurbiprofen) or NSAIDs that inhibit COX null tumor cells demonstrates an alternate COX independent mechanism of action for selected NSAID inhibition of some tumor cells. In this context, NSAIDs exhibit selective activity to induce p75NTR-dependent cell death (Khwaja et al., 2004). The propionic acids, ibuprofen and r-flurbiprofen, as well as the indolacetic acid, indomethacin, exhibit greater pharmacological activity to induce p75NTR-dependent cell death than the salicyclate, aspirin, or acetaminophen (Khwaja et al., 2004). Within the aryl propionic acid NSAIDs, r-flurbiprofen exhibits greater activity to induce p75NTR in descending rank-order than ibuprofen, oxaprozin, fenoprofen, naproxen and least of all ketoprofen (Quann et al., 2007a). Significantly, this activity appears relatively selective for induction of p75NTR (Quann et al., 2007a), since r-flurbiprofen and ibuprofen do not induce expression of Fas, p55TNFR, DR3, DR4, DR5 or DR6 in prostate cancer cells (Quann et al., 2007a). Some other NSAIDs have also been reported to induce expression of certain TNF receptor super family members, particularly DR5.

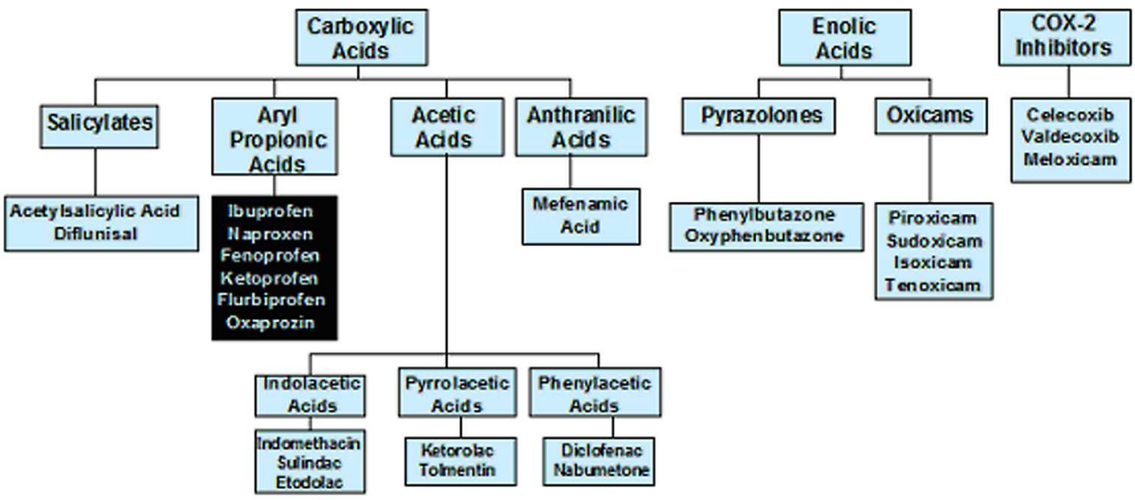

Fig. 4. Classification of the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) into three categories of carboxylic acids, enolic acids and COX-2 inhibitors. Sub-classifications of NSAIDs are further delineated with specific examples.

For instance, sulindac sulfide induces DR5 associated cell death in prostate cancer cells (Huang et al., 2001) and celocoxibs induce DR5 in both prostate and colon cancer cells (He et al., 2008). Moreover, aryl propionic acid induction of p75NTR appears somewhat selective for urogenital cancer cell lines such as prostate, bladder, kidney, ovary, and colon (Khwaja et al., 2004), whereas cell lines derived from the lung, or breast do not exhibit induction of the p75NTR protein (Khwaja et al., 2004). Hence, induction of p75NTR appears to represent a COX independent mechanism for NSAID associated reduced risk of prostate cancer.

7. NSAID induced phosphorylation of p38 MAPK is necessary for induction of $p75^{NTR}$ expression

NSAIDs exhibit a range of efficacy to inhibit survival of prostate cancer cells (Andrews et al., 2002). Induction of $p75^{NTR}$ dependent cell death by selected NSAIDs (R-flurbiprofen, ibuprofen) occurs through hyper-phosphorylation of p38 MAPK (Quann et al., 2007b). Although $p75^{NTR}$ is transcribed at a high level (Quann et al., 2007b; Krygier & Djakiew, 2001b), prostate cancer cells have very little $p75^{NTR}$ mRNA or protein due to increased mRNA instability mediated through the 3'UTR (Krygier & Djakiew, 2001b). Since, increased 3'UTR length provides increased potential for post-transcriptional regulation through the 3'UTR (Mazumder et al., 2003) R-flurbiprofen and ibuprofen appear to modulate mRNA stability as a determinant in regulating the expression level of $p75^{NTR}$ protein (Quann et al., 2007b). Significantly, activity of the p38 MAPK pathway is an important regulator of mRNA stability (Zarubin & Han, 2005; Kennedy et al., 2007; Gaestel, 2006). Pretreatment of prostate cancer cells with a p38 MAPK selective pharmacological inhibitor or siRNA knockdown of p38 MAPK prior to R-flurbiprofen and ibuprofen treatment prevents induction of $p75^{NTR}$ protein. In addition, the phytoestrogens biochanin A and to a lesser extent genestein, inhibit ibuprofen induced phosphorylation of p38 MAPK which in turn suppresses $p75^{NTR}$ expression and increases cell survival (El Touny et al., 2010). R-flurbiprofen and ibuprofen cause increased p38 MAPK phosphorylation within 5 minutes of treatment (Quann et al., 2007b). Whereas, p38 MAPK can be phosphorylated by MKK6 and MKK3, R-flurbiprofen and ibuprofen induce hyperphosphorylation of only MKK6 but not MKK3 within 30 seconds of treatment (Figure 5) indicating that the target molecule of these NSAIDs is immediately proximal to MKK6. Significantly, several oxidative stress pathways converge upstream of MKK6, thereby providing a basis by which NSAID inhibition of inflammation (Masferrer et al., 1995; Tegeder et al., 2001) may regulate p38 MAPK dependent expression of the $p75^{NTR}$ tumor suppressor to reduce the incidence of prostate cancer. Downstream of p38 MAPK R-flurbiprofen and ibuprofen induced activation of the kinase MK2 (Quann et al., 2007b). MK2 and the closely related MK3 are known to be responsible for mediating the mRNA stabilizing effects of the p38 MAPK pathway (Ronkina et al., 2007). Moreover, siRNA knockdown of both MK2 and MK3 together prevents induction of $p75^{NTR}$ by R-flurbiprofen or ibuprofen to a greater extent than knockdown of either MK2 or MK3 separately, indicating that p38 MAPK is able to induce $p75^{NTR}$ by acting through both MK2 and MK3 (Quann et al., 2007b).

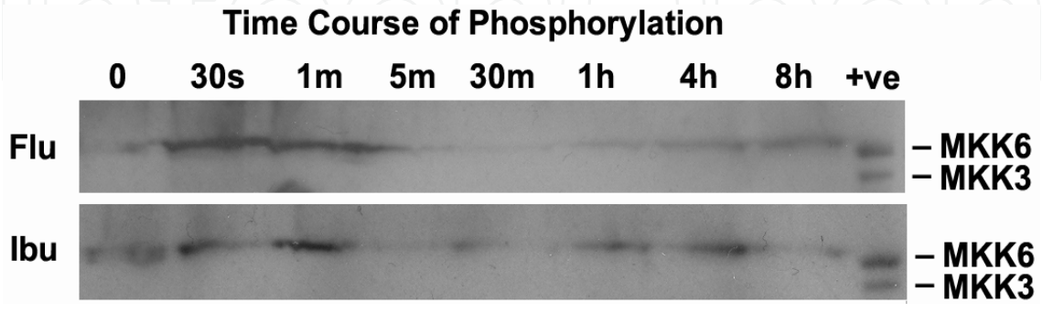

Fig. 5. Western blot showing the time course in seconds (s), minutes (m) and hours (h) of the phosphorylation forms of MKK6, but not MKK3, in PC-3 prostate cancer cells treated with r-flurbiprofen (Flu), or ibuprofen (Ibu). The positive controls for the phosphorylated forms of both MKK6 and MKK3 are shown to the right.

The mRNA stabilizing effects of the p38 MAPK pathway (Ronkina et al., 2007) also involves the RNA binding protein HuR (Tran et al., 2003; Lin et al., 2006; Jin et al., 2007; Song et al., 2005). Its ability to stabilize target mRNAs is linked to its subcellular localization, and activation of p38 MAPK and MK2 have been shown to cause translocation of HuR from the nucleus to the cytoplasm, resulting in increased mRNA stability of a number of p38 MAPK regulated genes (Tran et al., 2003; Lin et al., 2006; Jin et al., 2007; Song et al., 2005). HuR has repeatedly been shown to stabilize transcripts containing the AUUUA sequence (Tran et al., 2003; Song et al., 2005). The human p75NTR transcript contains AUUUA sites located in the 3'UTR at positions 2946 and 3124, suggesting they may be involved in regulating p75NTR expression. Significantly, treatment with R-flurbiprofen or ibuprofen results in an increase in the cytoplasmic level of HuR and binding to the p75NTR transcript (Quann et al., 2007b) although this is not the sole mechanism responsible for increased p75NTR expression. Indeed, eIF4E is also phosphorylated by kinases downstream of p38 MAPK (Scheper & Proud, 2002). eIF4E has also been shown to control the nuclear export as well as translation of a subset of transcripts (Culjkovic et al., 2007). eIF4E has been linked to the control of mRNA stability by removal of the 5'-cap during mRNA degradation (von der Haar et al., 2004). R-flurbiprofen or ibuprofen treatment increases the level of phosphorylated eIF4E (Quann et al., 2007b) involved in translation initiation and this appears to occur at least partially through the p38 MAPK pathway since the increase in phosphorylation is substantially inhibited in the presence of p38 MAPK siRNA. Therefore, modulation of eIF4E activity is another mechanism by which the p38 MAPK pathway may control post-transcriptional events in response to R-flurbiprofen or ibuprofen treatment (Figure 6). R-flurbiprofen or ibuprofen stabilization of the p75NTR transcript allows levels of the p75NTR protein to accumulate (Quann et al., 1997a, Quann et al., 197b) that then exhibit biological activity to inhibit prostate cancer cell survival and induce apoptosis (Quann et al., 1997a) consistent with its tumor suppressor activity (Krygier & Djakiew, 2001a). Significantly, NSAID induction of p38 MAPK dependent p75NTR expression and tumor suppressor activity may represent a new pathway to medicinal drug design. Rather that inhibit kinase dependent proliferation pathways, pharmacological induction of the p75NTR tumor suppressor, as shown with NSAIDs (Figure 6), may represent an alternate approach to the targeting of cancer cell survival pathways. Presumably, target molecules that activate this pathway appear to occur immediately proximal to MKK6 and the p38 MAPK (Figure 5).

8. NSAIDs induce expression of NAG-1 down stream of p75NTR via the p38 MAPK pathway

R-flurbiprofen and ibuprofen treatment of prostate cancer cells induces expression of the NSAID activated gene-1 (Nag-1) protein, a divergent member of the transforming growth factor beta (TGF-β) family (Wynne & Djakiew, 2010). Moreover, a selective pharmacological inhibitor of p38 MAPK and p38 MAPK specific siRNA, both reduce Nag-1 induction following NSAID treatment. Hence, NSAID induced Nag-1 expression is regulated by the p38 MAPK pathway (Figure 6). Interestingly, p75NTR specific siRNA pretreatment abrogates Nag-1 induction by NSAIDs (Wynne & Djakiew, 2010) thereby demonstrating that Nag-1 is downstream of p75NTR induction (Figure 6). Functionally, decreased survival of NSAID treated cells is rescued by p75NTR specific siRNA (Quann et al., 2007a; Wynne & Djakiew, 2010) but not by Nag-1 siRNA. Transwell chamber and *in vitro* wound healing assays demonstrate decreased cell migration upon NSAID treatment (Wynne & Djakiew, 2010). Pre-treatment of prostate cancer cells with p75NTR and Nag-1 specific siRNA shows that

NSAID inhibition of cell migration is mediated by Nag-1 and p75NTR (Wynne & Djakiew, 2010). Additionally, prostate cancer cells stably expressing Nag-1 exhibit decreased migration relative to the parental cell line (Wynne & Djakiew, 2010), thereby independently confirming a role for this protein in reduced prostate cancer cell migration. Hence, it appears that NSAID induction of Nag-1 functions in the inhibition of cell migration, but not survival (Figure 6). Interestingly, NSAIDs have been linked to metastasis suppression in a variety of cancers including prostate cancer (Lloyd et al., 2003; Jin et al., 2010; Kamei et al., 2009). Hence, NSAID induction of Nag-1 via the p38 MAPK pathway may contribute to the metastasis suppressor activity of p75NTR (Krygier & Djakiew, 2002).

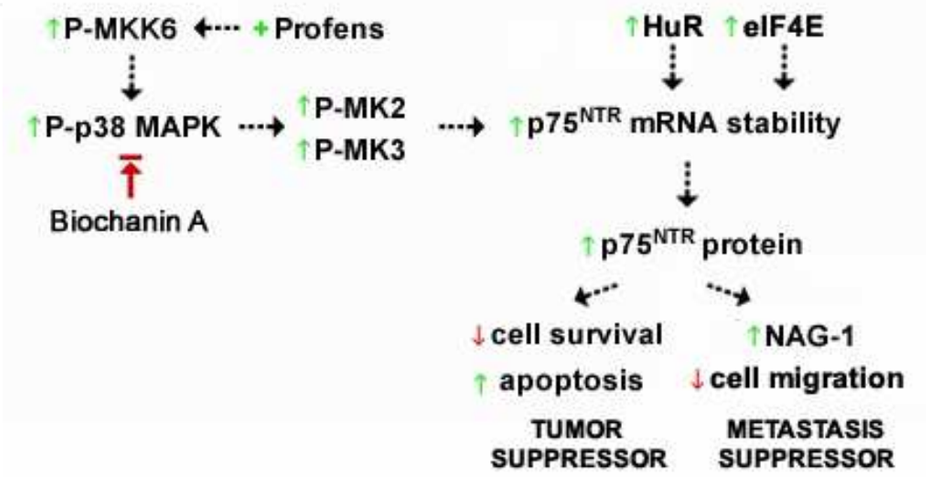

Fig. 6. Schematic diagram showing the biochemical pathway by which profen NSAIDs positively stimulate and the phytoestrogen, biochanin A, negatively inhibits phosphorylation of the p38 MAPK pathway leading to p75NTR expression with consequent tumor suppressor and metastasis suppressor activity.

9. Summary and conclusions

Paracrine regulated growth of the prostate is mediated, in part, by neurotrophin dependent interactions with the Trk family of receptors and the p75NTR (Djakiew, 2000). In the normal prostate neurotrophins stimulate proliferation via the Trk family of receptors and abrogate p75NTR apoptotic activity. However, p75NTR protein expression progressively declines in human prostate cancer (Perez et al., 1997; Pflug et al., 1995; Djakiew et al., 1996). Hence, in the absence of p75NTR inhibition of growth, prostate tumor cells respond to neurotrophins with a stiochiometry that favors Trk family dependent proliferation. Even though the p75NTR protein is no longer expressed in many prostate cancer cells the gene has remained intact (Krygier & Djakiew, 2001b). Indeed, reduced p75NTR protein in cancer cells occurs via loss of mRNA stability (Krygier & Djakiew, 2001b). Ectopic re-expression of p75NTR in cancer cells induces tumor suppressor (Krygier & Djakiew, 2001a), metastasis suppressor (Krygier & Djakiew, 2002) and differentiation phenotypes (Nalbandian et al., 2005). The tumor suppressor activity of p75NTR is manifest as a suppression of the NFκB and JNK pathways, modification of cyclin-dependent holoenzyme complexes resulting in accumulations of cells in G1 and restriction of entry into the S1 phase of the cell cycle, and modification of mitochondrial effector proteins

that activate the caspase cascade leading to apoptosis. The metastasis suppressor activity of p75NTR is manifest as down-regulation of urokinase plasminogen activator and type IV collagenases (MMP-2, MMP-9) as well as increased expression of the tissue inhibitor of matrix metalloproteinase-1 (Nalbandian & Djakiew, 2006). The differentiation activity of p75NTR is manifest as up-regulated expression of CRABPI for localized sequestration of retinoids that are available to newly up-regulated RAR-β, RXR-α, and RXR-β proteins (Nalbandian et al., 2005). Moreover, certain aryl propionic acid type NSAIDs (profens) restore p75NTR protein levels that inhibit growth via a COX independent mechanism of action. Indeed, these profens induce hyperphosphorylation of p38 MAPK that initiates a signal transduction cascade leading to mRNA stability of the p75NTR transcript and increased protein levels (Quann et al., 2007a; Quann et al., 2007b). Profen NSAIDs also induce Nag-1 expression downstream of p75NTR (Wynne & Djakiew, 2010). Functionally, profen dependent induction of p75NTR inhibits growth and downstream Nag-1 inhibition of cell migration consistent with the tumor suppressor (Krygier & Djakiew, 2001a) and metastasis suppressor (Krygier & Djakiew, 2002) activities of p75NTR expression, respectively. Hence, these profen NSAIDs induce multiple activities of the p75NTR and downstream Nag-1 consistent with observations that chronic consumption of NSAIDs is associated with a reduced incidence of prostate cancer (Nelson & Harris, 2000).

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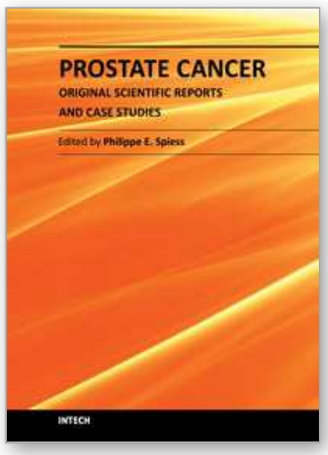

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