MINIREVIEW

Pharmacological Targeting of the Integrated Protein Kinase B, Phosphatase and Tensin Homolog Deleted on Chromosome 10, and Transforming Growth Factor-β Pathways in Prostate Cancer

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ABSTRACT

Prostate cancer is a highly heterogenous disease in which a patient-tailored care program is much desired. Central to this goal is the development of novel targeted pharmacological interventions. To develop these treatment strategies, an understanding of the integration of cellular pathways involved in both tumorigenesis and tumor suppression is crucial. Of further interest are the events elicited by drug treatments that exploit the underlying molecular pathology in cancer. This review briefly describes the evidence that suggests integration of three established pathways: the tumorigenic phosphoinositide 3-kinase/protein kinase B (AKT) pathway, the tumor suppressive phosphatase and tensin homolog deleted on chromosome 10 pathway, and the tumor suppressive transforming growth factor-β pathway. More importantly, we discuss novel pharmaceutical agents that target key points of integration in these three pathways. These new therapeutic strategies include the use of agents that target iron to inhibit proliferation via multiple mechanisms and suppression of AKT by cytosolic phospholipase A2 inhibitors.

Prostate cancer is the most commonly diagnosed noncutaneous cancer in men and is the second leading cause of death (Assinder and Nicholson, 2007). It is estimated that approximately 186,000 new cases of prostate cancer will be diagnosed in the United States during 2008, accounting for approximately 22,000 deaths (available from the American Cancer Society, http://www.cancer.org).

Radical prostatectomy (surgical removal) is the most common treatment strategy for organ-confined tumors (Steineck et al., 2002). Although this procedure has a 10-year survival of 60%, surgery has a 2% mortality rate, 70% of patients develop erectile dysfunction, and 50% have urine leakage with 2 to 5% of patients being left incontinent (Steineck et al., 2002). The most common treatment option for advanced metastatic prostate cancer is androgen deprivation either by surgical or chemical castration. However, in the majority of patients, the cancer becomes insensitive to androgen deprivation, leading to relapse, and they inevitably die from androgen-independent metastatic prostate cancer (Hussain and Dawson, 2000). Thus, improved treatment options are desperately needed.

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ABBREVIATIONS: PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; AA, arachidonic acid; COX, cyclooxygenase; cPLA2-α, cytosolic phospholipase A2-α; DFO, desferrioxamine; Dp44mT, di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone; GSK3β, glycogen synthase kinase 3β; HIF-1α, hypoxia inducible factor-1α; LOX, lipooxygenase; mTOR, mammalian target of rapamycin; NDRG1, N-myc downstream regulated gene-1; PIP2, phosphatidylinositol-4,5-bisphosphate; PGE2, prostaglandin E2; EGR-1, early growth response gene; siRNA, small interfering RNA; MK886, 3-(1-(4-chlorobenzyl)-3-t-butylthio-5-isopropylindol-2-yl)-2,2-dimethylpropanoic acid; 311, 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone.
Key to developing improved pharmacological interventions for prostate cancer is an understanding of the integration of pathways known to be involved in the pathophysiology of prostate cancer. This review 1) briefly describes the tumorogenic phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), and transforming growth factor β (TGF-β) tumor suppressive pathways; 2) examines current evidence for the integration at key points of these pathways; and 3) discusses novel pharmaceutical agents that target these key points.

Biochemical Pathways Known to Play a Role in Prostate Cancer

The PI3K/AKT Pathway. A high level of activated (phosphorylated) AKT (pAKT) is correlated with poor prognosis of prostate cancer, whereas in normal prostate tissue, pAKT is undetectable (Wegiel et al., 2008). It is estimated that 30 to 40% of solid tumors have constitutively activated pAKT (Samuels and Ericson, 2006).

Activation of a tyrosine kinase receptor, such as the insulin-like growth factor receptor, activates phosphatidylinositol-3 kinase (PI3K) (Fig. 1A). Thereafter, PI3K catalyzes phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to form phosphatidylinositol-4,5,6-trisphosphate (PIP3) (Cantley and Neel, 1999). PIP3 acts as a platform and brings AKT in close proximity to 3-phosphoinositide-dependent kinases that subsequently phosphorylate and activate AKT. Activated AKT results in signaling cascades involving various downstream signaling proteins (Gao et al., 2003; Fig. 1A).

Activated AKT affects many targets and can inhibit glycosynthe kinase 3β (GSK3β; Fig. 1A), which normally prevents up-regulation of cellular proliferation due to increased cyclin D1 degradation and suppression of expression, possibly via cytosolic (free) β-catenin (de la Taille et al., 2003; Lee et al., 2007). An excessive rate of cyclin D1 production promotes cell cycle progression (Chen et al., 1998) as a result of increased levels of cyclin D1/cyclin-dependent kinase 4 complexes that promote G1/S progression. On reaching appropriate levels, these complexes phosphorylate retinoblastoma protein and cause the dissociation of the E2F transcription factor, which heralds the progression of the cell cycle from G1 to S phase (Yu et al., 2007).

Another key effector downstream of pAKT is the serine/threonine kinase known as the mammalian target of rapamycin (mTOR; Fig. 1A) (Vignot et al., 2005). It plays a central role in protein translation, cell proliferation, and evasion of apoptosis (Vignot et al., 2005). Activation of AKT also helps to evade apoptosis directly by phosphorylation and inactivation of the proapoptotic protein, Bad (Grünwald et al., 2002).

The PTEN Pathway. Fifty percent of prostate cancers display a loss of PTEN (Facher and Law, 1998). Re-expression of normal PTEN in prostate cancer cell lines causes apoptosis (Davies et al., 1999; Sharrard and Maitland, 2000). Furthermore, Pten-null mice have increased numbers of tentative prostate stem cells and develop prostate cancer with pathological changes similar to human disease (Wang et al., 2006). The major tumor suppressive activity of PTEN is via antagonism of the AKT pathway by dephosphorylation of PIP3, converting it back to PIP2 (Cantley and Neel, 1999). PTEN thus modulates AKT signaling, with opposite effects from PI3K on cell proliferation and survival (Fig. 1B).

Interaction of PTEN with p53 also plays a significant role in tumor suppression (Fig. 1B) (Stambolic et al., 2001). PTEN suppresses the expression of the p53 repressor MDM2 (Mayo et al., 2002). Furthermore, nuclear PTEN interacts directly with p53 to enhance p53-mediated cell cycle arrest and apoptosis in prostate cancer cells (Mayo et al., 2002; Chang et al., 2008) (Fig. 1B).

The Tumor-Suppressive TGF-β Pathway. TGF-β acts on normal prostate epithelial cells and some prostate cancer cell lines to inhibit proliferation and induce apoptosis (Wilding, 1991; Sutkowski et al., 1992). In prostate cancer specimens, it is common to find down-regulation of TGF-β receptors (Shariat et al., 2004). In particular, down-regulation of the type II receptor is associated with aggressive tumors (Shariat et al., 2004).

TGF-β signaling is activated by binding to the TGF-β receptor II and subsequent recruitment and phosphorylation of TGF-βRI (Shi and Massagué, 2003) (Fig. 1C). This activates a SMAD signaling cascade (Ten Dijke et al., 2002), resulting in the up-regulation of cyclin-dependent kinase inhibitors (Guo and Kyriianou, 1998; Li et al., 2006) and down-regulation of c-Myc (Massagué et al., 2000), leading to suppressed cellular proliferation (Fig. 1C). Apoptosis is promoted by TGF-β-induced expression of proapoptotic Bax, down-regulation of antiapoptotic Bcl-2, and increased expression and activation of the effector caspases (Guo and Kyriianou, 1999). Additional apoptotic cross-talk with the androgen receptor also occurs depending on the mutational status of this protein (Shariat et al., 2004; Zhu et al., 2008).
Interactions of the PI3K/AKT, PTEN, and TGF-β Pathways: Implications for Pharmacological Targeting

TGF-β and PTEN Integration Act to Oppose AKT. pAKT suppresses TGF-β-activated SMAD-signaling (Fig. 1), whereas PTEN inhibits AKT suppression (Song et al., 2003). In turn, TGF-β induces PTEN expression through its classic SMAD-dependent pathway (Fig. 1C) and stimulates a tumor-suppressive response (Chow et al., 2007). Considering this, it is known that iron chelation up-regulates TGF-β (Yoon et al., 2002), and this may potentially increase PTEN levels, although further studies are needed to investigate this. As mentioned above, SMAD activation suppresses oncogenic c-Myc (Massagué et al., 2000) and Bcl-2 expression (Guo and Kyprianou, 1999) but increases expression of the cyclin-dependent kinase inhibitors p15, p21, and p27 (Fig. 1) (Guo and Kyprianou, 1998; Li et al., 2006). However, AKT activation has the opposite effect (Vignot et al., 2005) (Fig. 1).

The Metastasis Suppressor N-myc Downstream Regulated Gene-1: A Possible Common Point of AKT, PTEN, and TGF-β Integration. It has been shown that expression of both the N-myc downstream regulated gene-1 (NDRG1) and PTEN are repressed in prostate tumors (Bandypadhyay et al., 2004b). Forced expression of PTEN up-regulates NDRG1 expression in the prostate cancer cell lines PC-3 and DU145 via suppression of the AKT pathway (Bandypadhyay et al., 2004a) (Fig. 2). It is therefore hypothesized that AKT activation acts to inhibit NDRG1 expression, whereas PTEN antagonizes this effect (Fig. 2).

Up-regulation of NDRG1 expression after hypoxia or cellular Fe-depletion is driven, at least in part, by hypoxia inducible factor-1α (HIF-1α) (Le and Richardson, 2004), which stimulates NDRG1 expression (Kovacevic and Richardson, 2006). It is noteworthy that increased HIF-1α levels during hypoxia correlate with increased TGF-β expression (Berger et al., 2003), mediating further potential integration between the AKT, PTEN, and TGF-β pathways. In fact, as already discussed, there is up-regulation of TGF-β after iron chelation (Yoon et al., 2002) that may act to increase PTEN, which subsequently could up-regulate NDRG1 expression. PI3K/AKT and PTEN have completely opposite effects on the activity of HIF-1α (Emerling et al., 2008). PTEN inhibits the transcriptional activity of HIF-1α, whereas AKT induces HIF-1α transcriptional activity via suppression of the fork-head transcription factor FOXO3a (Emerling et al., 2008).

This effect of tumor-suppressive PTEN inhibiting HIF-1α activity can be seen as both logical and counterintuitive. For instance, the PTEN-mediated decrease in HIF-1α would lead to the appropriate decrease in expression of one of its classic targets, *vascular endothelial growth factor 1*, that promotes angiogenesis and tumor progression. However, paradoxically, PTEN would also potentially lead to decreased expression of the metastasis suppressor, NDRG1, which can be up-regulated by a HIF-1α-dependent mechanism (Le and Richardson, 2004). However, NDRG1 can also be up-regulated by an HIF-1α independent process (Le and Richardson, 2004), and it is probable that the regulation of this metastasis suppressor complex is complex. Moreover, it may be that HIF-1α serves more than one function, and this needs to be examined in detail. Indeed, overexpression of HIF-1α has been found in various cancers, and down-regulation of this molecule is currently evaluated as a therapeutic target for cancer treatment (Greenberger et al., 2008; Groot et al., 2008; Yasui et al., 2008).

The Arachidonic Acid and Eicosanoid Signaling Pathway: A Possible Regulator of AKT and PTEN. Arachidonic acid (AA) is an ω6 polyunsaturated essential fatty acid (Burr and Burr, 1929). As such, it cannot be synthesized by cells de novo. Rather, it is obtained from the diet or synthesized from its precursor linoleic acid (Brenner, 1974). In resting cells, AA is stored within the phospholipid bilayer of the cell membrane (Hughes-Fulford et al., 2001). Stimulation of cells by a number of diverse agonists leads to the activation of intracellular phospholipases, namely cytosolic phospholipase A2-α (cPLA2-α), that then releases AA from the cell membrane (Clark et al., 1995; Niknami et al., 2008). When AA is released, it can either become reincorporated into the membrane phospholipid bilayer, diffuse out of the cell, or be metabolized via the lipooxygenase (LOX) or cyclooxygenase (COX) enzymes to eicosanoids such as prostaglandin E2 (PGE2) (Fig. 2; Niknami et al., 2008).

Previous studies have demonstrated that the eicosanoid synthetic rates from labeled AA are significantly higher in malignant than in benign prostate tissue, suggesting an increased AA flux through the COX and LOX pathways (Chaudry et al., 1994; Faas et al., 1996). Eicosanoids can contribute to cancer progression by promoting cell proliferation, motility, invasion, and angiogenesis (Nie et al., 1998, 2001; Pidgeon et al., 2002; PORKKA and Visakorpi, 2004). Other evidence also supports a role for eicosanoids in prostate carcinogenesis. For example, eicosanoid inhibitors effectively reduce the size of prostate cancer xenografts (Hsu et al., 2000). Treatment of the androgen-independent human prostate carcinoma cell line, PC-3, with linoleic acid stimulates growth (Tjandrawinata et al., 1997). Furthermore, a study by Hughes-Fulford and associates (2001) demonstrated that linoleic acid, arachidonic

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**Fig. 2.** The metastasis suppressor NDRG1 and the potentially tumorigenic fatty acid AA provide targets for pharmacological modulation of cancer cell proliferation. cPLA2-α releases AA into the cytosol from membrane phospholipids. AA is converted to eicosanoids (e.g., PGE2) by lipooxygenases and cyclooxygenases (COX and LOX, respectively) that then releases AA from the cell membrane (Clark et al., 1995; Niknami et al., 2008). When AA is released, it can either become reincorporated into the membrane phospholipid bilayer, diffuse out of the cell, or be metabolized via the lipooxygenase (LOX) or cyclooxygenase (COX) enzymes to eicosanoids such as prostaglandin E2 (PGE2).
acid, and PGE2 all stimulate prostate tumor growth and alter gene expression in PC-3 cells. In mice, diets high in corn oil (hence rich in the AA precursor linoleic acid) markedly stimulate the growth of human prostate cancer xenografts (Wang et al., 1995). Together, these studies suggest a stimulatory effect of dietary ω6 fatty acid on prostate tumor cell growth, which may be critical for the development and progression of cancer.

In humans, it was shown that an increase in serum prostate-specific antigen levels after prostatectomy or radiotherapy was slowed in patients treated with COX-2 inhibitors (Pruthi et al., 2006; Smith et al., 2006). However, an increased risk of thrombosis was found in patients treated with COX-2 inhibitors as a result of the sparing effect on COX-1 (Marcus et al., 2002). In addition, COX-2 inhibitors inhibit the production of the vasodilator prostacyclin with no effect on the synthesis of the vasoconstrictive thromboxane A2, thus potentially tipping the balance toward vasoconstriction and thrombosis (Funk and FitzGerald, 2007).

In the past few years, it has become clear that AA and/or eicosanoids can lead to increased AKT activation. In pancreatic cancer cells, AA and/or eicosanoids can augment AKT activation indirectly by increasing the inactivation of PTEN by oxidation (Covey et al., 2007; Fig. 2). Alteration of PLA2 can directly regulate PI3K/AKT in the prostate (Hsu et al., 2000; Patel et al., 2005; Hughes-Fulford et al., 2006) and vascular smooth muscle cells (Li and Malik, 2005a,b; Wilk and Freeman, 2006). Inhibition of COX-2 by celecoxib has been shown to induce apoptosis in both androgen-responsive prostate cancer and pancreas cells, AA and/or eicosanoids can augment eicosanoids can also lead to increased AKT activation. In humans, it was shown that an increase in serum prostate-specific antigen levels after prostatectomy or radiotherapy was slowed in patients treated with COX-2 inhibitors (Pruthi et al., 2006; Smith et al., 2006). However, an increased risk of thrombosis was found in patients treated with COX-2 inhibitors as a result of the sparing effect on COX-1 (Marcus et al., 2002). In addition, COX-2 inhibitors inhibit the production of the vasodilator prostacyclin with no effect on the synthesis of the vasoconstrictive thromboxane A2, thus potentially tipping the balance toward vasoconstriction and thrombosis (Funk and FitzGerald, 2007).

The classic iron chelator, DFO (Fig. 3A), that is used for treating iron overload is the best studied in terms of its antitumor efficacy (Kalinowski and Richardson, 2005). However, because of its limited membrane permeability and short half-life, DFO has shown modest antitumor activity (Richardson et al., 1994; Kalinowski and Richardson, 2005). There has been continuing efforts to improve the efficacy of iron chelators as cancer treatments. Indeed, the potential of iron chelators to act as antitumor agents (Buss et al., 2003; Kalinowski and Richardson, 2005). The classic iron chelator, DFO (Fig. 3A), that is used for treating iron overload is the best studied in terms of its antitumor efficacy (Kalinowski and Richardson, 2005). However, because of its limited membrane permeability and short half-life, DFO has shown modest antitumor activity (Richardson et al., 1994; Kalinowski and Richardson, 2005). There has been continuing efforts to improve the efficacy of iron chelators as cancer treatments. Indeed, the potential of iron chelators to act as antitumor agents (Buss et al., 2003; Kalinowski and Richardson, 2005). The classic iron chelator, DFO (Fig. 3A), that is used for treating iron overload is the best studied in terms of its antitumor efficacy (Kalinowski and Richardson, 2005). However, because of its limited membrane permeability and short half-life, DFO has shown modest antitumor activity (Richardson et al., 1994; Kalinowski and Richardson, 2005). There has been continuing efforts to improve the efficacy of iron chelators as cancer treatments. Indeed, the potential of iron chelators to act as antitumor agents (Buss et al., 2003; Kalinowski and Richardson, 2005).
agents was confirmed by the entrance of the chelator Triapine into clinical trials (Yu et al., 2006; Fig. 3A).

DpT and 2-Benzoylpyridine Thiosemicarbazone Chelators Possess Marked and Selective Antitumor Activity. The development of novel arylhydrazone chelators such as compound 311 (Fig. 3A) have resulted in compounds that show far greater antitumor and iron chelation efficacy than DFO (Richardson et al., 1995; Richardson and Milnes, 1997; Darnell and Richardson, 1999). More recently, novel chelators of the DpT class have been generated (Fig. 3A) (Lovejoy and Richardson, 2002; Becker et al., 2003; Yuan et al., 2004; Richardson et al., 2006; Whitnall et al., 2006). Some of these chelators are far more effective than DFO at entering cells, inducing cellular iron efflux, and preventing iron uptake from Tf (Yuan et al., 2004). A control DpT analog known as Dp2mT (Fig. 3A) that does not bind iron has also been synthesized and demonstrates that the mechanism of activity of these compounds is due to their ability to bind metal ions (Yuan et al., 2004).

Studies in vivo showed that dipyrindylketone 4,4-dimethylthiosemicarbazone (Dp44mT) significantly decreased tumor weight in mice bearing the chemotherapy-resistant lung carcinoma to 47% of the control after only 5 days (Yuan et al., 2004). It is significant that no changes in animal weight or hematological indices were found, demonstrating that the chelator acts selectively to inhibit tumor growth (Yuan et al., 2004). In addition, Dp44mT has been shown to be highly effective in vivo using a panel of human tumor xenografts and a wide range of cultured tumor cells in vitro (Whitnall et al., 2006). It is important to note that little or no toxicity was seen in normal tissues at optimal doses.

More recent studies have resulted in the development of the 2-benzoylpyridine thiosemicarbazone (BpT) class of chelators (Fig. 3B), which show a general increase in antitumor activity relative to the DpT group of ligands (Kalinowski et al., 2007). In these compounds, the noncoordinating 2-pyridyl group of the DpT ligands is replaced with a phenyl ring (Kalinowski et al., 2007), which increases the lipophilicity of the molecule that probably allows greater access to the tumor microenvironment (Tredan et al., 2007). These chelators show selectivity against tumor cells being far less active in normal fibroblasts (IC50 value, 1.86 to >6.25 µM; Kalinowski et al., 2007). In addition, relative to the DpT ligands, the BpT series shows a marked increase in redox activity that is vital for antitumor efficacy (Kalinowski et al., 2007).

Iron Chelators Affect Multiple Molecular Targets. Studies have revealed that the successful antitumor activity of iron chelators is due to their effects on multiple molecular targets (Le and Richardson, 2004; Fu and Richardson, 2007; Nurtjahja-Tjendraputra et al., 2007). These include the classic target RR (Le and Richardson, 2002; Richardson, 2005) and their ability to 1) up-regulate the iron-regulated metastasis suppressor NDRG1 (Le and Richardson, 2004; Kovacevic et al., 2008); 2) prevent iron uptake from transferrin in vitro (Yuan et al., 2004); 3) increase iron efflux from cells (Yuan et al., 2004); and 4) affect the expression of molecules involved in cell cycle progression that can inhibit proliferation and lead to apoptosis (e.g., p53, cyclin D1, p21WAF1/CIP1) (Li and Richardson, 2003; Yuan et al., 2004; Fu and Richardson, 2007). It is noteworthy that the novel mechanism of action of these drugs means that they overcome resistance to established chemotherapeutics (Whitnall et al., 2006).

Iron Chelators Up-Regulate the Growth and Metastasis Suppressor NDRG1. As described above, NDRG1 expression is up-regulated by hypoxia (Le and Richardson, 2004). Several studies have also shown that NDRG1 is up-regulated by iron depletion (Le and Richardson, 2004; Dong et al., 2005). The transcription factor HIF-1α is expressed in response to hypoxia and iron depletion and has been found to up-regulate NDRG1 (Cangul, 2004; Le and Richardson, 2004). However, the up-regulation of NDRG1 by iron-depletion is mediated by both HIF-1α-independent and -dependent mechanisms (Le and Richardson, 2004).

It has been shown that iron depletion using chelators stabilizes HIF-1α by inhibiting the activity of prolyl hydroxylase that acts to degrade this transcription factor (Ivan et al., 2001; Jaakkola et al., 2001). More recently, in cancer cell types, it has been suggested that DFO up-regulates COX-2 through an extracellular signal-regulated kinase signaling mechanism (Tanji et al., 2001; Woo et al., 2006). The elevated activity of COX-2 is believed to increase HIF-1α (Woo et al., 2006). It is of interest that TGF-β1 increases HIF-1α protein stability by decreasing HIF-1α-associated prolyl hydroxylase through the SMAD signaling pathway (McMahon et al., 2006). This observation follows the intriguing finding by others that TGF-β1 is up-regulated by DFO (Yoon et al., 2002), and this may lead to increased PTEN that inhibits the AKT pathway. As described above, PTEN and PI3K/AKT have completely opposite effects on the activity of HIF-1α and hence probably also NDRG1 expression (Emerling et al., 2008).

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It is of interest that DFO has been shown to inhibit pAKT in the premalignant keratinocyte cell line HaCaT (Faurcseh and Gniadecki, 2008). In contrast, DFO was shown recently to increase the phosphorylation status of AKT and its targets FoxO1 and GSK3β in HepG2 hepatoma cells (Dongiovanni et al., 2008). It remains to be determined whether the up-regulation of NDRG1 by iron chelation in cancer cells is influenced by the inhibition of pAKT. It has also been shown that the early growth response gene (EGR-1) transcription factor mediates the expression of NDRG1 in response to hypoxia and iron depletion in some cells through direct binding to the NDRG1 promoter (Zhang et al., 2007). In addition, it was found recently that EGR-1 regulates the HIF-1α gene during hypoxia (Sperandio et al., 2008), suggesting another mechanism that may modulate NDRG1 expression. There seems to be many points of integration between pathways that act to regulate NDRG1 and its metastasis suppressor function. However, increased expression of EGR-1 is found in prostate cancer cells (Thigpen et al., 1996), suggesting an alteration of the coupling mechanism between EGR-1 and NDRG1. Thus, the role of EGR-1 in the up-regulation of NDRG1 and HIF-1α and the link between the three proteins clearly need to be investigated further, particularly in the context of prostate cancer. Because many studies have shown that the up-regulation of NDRG1 plays a vital role in preventing metastatic spread in cancer (Bandyopadhyay et al., 2003, 2004a,b), the up-regulation of NDRG1 by iron chelators is of significance. In summary, novel iron chelators show great promise as future anticancer agents through their effect on multiple targets such as the metastasis suppressor NDRG1.

Targeting Arachidonic Acid and Eicosanoid Formylation for Suppression of Tumor Growth. The phospholipases can be classified into four classes on the basis of their nucleotide and amino acid sequence homology (Patel et al., 2008a). These enzymes are differentially expressed in a tis-
Inhibitors of key enzymes of the AA pathway. The enzyme cPLA2-α liberates AA from the plasma membrane. The release of AA can be tumorigenic leading to activation of AKT. However, this enzyme can be inhibited by Efipladib (see insert for structure) (Ni et al., 2006). The AA can also be metabolized further by COX-1 and -2, leading to prostanoids (e.g., PGE2). COX-1 and -2 inhibitors are well known and include celecoxib. Liberated AA can also be acted upon by 5-lipoxygenase (5-LOX) or 12-lipoxygenase (12-LOX), leading in turn to the hydroxyeicosatetraenoic acids 5-HETE and 12-HETE. The inhibitors MK886 and baicalein prevent the activity of 5-LOX and 12-LOX, respectively.

**Fig. 4.** Inhibitors of key enzymes of the AA pathway. The enzyme cPLA2-α liberates AA from the plasma membrane. The release of AA can be tumorigenic leading to activation of AKT. However, this enzyme can be inhibited by Efipladib (see insert for structure) (Ni et al., 2006). The AA can also be metabolized further by COX-1 and -2, leading to prostanoids (e.g., PGE2). COX-1 and -2 inhibitors are well known and include celecoxib. Liberated AA can also be acted upon by 5-lipoxygenase (5-LOX) or 12-lipoxygenase (12-LOX), leading in turn to the hydroxyeicosatetraenoic acids 5-HETE and 12-HETE. The inhibitors MK886 and baicalein prevent the activity of 5-LOX and 12-LOX, respectively.


