Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Targeting PI3K/Akt/mTOR signaling pathway in the treatment of prostate cancer radioresistance

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Contents

ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form 20 May 2015
Accepted 8 July 2015

Keywords:
Prostate cancer
Radiation therapy
Radioresistance
Inhibitors
PI3K/Akt/mTOR

ABSTRACT

The phosphatidylinositol-3-kinase/Akt and the mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is one of the most frequently activated signaling pathways in prostate cancer (CaP) and other cancers, and responsible for the survival, metastasis and therapeutic resistance. Recent advances in radiation therapy indicate that activation of this pathway is closely associated with cancer radioresistance, which is a major challenge for the current CaP radiation treatment. Therefore, targeting this pathway by inhibitors to enhance radiosensitivity has great potential for clinical benefits of CaP patients. In this review, we summarize the recent findings in the PI3K/Akt/mTOR pathway in CaP radiotherapy research and discuss the potential use of the PI3K/Akt/mTOR pathway inhibitors as radiosensitizers in the treatment of CaP radioresistance in preclinical studies to explore novel approaches for future clinical trials.

1. Introduction

Prostate cancer (CaP) remains a significant medical burden in developed countries and accounts for estimated 94,000 deaths in Europe and 28,170 in the United States in 2012 (Siegel et al., 2012). Around 70% of these patients present with organ-confined disease, with the majority presenting with low- or intermediate-risk CaP (Jemal et al., 2011). For localized CaP, radical prostatectomy (RP) and radiation therapy (RT) are the two main treatment options. RT including external beam radiation therapy (EBRT) and radioactive isotopes such as brachytherapy is a relatively effective therapeutic modality for clinically-localized CaP. Although radiation has been serving as an indispensable component of therapy for CaP patients, radioresistance is a major problem in RT which occurs in almost one third of CaP patients under curative dosage (Lam and Belldegrun, 2004). RT dose escalation techniques have been used to counteract radioresistance. However, further dose escalations to 82 Gy in a

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http://dx.doi.org/10.1016/j.critrevonc.2015.07.005
1040-8428/

phase II trial for localized CaP yielded significant acute and late morbidity (Coen et al., 2011). Although three dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) and image guide radiation therapy (IGRT) can increase dose to local CaP and improve control rate (Horwitz and Hanks, 2000), the clinical outcomes indicate these advanced approaches cannot completely overcome radioresistance in CaP (Vora et al., 2013). Radiosensitizers enhance tumor-specific DNA damage by inhibiting major signaling and repair pathways in tumor cells and thus facilitate tumor cell death (Mukherji et al., 2012). Therefore it is critical to investigate the mechanisms of specific signaling pathways that impact the radiosensitivity; and to develop novel treatment approaches to overcome recurrence after RT in CaP patients.

The phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway regulates cell growth and proliferation and is often dysregulated in cancer due to mutation, amplification, deletion, methylation and post-translational modifications. This pathway is an intracellular signaling pathway important for apoptosis, malignant transformation, tumor progression, metastasis and radioresistance (Ni et al., 2013; Chang et al., 2013). Phosphatase and tensin homolog (PTEN) is a negative regulator of PI3K/Ak/mTOR pathway (Chang et al., 2014a). PTEN is a highly effective tumor suppressor and frequently mutated, deleted, or epigenetically silenced in various human cancers including CaP (Sircar et al., 2009; de Muga et al., 2010). Due to the important role of the PI3K/Akt/mTOR pathway in cancer research, many valuable inhibitors targeting one signaling node (single inhibitor) or two nodes at the same time (dual inhibitor) in the pathway have been developed in recent years. In the last decade, significant progresses have been made in developing combination therapy with PI3K/Akt/mTOR inhibitor (as radiosensitizers) and RT to overcome CaP radioresistance in preclinical studies.

Here we discuss the recent progress in studying roles of PI3K/Akt/mTOR pathway in CaP radiotherapy, and mainly focus on the effect of single or dual inhibitors targeting this signaling pathway in the treatment of CaP to improve radiosensitivity in preclinical studies using cancer cell lines and animal models for future clinical trials.

2. The structure of PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR signaling pathway is implicated in a diverse array of cellular functions including survival, growth, proliferation, differentiation, stem cell-like properties, metabolism, and angiogenesis. Based on primary structure, regulation, and *in vitro* lipid substrate specificity, the PI3K family is divided into three different classes: Class I, Class II, and Class III (Leevers et al., 1999). Class I PI3K are heterodimeric molecules composed of a regulatory (p85) and a catalytic subunit (p110) which are further divided into two subclasses: subclass IA (PI3Kα, β and δ) which is activated by receptor tyrosine kinases (RTKs) and subclass IB (PI3Kγ) which is activated by G-protein-coupled receptors and rat sarcoma (RAS) oncogene. Class II and Class III are differentiated from Class I PI3K by their structure and function. Class II comprises three catalytic isoforms (C2α, C2β, and C2γ) and catalyzes the production of PI(3)P from PI and PI(3,4)P2 from PIP, whereas Class III exists as a heterodimer of a catalytic (Vps34) and a regulatory (Vps15/p150) subunits and produces only PI(3)P from PI (Leevers et al., 1999). PI3K serves to phosphorylate a series of membrane phospholipids including phosphatidylinositol 4-phosphate (PI(4)P) and phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2), catalyzing the transfer of ATP-derived phosphate to the D-3 position of the inositol ring of membrane phosphoinositides, thereby forming the second messenger lipid phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) (Martelli et al., 2011). PI(3,4,5)P3 then recruits a subset of signaling proteins with pleckstrin homology (PH) domains to the membrane, including 3-Phosphoinositide-dependent protein kinase-1 (PDK1) and Akt/PKB (Fresno Vara et al., 2004; Fruman et al., 1998). Akt/PKB then regulates several cellular processes including survival and cell cycle. Chen et al. found that activation of Akt/PKB is associated with an increased resistance to apoptosis in CaP mediated by TRAIL/APO-2L (Chen et al., 2001).

PI3K activates a number of downstream targets including the serine/threonine kinase Akt which activates mTOR. Akt is composed of three structurally similar isoforms, Akt1, Akt2 and Akt3, which are encoded by the genes PKBα, PKBβ and PKBγ, respectively. They consist of three domains, an N-terminal PH domain, a central kinase CAT domain, and a C-terminal extension with a hydrophobic motif. The activating process of Akt includes docking of the PH domain to PI(3,4,5)P3 on the membrane and phosphorylation of two crucial amino-acid residues (Stephens et al., 1998; Alessi et al., 1997). Once Akt is phosphorylated and activated, it phosphorylates many other downstream proteins such as mTOR, GSK3, IRS-1 (Porta et al., 2014), whereby playing a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, cell migration and therapeutic resistance (Manning and Cantley, 2007).

As a Akt substrate and having the most significant role in tumorigenesis, mTOR is a seine/threonine protein kinase that plays an important role in the regulation of cell growth, proliferation, motility, survival, protein synthesis, and transcription (Hay and Sonenberg, 2004). mTOR has two structurally distinct complexes mTORC1 and mTORC2 which both localize at different subcellular compartments, thus affecting their activation and function (Wullschleger et al., 2006; Betz and Hall, 2013). mTORC1 is composed of the mTOR catalytic subunit, raptor, PRAS40 and the protein mLST8 (Wullschleger et al., 2006). The activity of mTOR1 is stimulated by insulin, growth factors, serum, phosphatidic acid, amino acids (particularly leucine), and oxidative stress (Kim et al., 2002; Fang et al., 2001). Depending on the stimuli and microenvironment, mTORC1 controls the cell growth through phosphorylation of S6K and 4E-BP1 (Sparks and Guertin, 2010). mTORC2 is composed of mTOR, Sin1, rictor and the protein mLST8 (Sabatini, 2006). It is less sensitive to rapamycin and it phosphorylates Akt/PKB at the serine residue S473, thus affecting metabolism and survival (Betz et al., 2013). mTOR activation results in an increased level of multiple proteins such as cyclin D1 (Grewe et al., 1999) and vascular endothelial growth factor (VEGF) (Abraham, 2004), leading to upregulated tumourigenesis.

PTEN, the gene for which is located on chromosome l0q23, is a PI(3,4,5)P3 phosphatase which antagonizes the PI3K/Akt/mTOR signaling pathway by dephosphorylation of PI(3,4,5)P3 to PI(3,4)P2. The PTEN phosphatase serves at the molecular level to counteract the functions of PI3K, which promotes proliferation and cell survival, in part through activation of mTOR (Sansal and Sellers, 2004). In addition, through the signaling pathway net, the PI3K/Akt/mTOR pathway is closely linked with other pathways such as androgen receptor (AR) pathway (Lin et al., 2001), Ras/Raf/MEK/ERK pathway (De Luca et al., 2012) for cancer survival, metastasis, progression and resistance (De Luca et al., 2012). The structure of the PI3K/Akt/mTOR pathway and the link with other pathways are shown in Fig. 1.

3. Activation of PI3K/Akt/mTOR pathway in human CaP progression

Activation of the PI3K/Akt/mTOR pathway has been strongly implicated in CaP progression (Taylor et al., 2010; Reid et al., 2010). Preclinical studies suggest that the PI3K/Akt/mTOR pathway is

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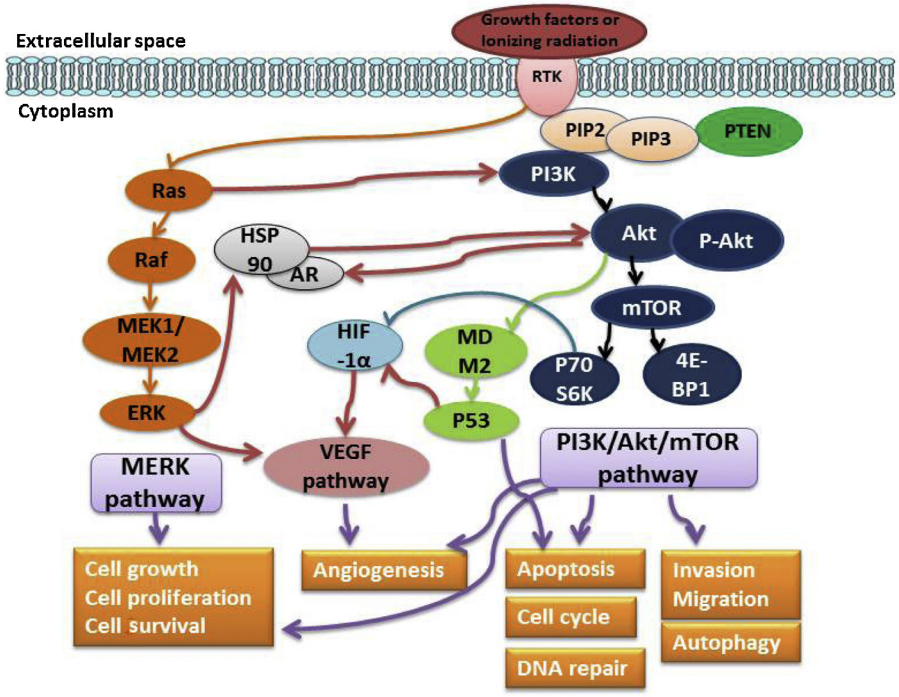

Fig. 1. PI3K/Akt/PTEN/mTOR signaling pathway. This pathway plays a crucial role in regulating a broad range of cellular functions including cell growth, proliferation, cell survival, angiogenesis, invasion and migration, apoptosis, autophagy, cell cycle, DNA repair, chemoresistance and radioresistance in cancer cells. PI3K converts PIP2 into PIP3, while PTEN antagonizes PI3K function by converting PIP3 back to PIP2, and thus inhibiting downstream signaling. Akt, which is the downstream in the pathway, is activated and phosphorylated by PIP3 which subsequently causes alteration of numerous cell functions including the activation of mTOR and its substrates. This pathway is closely linked with Ras/Raf/Mek/Erk pathway, AR pathway and VEGF pathway. AR: androgen receptor; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-3-kinase; PTEN: phosphatase and tensin homolog; RTK: receptor tyrosine kinase.

important in maintaining a cancer stem cell (CSC) population in CaP cells. It was demonstrated that activation of Akt signaling in CaP induces a TGFβ-mediated restraint on cancer progression and metastasis in transgenic animal models (Bjerke et al., 2013). In particular, it has been suggested that CRPC compensate for reduced AR signaling by activation of Akt/mTOR signaling (Floc'h and Abate-Shen, 2012).

Morgan et al. demonstrated that the aberrant PI3K/Akt signaling proteins were detected in CaP cell lines and xenografts as well as 30–50% of human primary CaP tissues (Morgan et al., 2009). Taylor et al. found that alterations in the PI3K/Akt/mTOR pathway have been found in 42% of primary prostate tumors and 100% of metastatic tumors (Taylor et al., 2010). Clinical CaP specimens were also reported to show up-regulation of the PI3K/Akt pathway associated with phosphorylation of the AR during the development of CRPC (McCall et al., 2008). PI3K activation can also lead to the development of chemoresistant CaP cells, through the up-regulation of multidrug resistance protein 1 (MRP-1) (Lee et al., 2004). Teng's study indicated that 42% of CaP tissues had abnormal PTEN/Akt expression (Teng et al., 1997). Using antibodies against Akt, PTEN, its downstream targets and the respective phosphorylated proteins, Jendrossek et al. demonstrated that up-regulated expression and phosphorylation of Akt (p-Akt) in the CaP tissues was found in 78% and 82% of patients, respectively, and in patients with Gleason scores of ≥6, the numbers were even higher (84% and 100%, respectively). PTEN expression levels of cancer cells relative to adjacent benign cells were diminished in only 20% of the CaP tissues compared with benign tissues, and the rate was 30% in those with Gleason scores of ≥6, while the expression level of p-Akt was elevated without obvious abrogation of PTEN-function in a proportion of the patients (Jendrossek et al., 2008). These data suggest both PTEN-dependent and PTEN-independent mechanisms of Akt-activation in localized CaP and demonstrate the important role of deregulation of the PI3K/PTEN/Akt pathway in localized CaP. Additional data also demonstrated that loss of PTEN expression was correlated with Gleason score and pathologic stage of primary tumors (McMenamin et al., 1999; Dreher et al., 2004) and increased the incidence of development of lymph node metastases (Schmitz et al., 2007).

It was reported that the levels of mTOR and cytoplasmic phospho-mTOR were greater in CaP tissue *versus* normal prostatic epithelium, with mTOR levels in cancer cells were twice than that of benign tissue (Kremer et al., 2006). 4E-BP1 and S6 also showed higher levels in CaP *versus* normal cells (Kremer et al., 2006). These results support that the PI3K/Akt/mTOR pathway plays a prominent role in the development and progression of CaP.

4. PI3K/Akt/mTOR pathway in CaP radioresistance

Radioresistance is a major problem in radiation oncology and can be classified into intrinsic radioresistance and acquired resistance during fractionated RT. Accumulating evidence indicate that a broad variety of the microenvironmental conditions surrounding CSC niches as well as genetic and epigenetic changes of CSC during tumor development make molecular mechanisms of radioresistance dynamic in nature (Rycaj and Tang, 2014; Kreso and Dick, 2014). Understanding the mechanisms and signaling pathways in the regulation of radioresistance is very important in developing combination approaches to overcome radioresistance. With fast development in biomedical research using modern advanced techniques such as genomics and proteomics, significant progresses have been made in the investigation of radioresistance associated pathways. Among the identified pathways, the PI3K/Akt/mTOR pathway is mostly investigated.

Skvortsova et al. established three radioresistant CaP cell lines from PC-3, DU145 and LNCaP and found higher levels of AR and

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epidermal growth factor receptor (EGFR) were detected in the RR cell lines compared with the parental cell lines, accompanied by the activation of their downstream pathways including Ras-mitogen-activated protein kinase (MAPK) and PI3K/Akt and Jak/STAT (Skvortsova et al., 2008), suggesting the PI3K/Akt/mTOR signaling pathway contributes to CaP radioresistance. It has been reported that the PI3K/Akt activity contributes to the resistance of human cancer cells to ionizing radiation *via* three major mechanisms: intrinsic radioresistance, tumor-cell proliferation and hypoxia. PI3K/Akt/mTOR pathway is very important for tumor angiogenesis. Tumor hypoxia was found to be involved in cancer cell aggressiveness and radioresistance which can cause poor clinical outcome (Hennessey et al., 2013). It was reported that hypoxia cells could be more resistance to radiation than normal cells in CaP (Hennessey et al., 2013). Hypoxia-inducible factor 1 (HIF-1) is a transcriptional activator that functions as a master regulator of O2 homeostasis (Semenza, 2002). HIF-1 target genes encode proteins including VEGF and activation of the PI3K/Akt pathway in tumor cells can also increase VEGF secretion by HIF-1 (Karar and Maity, 2011). CaP cells have been shown to overexpress HIF-1α and VEGF in a PI3K-dependent manner as a result of EGFR signaling. In addition, radiation can enhance EGFR expression, which in turn, stimulates HIF-1α expression, increasing radioresistance in CaP (Zhong et al., 2000). Hennessey et al. suggested that the effect of post-irradiation hypoxic exposure correlates with modified cellular responses induced by hypoxia which was mediated by HIF-1α in CaP cells (Hennessey et al., 2013). Another study reported that targeting the PI3K pathway using LY294002 or rapamycin inhibited the expression of HIF-1 dependent reporter gene induced by the certain nitric oxide (NO) donor (Kasuno et al., 2004). All these studies indicate that activation of the PI3K/Akt/mTOR signaling may be associated with HIF1-dependent hypoxia mechanisms in CaP-RR cells. In addition, hypoxia may also assist to create a microenvironment enriched in poorly differentiated tumor cells and undifferentiated stromal cells, which appears to play an important role in tumor cell differentiation (Kim et al., 2009). It has been shown that tumor metastasis, survival and self-renewal could be promoted by hypoxia *via* inducing expression of stem cell genes such as CXCR4 (Hermann et al., 2007). Furthermore, hypoxia could regulate maintenance and differentiation of stem cells *via* directly preventing CSCs from undergoing differentiation, inhibiting niche stromal cells differentiation and inducting expression of paracrine factors (Kim et al., 2009). Thus, hypoxia could be considered as a factor reducing CaP sensitivity to radiation and one of the major sources of CSCs. Using a label-free quantitative liquid-chromatography/tandem-mass spectrometry (LC–MS/MS) proteomic approach, we have identified the PI3K/Akt/mTOR signaling pathway proteins as the most activated pathway associated with radioresistance in three CaP RR cell lines (PC-3RR, DU145RR and LNCaPRR) developed in our lab (unpublished data), further confirming the importance of this pathway in CaP radioresistance.

The CSC concept is becoming a hot research spot in studying cancer radioresistance as the CSC model provides a plausible account for poorly understood clinical phenomena, such as chemo/radioresistance. CSCs are malignant cell subsets capable of tumor initiation and self-renewal, which give rise to bulk populations of non-tumorigenic cancer cell progeny through differentiation (Zhou et al., 2009). CSCs embody the refractory nature observed among many cancers: very competent initial establishment, extremely aggressive metastatic nature, resistance to chemo-/radiotherapy, correlation with advanced disease and resistance to current therapies. Therefore, if CSCs survive after anti-cancer treatment, recurrence and metastasis are expected due to the ability of these cells to give rise to new tumors. There is considerable evidence to suggest that, under certain experimental conditions, CSCs exhibit RR features (Eyler and Rich, 2008). Martelli et al. recently reviewed the evidence which links the signals deriving from the PI3K/Akt/mTOR network with CSC biology and highlighted how therapeutic targeting of PI3K/Akt/mTOR signaling with small molecule inhibitors could improve cancer patient outcome, by eliminating CSCs (Martelli et al., 2011). It was reported that $CD133^{high}/CD44^{high}$ CSCs expressing in colon cancer cells are associated with Akt and increased radiation resistance, that different Akt isoforms have varying effects on the expression of CSC markers (Sahlberg et al., 2014). Dubrovska et al. demonstrated that the PTEN/PI3K/AKT/mTOR pathway is critical for the *in vitro* maintenance of $CD133^{+}/CD44^{+}$ CaP progenitors and that the combination of the PI3K/mTOR modulator BEZ235 targeting CaP progenitor populations and the chemotherapeutic drug Taxotere can more effectively eradicate tumors in a CaP xenograft model than monotherapy (Dubrovska et al., 2010), indicating the importance of CSC and PI3K/Akt/mTOR pathway in the CaP treatment. We have demonstrated the siRNA knock down of CSC markers CD326 and CD44v6 can increase radiosensitivity in CaP cells *via* the PI3K/Akt/mTOR signaling pathway (Ni et al., 2013, 2014), suggesting the importance of this pathway in the regulation of CaP radioresistance. Under a low dose radiation treatment, we have recently developed three CaP-RR cell lines which display more aggressive characteristics including increased colony formation, invasion ability, sphere formation capability and enhanced epithelial mesenchymal transition (EMT) and CSC phenotypes (Fig. 2) and activation of the PI3K/Akt/mTOR signaling pathway (Fig. 3) (Chang et al., 2013). In addition, we also found the PI3K/Akt/mTOR pathway is closely linked with EMT and CSCs (Chang et al., 2013). Therefore, these CaP-RR cells, representative of the possible source of recurrence after RT, provide a very good model to mimic a clinical radioresistance condition as well as to examine the efficacy of these single and dual PI3K/Akt/mTOR inhibitors for their radiosensitization effects. The treatment of CaP with combination of single or dual PI3K/Akt/mTOR inhibitors with RT will be discussed in detail in the following sections.

5. PI3K/Akt/mTOR pathway inhibitors as radiosensitizers in the treatment of CaP

PI3K/Akt/mTOR signaling pathway plays an important role in CaP radioresistance. Currently, numerous small molecular drugs that target single PI3K, Akt or mTOR signaling proteins (single inhibitor) or target both PI3K and mTOR signaling proteins at the same time (dual inhibitor) have been developed for preclinical studies and clinical trials for cancer treatments. The ability of molecular targeting the various drivers of PI3K/AKT/mTOR pathway activation allows reversal of resistance to upstream therapy, such as anti-EGFR treatment and other receptor tyrosine kinase (RTK)-targeted therapies. In this section, we only focus on combination of a PI3K/Akt/mTOR inhibitor with RT in the treatment of CaP in preclinical studies. The different inhibitors targeting different PI3K/Akt/mTOR pathway proteins are shown in Fig. 4. The approaches using combination of different pathway inhibitors with RT in preclinical studies are summarized in Table 1.

5.1. PI3K inhibitors

LY294002 and wortmannin are both well-studied PI3K inhibitors. While LY294002 is a reversible pan-PI3K inhibitor, wortmannin acts irreversibly. LY294002 is the first synthetic molecule known to inhibit PI3α/β/δ and also blocks autophagosome formation. LY294002 resulted in cell-cycle arrest of LNCaP CaP cells and sensitized the cell line to ionizing radiation through inactivation of PKB (Gottschalk et al., 2005). It was also reported that the combination of LY294002 and radiation resulted in

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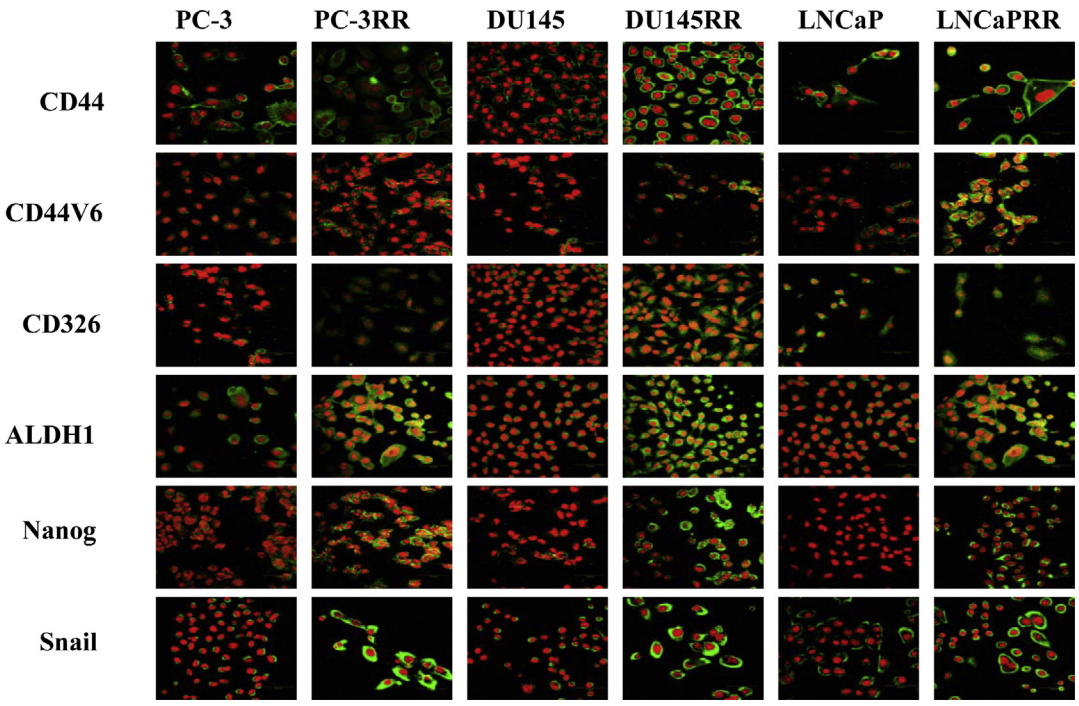

Fig. 2. CSC phenotypic expression in CaP-RR and CaP-control cells. The enhanced CSC phenotypes were seen in CaP-RR (PC-3RR, DU145RR and LNCaPRR) cells. Representative immunofluorescence images of membranous or cytoplasmic expression of CD44, CD44v6, CD326, ALDH1, Nanog and Snail (CSC markers) are shown in CaP-RR and CaP-control cells. Green indicates positive staining for CSC markers. Nuclei were stained with PI (red). Magnification ×600 in all images. RR: radioresistance. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

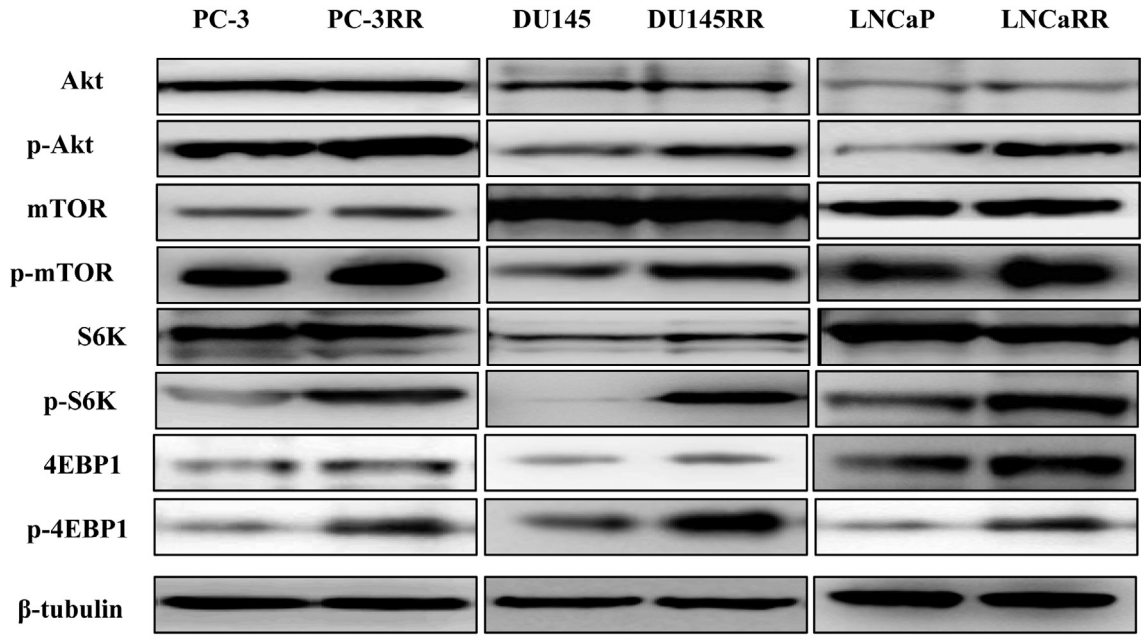

Fig. 3. CaP-RR cells activate PI3K/Akt/mTOR pathway. Eight signal transduction molecules (mTOR, p-mTOR, Akt, p-Akt, 4EBP1, p-4EBP1, S6K, p-S6K) were assessed to investigate the roles of the PI3K/Akt/mTOR signaling proteins in CaP radioresistance. The levels of p-Akt, p-mTOR, p-S6K and p-4EBP1 were increased in CaP-RR cells compared to CaP-control cells while no change was found in total of Akt, mTOR, S6K and 4EBP1 proteins in both CaP-RR and control cells. p-mTOR: phosphorylated-mTOR; p-Akt: phosphorylated-Akt; p-4EBP1: phosphorylated-4EBP1; p-S6K: phosphorylated-S6K; RR: Radioresistant.

significant and synergistic reduction in clonogenicity and growth delay, and has a synergistic enhancement effect in bladder cancer cell lines (Gupta et al., 2003). However, Kim reported that LY294002 did not affect the radiosensitization in human prostate epithelial 267B1/K-ras cells (Kim et al., 2005), suggesting that the radiosensitization effect of this inhibitor depends on cell type.

Wortmannin, a microbial product, is another potent irreversible pan-PI3K inhibitor. It displays a similar potency *in vitro* for the class I, II, and III PI3K members although it can also inhibit other PI3K-related enzymes such as mTOR, DNA-PK, some phosphatidylinositol 4-kinases, myosin light chain kinase (MLCK) and mitogen-activated protein kinase (MAPK) at high concentrations

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Table 1
Pre-clinical studies using combination of RT and PI3K/Akt/mTOR pathway inhibitors in CaP radiotherapy.

Agent	Target	Manufacturer	Radiotherapy	Experimental model	Reference
LY294002	Class I PI3K	Cell Signalling	2, 4, 6 Gy	LNCaP	Gottschalk et al. (2005)
LY294002	Class I PI3K	Cell Signalling	2, 5, 10 Gy, single dose	PC-3, DU145, LNCaP	Rudner et al. (2010)
Wortmannin nanoparticles	Class I PI3K	Sigma–Aldrich and LC Laboratories	2, 4, 6, 8 Gy, single dose	PC-3	Karve et al. (2012)
Wortmannin	Class I PI3K	Sigma Chemical Co.	2 Gy	PC-3, DU145	Rosenzweig et al. (1997)
BKM120	Class I PI3K	Selleck Chemicals	6 Gy	PC-3RR, DU145RR, LNCaPRR	Chang et al. (2014b)
Erufosine	Akt	Max Planck Institute of Biophysical Chemistry	2, 5, 10 Gy, single dose	PC-3, DU145, LNCaP	Rudner et al. (2010)
Perifosine	Akt	Selleck Chemicals	2, 4, 6, 8 Gy	CWR22RV1	Ishiyama et al. (2013)
Perifosine	Akt	Selleck Chemicals	2, 4, 6, 8 Gy 10 Gy in 2 fractions	CWR22RV1 CWR22RV1 subcutaneous (s.c.)	Gao et al. (2011)
Palomid 529	Akt	Paloma Pharmaceuticals	2, 4, 8 Gy	PC-3	Diaz et al. (2009)
			6 Gy, single dose	PC-3 s.c.	
Palomid 529	Akt	Paloma Pharmaceuticals	2, 4, 6 Gy	LNCaP, 22RV1, DU145, PC-3, LAPC-4, C4-2B	Gravina et al. (2014)
			4 Gy, single dose	PC-3, 22RV1, s.c.	
Rapamycin	mTOR	Sigma–Aldrich	^{177}Lu-RM2: 1850 kBq ^{177}Lu-RM2: 36, 72, 144 MBq in 6 fractions	PC-3 PC-3 s.c.	Dumont et al. (2013)
Rapamycin	mTOR	Selleck Chemicals	6 Gy	PC-3RR, DU145RR, LNCaPRR	Chang et al. (2014b)
Rapamycin, temsirolimus	mTOR	Calbiochem	2, 4, 6, 8 Gy	LNCaP, C4-2B, LAPC-4	Schiewer et al. (2012)
RAD001 (Everolimus)	mTOR	Novartis Pharmaceutical	5 Gy, single dose	DU145, PC-3	Cao et al. (2006)
NVP-BEZ235	PI3K, mTOR	Cayman	2 Gy, single dose	PC-3-RR, DU145-RR, LNCaP-RR	Chang et al. (2013)
NVP-BEZ235	PI3K, mTOR	Novartis Pharmaceutical	2, 4, 6 Gy, hypoxia	PC-3, DU145	Potiron et al. (2013)
			12 Gy in 3 fractions, hypoxia	PC-3 s.c.	
NVP-BEZ235	PI3K, mTOR	Novartis Pharmaceutical	2, 4, 8 Gy	PC-3	Zhu et al. (2013)
NVP-BEZ235	PI3K, mTOR	Cayman Chemical	6 Gy	PC-3RR, DU145RR, LNCaPRR	Chang et al. (2014b)
PI103	PI3K, mTOR	Cayman Chemical	6 Gy	PC-3RR, DU145RR, LNCaPRR	Chang et al. (2014b)

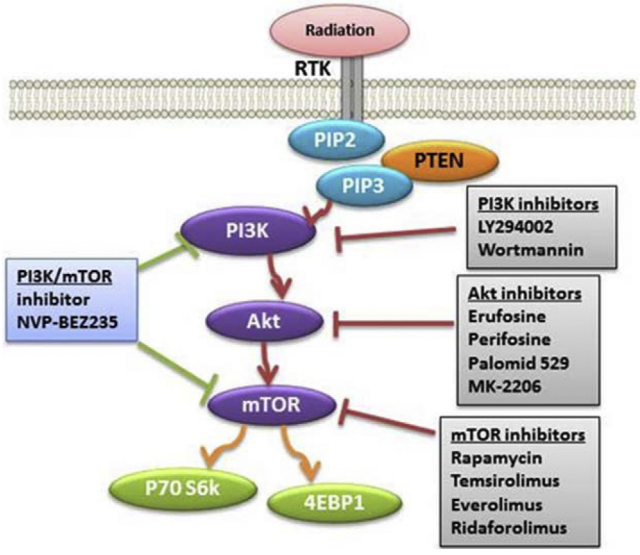

Fig. 4. Overview of the PI3K/Akt/mTOR pathway inhibitor targets. All the listed single or dual pathway inhibitors have been used in preclinical studies as radiosensitizers. The details of combination treatments with these inhibitors and RT are summarized in Table 1. mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-3-kinase; PTEN: phosphatase and tensin homolog.; RTK: receptor tyrosine kinase.

(Vanhaesebroeck et al., 2001). This inhibitor could induce apoptosis and radiosensitize DU145 CaP cells (Lin et al., 1999; Seol et al., 2005). Rosenzweig reported that the radiosensitivity was significantly increased in wortmannin-treat PC-3 and DU145 CaP cells due to inhibition of cellular DNA-PK (Rosenzweig et al., 1997). Unfortunately, *in vivo* use of both, LY294002 and wortmannin, has accompanied with adverse effects. LY294002 lacked favorable pharmacological properties and had many off-target effects (Prawettongsopon et al., 2009). It was reported that LY294002 could cause severe respiratory depression and lethargy in mice (Gupta et al., 2003), and wortmannin has been ruled out for a viable drug target due to its chemical instability and toxic side effects (Howes et al., 2007).

NVP-BKM120 (BKM120), a 2,6-dimorpholino pyrimidine derivative, is a novel, potent, and highly selective pan-class I PI3K inhibitor. In preclinical studies it has been shown to be active in suppressing proliferation and inducing apoptosis of cancer cell lines and in inhibiting the growth of human tumor xenografts in mice at tolerated doses (Maira et al., 2012; Koul et al., 2012). Abazeed et al. reported that BKM120 decreased NRF2 protein levels and sensitized NFE2L2 or KEAP1-mutant squamous cell lung cancer cells to radiation and the resulting analysis of identified pathways implicated in cell survival, genotoxic stress, detoxification, and innate and adaptive immunity as key correlates of radiation sensitivity (Abazeed et al., 2013). Our data showed that BKM120 can sensitize CaP-RR cells developed in our lab (Chang et al., 2014b). Phase I clinical trials showed that BKM120 was well

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tolerated (Rodon et al., 2014) and showed preliminary activity in patients with advanced tumors while phase II and III clinical trials are still ongoing.

Aside from pan-PI3K single inhibitors with relatively high incident of adverse effects, an alternative strategy is targeting specific PI3K p110 isoforms because of the different roles they play in the tumor development, which might lead to improved side effect profile. For example, p110β is necessary for tumorigenesis driven by PTEN loss that is associated with aggressive and radioresistant characteristics of advanced CaP (Lee et al., 2010), to this end, a very novel p110β inhibitor GSK2636771 is in Phase I clinical trial now (NCT01458067). Given the high prevalence of PTEN loss in CaP, isoform-specific inhibitors may be promising in targeting PI3K and treating CaP to overcome radioresistance.

Moreover, to the best of our knowledge, there has been no report about combination therapy of PI3K inhibitors and radiation in CaP management in clinical trials yet. Given our preliminary data that BKM120 sensitizes CaP cells *in vitro*, it also provides us with a guideline for development of new therapeutic strategies.

5.2. Akt inhibitors

As a major regulator of the PI3K pathway, Akt is a target for radiosensitization. Palomid 529 (P529) is a novel and potent Akt inhibitor without *in vivo* toxicity (Xue et al., 2008). Diaz et al. reported that P529 combined with RT could increase radiosensitivity in PC-3 CaP cells *in vitro* compared to RT alone, and retard tumor growth in a PC-3 xenograft animal model (Diaz et al., 2009). It was also demonstrated that P529 combined with RT induced more apoptosis and DNA double strand break (DSB) resulting in cellular radiosensitization and growth delay of PC-3 and 22RV1 s.c. tumor xenografts. The radiosensitizing properties of P529 were partially linked to delayed DSB repair, partially to GSK-3β, cyclin-D1, and c-myc modulation with associated inhibition of CRM1-mediated nuclear export of survivin. Importantly, autophagy and tumor senescence were also involved (Gravina et al., 2014). Moreover, besides Akt, P529 also targeted pathways involving VEGF, Id-1, MMP-9, MMP-2, and Bcl-2/Bax (Gravina et al., 2014). The ability to act at different pathway levels makes this compound a promising agent that might limit the possible tumor escaping routes. A new compound erucylphospho-N,N,N-trimethylpropanolamine (erufosine, ErPC3) is an Akt inhibitor with the cytotoxic action and was synthesized by H. Eibl, Max Planck Institute of Biophysical Chemistry (Goettingen, Germany). It was reported that combination of ErPC3 with RT can induce higher levels of radiation-induced apoptotic cell death in PC-3, DU145 and LNCaP CaP cells compared with the individual treatment (Rudner et al., 2010).

Perifosine is an orally applicable alkylphosphocholine analog which is an effective Akt inhibitor with antitumorigenic activity and radiosensitizing properties in preclinical models (Vink et al., 2006a).

Based on its favorable properties, this drug is considered to be a promising candidate for combination therapy with RT (Belka et al., 2004). Gao et al. reported that perifosine enhances radiosensitivity in CWR22RV1 CaP cell line, as well as in s.c. mice models *in vivo*, and phosphorylation of Akt was suppressed in the treatment process (Gao et al., 2011). These data provided us a strong support for further development of combination therapy in clinical studies. The results of several Phase II clinical trials of perifosine failed to show significant therapeutic response in the management of CaP when used as a single agent (Chee et al., 2007; Posadas et al., 2005). However, in a Phase I study where one advanced CaP patient was recruited, Vink et al. reported that the CaP patient achieved a partial response with a combination therapy of perifosine and fractionated external beam irradiation (Vink et al., 2006b), and overall it is well tolerated by patients at a dose of up to 150 mg/kg p.o. Other potential targets of perifosine in radiosensitization may include stimulation of the SAP/JNK pathway and inhibition of the MAPK/ERK pathway (Zhou et al., 1996). Therefore, further studies need to be done to confirm other pathways involved in the antitumor effect of combined perifosine and radiation treatment of CaP. All data present indicate that Akt inhibitors are promising in combination therapies to enhance the sensitivity of RT in CaP treatment.

5.3. mTOR inhibitors

mTOR is an established therapeutic target and proof of principle that PI3K pathway can be successfully targeted for clinical use in CaP has been demonstrated by the development of rapamycin analogs that inhibit mTORC1 kinase (Sun, 2013). Rapamycin (sirolimus) is an immunosuppressive macrocylic lactone produced by *Streptpmyces hygroscopicus*. It was originally used to prevent organ transplant rejection. However, since the important role of mTOR was discovered in the process of tumorigensis and tumor progression, rapamycin has been investigated as a tumor suppressive agent. Rapamycin binds to immunophilin, FKBP-12, to generate an immunosuppressive complex which is able to inhibit mTOR and the G1 to S phase transition (Heavey et al., 2014). The capability in alteration on cell cycle of rapamycin suggests its potential role in radiosensitivity. Schiewer et al. demonstrated that mTOR is a selective effector of the RT response in AR-positive CaP, and mTOR inhibitors (sirolimus and temsirolimus) exhibit schedule-dependent effects on the RT response in CaP cells and confer significant radiosensitization effects when used in the adjuvant setting (Schiewer et al., 2012). Dumont et al. reported that combination of rapamycin treatment with 37 MBq of ^{177}Lu-RM2 led to significantly longer survival than with either agent alone (Dumont et al., 2013), making it a great candidate for improving the efficacy of RT whilst decreasing the dosage to prevent adverse effects of RT.

RAD001, also known as everolimus, is a derivative of sirolimus with a similar mechanism as a mTOR inhibitor, inhibiting mTORC1 while exerting no effect on mTORC2. Cao et al. tested the ability of RAD001 to enhance the effects of radiation on two CaP cell lines, PC-3 and DU145, and found that both cell lines became more vulnerable to irradiation after treatment with RAD001, with the PTEN-deficient PC-3 cell line showing greater sensitivity (Cao et al., 2006). There is also an ongoing Phase I trial on RAD001, combined with castration therapy, to treat patients with high-risk locally advanced CaP undergoing EBRT (NCT02106507).

Following the pre-clinical studies and early-stage investigation of these mTOR inhibitors in clinical trials, there was a certain level of disappointment, regarding both drug tolerance and clinical outcomes. Both rapamycin and RAD001, along with other tacrolimus, are associated with severe side effects such as dyslipidemia, lung toxicity, and renal toxicity since they are originally used as immunosuppressant (Zaza et al., 2014). Ridaforolimus is a novel non-drug analog of rapamycin, and Phase I trial in patients with advanced CaP showed that this drug is generally well-tolerated and has a boasted potent anti-tumor ability (Amato et al., 2012), indicating it holds promise for combination therapy with RT in the future.

Our recent observation also indicated that the radiosensitization effect in single mTOR inhibitor (rapamycin) is less effective than that in the combination with dual PI3K/mTOR inhibitors (BEZ235 or PI103) in CaP *in vitro* (Chang et al., 2014b). One reason could be that dual PI3K/mTOR inhibitors have a broader efficacy across more genotypes with proapoptotic effects identified in a wider range of cell lineages compared with agents targeting only one component of the pathway (Serra et al., 2008; Wallin et al., 2011). Another possible reason for dual PI3K/mTOR inhibitors inducing more radiosensitivity could be that dual inhibitors of PI3K and

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mTOR target the active sites of both holoenzymes, inhibiting the pathway both upstream and downstream of Akt, thus avoiding the problem of Akt activation following abolition of the mTORC1-S6K-IRS1 negative feedback loop, which is known to occur with single mTOR inhibitors (Serra et al., 2008).

5.4. Dual PI3K/Akt/mTOR inhibitors

With the further investigation of PI3K/Akt/mTOR inhibitors in CaP combination therapy, dual inhibitors are being paid more and more attention by researchers such as BEZ235, PI103 and GDC-0980. Here, we only discuss the combination of dual PI3K/mTOR inhibitors with RT in CaP therapy (see Table 1).

BEZ235 is a novel antitumor drug developed by Novartis Pharma, which functions as a dual PI3K/mTOR inhibitor (Maira et al., 2008). It has been shown to inhibit both PI3K (all four isoforms) and mTORC1/2, with increasing efficacy at halting PI3K pathway. BEZ235 displayed a statistically significant antitumor activity against PC-3M tumor xenografts and could avoid PI3K pathway reactivation (Maira et al., 2008). It was reported that BEZ235 induced cell death in a PTEN-independent manner, and selectively induced apoptotic cell death in the CaP cell line DU145, which harbors wild-type PTEN; however, in the PC-3 cell line, which is PTEN-null, treatment with BEZ235 resulted in autophagic cell death (Hong et al., 2014). Moreover, BEZ235 can lead to a decrease in the population of $CD133^+/CD44^+$ CaP progenitor cells *in vivo*, suggesting its great potency in suppressing CSC to overcome radioresistance (Dubrovska et al., 2010). Potiron et al. investigated the radiosensitization of BEZ235 in *in vitro* and *in vivo* using two CaP cell lines, PC-3 (PTEN(−/−)) and DU145 (PTEN(+/+)) under normoxic and hypoxic conditions and found that BEZ235 radiosensitized both cell lines under normoxia and hypoxia *in vitro* and enhanced the efficacy of RT on PC-3 xenograft tumors in mice without inducing intestinal radiotoxicity (Potiron et al., 2013). Zhu et al. also demonstrated that BEZ235 prominently improved the radiosensitivity of PC-3 CaP cells and sensitized tumor cells to irradiation *via* interruption of cell cycle progression and augmentation of cell apoptosis (Zhu et al., 2013). We have recently tested the combination treatment with BEZ235 and RT in CaP-RR (PC-3RR, DU145RR and LNCaPRR) cells and found that this combination can reduce the expression of p-Akt, p-mTOR, p-S6K and p-4EBP1 as well as EMT and CSC phenotypes, at the same time, greatly increase radiosensitivity and induce more apoptosis compared with single BEZ235 or RT treatment alone, indicating that BEZ235 could enhance radiosensitivity and overcome radioresistance in CaP-RR cells (Chang et al., 2013). In our following study, we further confirmed that the mechanisms of radiosensitization with this combination are associated with altering cell cycle distribution, reducing autophagy, suppressing non-homologous end joining (NHEJ) and homologous recombination (HR) repair pathways (Chang et al., 2014b).

BEZ235 was the first PI3K/mTOR inhibitor to enter clinical trials in 2006, and since then there have been 17 ongoing or completed clinical trials mainly combined with chemotherapy toward advanced solid tumors. From several Phase I studies, the orally administered drug was well tolerated and exerted strong antitumor activities. The preclinical results support that BEZ235 combined with RT holds promise for future clinical trials to overcome CaP radioresistance.

PI-103 is another multi-targeted PI3K and mTOR inhibitor which showed anti-proliferation activity against a range of human cancer cell lines *in vitro* as well as anti-tumor activity against tumor xenografts (Guillard et al., 2009). Remko Prevo et al. reported that PI-103 reduced radiation survival of tumor cells with Akt activation and combination treatment of PI-103 with radiation enhances the G2/M delay and increased radiosensitivity (Prevo et al., 2008). PI-103 potently inhibited proliferation and invasion of PC-3 CaP cells *in vitro* and exhibited therapeutic activity at well-tolerated doses (<15% weight loss) in a number of human tumor models including PC-3 prostate model. The recent findings from our team demonstrated that this dual PI3K/mTOR inhibitor has a similar radiosensitivity effect on CaP-RR cells as BEZ235, including altering cell cycle distribution, inducing apoptosis and reducing autophagy (Chang et al., 2014b). Although PI-103 has not been evaluated in the clinical trial due to poor 'drug-like' properties, it has served as a lead compound for other PI3K and mTOR selective inhibitors such as GDC-0941 (Folkes et al., 2008). The investigation of the effects of combination of BEZ235 or PI103 with RT in CaP-RR xenograft models is underway in our laboratory.

Currently, the dual PI3K/Akt/mTOR inhibitors have not been extensively used for combination with RT in CaP therapy. The mechanisms of the dual inhibitors as radiosensitizers are still unclear. In the future research, more efforts should be put in understanding how these new developed dual inhibitors improve radiosensitivity and reduce radiation dose to minimize the adverse effects.

Most of combination studies with PI3K/Akt/mTOR inhibitors and RT have been focused on preclinical studies and only very limited clinical trials were reported using such combination approach. Several side effects (including dysgeusia, hypercholesterolemia, hypertriglyceridemia, thrombocytopenia, neutropenia, thrombosis, dyspnea related to pulmonary embolus and fatigue) have been reported in cancer patients when PI3K or mTOR inhibitors (RAD001 or temsirolimus) were combined with radiation therapy (Sarkaria et al., 2010; Ma et al., 2014). Based on these preliminary observations, better therapeutic effects might be achieved by the optimization of the dosages of the PI3K/Akt/mTOR inhibitors and radiation.

6. Conclusions

Accumulating evidence from human CaP tissues and preclinical studies demonstrates that the PI3K/Akt/mTOR pathway plays a critical role in CaP progression and radioresistance *via* the activation of the pathway proteins or mutation, deletion, epigenetically silence of PTEN gene. CSCs are the "roots" of recurrence after RT, responsible for the CaP radioresistance and closely linked with the PI3K/Akt/mTOR pathway. Therefore, targeting the PI3K/Akt/mTOR pathway combined with RT could be useful in overcoming CaP radioresistance and improving radiosensitivity.

Preclinical studies with combination of PI3K/Akt/mTOR inhibitors with RT have demonstrated the enhanced radiosensitivity in CaP cell lines and animal models. However, the mechanisms of these inhibitors as radiosensitizers need to be further elucidated. Given that dual PI3K/mTOR inhibitor can target more active pathway proteins than a single inhibitor, these dual inhibitors can more effectively improve radiosensitivity and hold promise for future clinical trials.

Since the clinical trials in the treatment of CaP with PI3K/Akt/mTOR inhibitors are still in their early stages, it remains unclear what roles of these inhibitors will have in the care of patients with CaP. Based on the promising results from preclinical studies, future clinical trials with combination therapy of dual PI3K/mTOR inhibitors and RT should be considered, especially for those CaP patients with radioresistance.

Novel therapy concepts targeting the PI3K/Akt/mTOR pathway proteins with RT are currently being explored. Until recently, there were very few ongoing clinical trials available for CaP patients. Although RR cancer cell lines including CaP were developed and tested for radiation combination treatment, RR xenograft animal

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models are wanted to closely mimic clinical CaP RR conditions for the best testing the combination therapy with PI3K/Akt/mTOR pathway inhibitors and RT in future studies.

The PI3K/Akt/mTOR pathway is implicated in all major mechanisms of cancer therapeutic resistance including CaP. Emerging evidence suggests that PI3K/Akt/mTOR signaling pathway is associated with CSC, autophagy and glucose metabolisms in many cancers including CaP, contributing to cancer radioresistance. Further understanding the association of this pathway with CSC, autophagy, hypoxia response and glucose metabolisms will be very helpful in aiding to design innovative approaches to improve CaP radiosensitivity.

The PI3K/Akt/mTOR pathway is always linked with other signaling pathways such as Ras/Raf/MEK pathway, AR pathway or VEGF pathway (see Fig. 1) in promoting CaP radioresistance. The Ras/Raf/MEK pathway is involved in extensive cross-talk with the PI3K/Akt/mTOR pathway. ERK and RSK are two effector kinases downstream of Ras that can promote mTORC1 activity by phosphorylating TSC2 on residues that are distinct from Akt phosphor-acceptor sites, and activation of this pathway has been associated with decreased sensitivity to PI3K/Akt/mTOR pathway inhibitors. AR pathway plays a critical role in the development of CaP. There is significant cross-talk between PI3K/Akt/mTOR pathway and AR pathway which appears to impact on CaP through complex mutual communication mechanisms. In addition, activation of EGFR family members *via* PI3K/Akt/mTOR pathway is also associated with radioresistance by regulating HIF-1α and VEGF expression. Moreover, radiation can enhance EGFR activation which in turn increases radioresistance in cancer. As EGFR up-regulation is closely related to high Gleason score CaP, it may play an important role in CaP radioresistance. Therefore, future investigating the link between these associated signaling pathways and PI3K/Akt/mTOR pathway, and targeting these two pathways in the meantime may obtain more effective treatment than targeting either one pathway in CaP radioresistance which may hold promise to increase CaP radiosensitivity.

A variety of different PI3K/Akt/mTOR inhibitor classes have been developed over the last decades. Single PI3K/Akt/mTOR pathway inhibitors displayed many own demerits such as instability and toxic effect. More recently, dual PI3K/mTOR inhibitors have revealed potent antitumor effect in RT. However, currently, only BEZ235 is widely studied in preclinical investigations, with very limited reports in CaP radiation studies. Thus, more effective new PI3K/Akt/mTOR signaling pathway inhibitors are required in the future. Apart from the efforts put into developing new drugs with improved tolerability and efficacy, more attention should also be paid to alternative components in PI3K/Akt/mTOR rather than merely targeting PI3K, Akt or mTOR. For example, eIF4E and S6K, downstream effectors of mTORC1, could be useful targets for overcoming radioresistance. Furthermore, a better understanding of biology of targets, crosstalk and feedback will grant a passage for novel and effective PI3K/Akt/mTOR inhibitors development and investigation to overcome CaP radioresistance.

Conflict of interest

All authors have no conflicts of interest to declare.

Acknowledgements

Our prostate cancer research program was supported in part by NH&MRC Career Development Fellowship (630664), Cancer Care Centre Research Trust Fund, Urology Research Fund, Prostate and Breast Cancer Foundation, and China Scholarship Council. We appreciate support for Professor John Kearsley at Cancer Care Centre, St George Hospital (The Founder of Prostate Cancer Institute).

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Please cite this article in press as: L. Chang, et al., Targeting PI3K/Akt/mTOR signaling pathway in the treatment of prostate cancer radioresistance, Crit Rev Oncol/Hematol (2015), http://dx.doi.org/10.1016/j.critrevonc.2015.07.005

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Biographies

Dr Lei Chang is studying at the St George and Sutherland Clinical School, University of New South Wales, Sydney, Australia as a PhD candidate. Her current research project is to investigate the mechanisms of prostate cancer radioresistance and use combination therapy with small molecular inhibitors and radiotherapy to improve prostate cancer radiosensitivity. She has published 12 papers in peer-reviewed journals in cancer research area as the first author and co-author. In addition, she was awarded several travel grants, and scholarships from Prostate and Breast Cancer Foundation, Australia and Chinese Scholarship Council (CSC) for her excellent performance for her study.

Dr Peter Graham received his MB, BS, FRACS, FRANZCP and is currently a Senior Staff Specialist radiation oncologist at the St George Cancer Care Center and Associate Professor at the St George Clinical School, Faculty of Medicine, University of New South Wales. He is an expert in breast cancer and prostate cancer research. During the twelve years, he has established and expanded a substantial clinical research program that has enrolled over 4000 patients to a range of radiation oncology related phase I to III trials and surveys. This has involved cooperative participation in multicenter trials as well as development of single institution, state-based and national multicenter trials where St George is the lead institution.

Dr Jie Ni is studying at the St George and Sutherland Clinical School, Faculty of Medicine, University of New South Wales as a PhD candidate. His current research project is to investigate the EpCAM and CD44 isforms in prostate cancer progression and to develop innovative approaches to target CRPC. He has published 10 papers in peer-reviewed journals in cancer research area. He was awarded a travel grant, and scholarships from Prostate and Breast Cancer Foundation, Australia and Chinese Scholarship Council (CSC) for his excellent performance for his study.

Dr Jingli Hao received her Bachelor of Science at China Pharmaceutical University in 2006, China, Master of Science at University of New South Wales (UNSW) in 2008, Australia and PhD at UNSW in 2012, Australia. Dr Hao is a Postdoctoral Fellow (Hospital Scientist) at Cancer Care Center, St George Hospital and Conjoint Lecturer at St George and Sutherland Clinical School, UNSW. Her current research interests include (a) investigation of molecular mechanisms of prostate cancer radioresistance; (b) using combination approaches (radiosensitizers and radiotherapy) to perform preclinical studies to improve prostate cancer radiosensitivity; (c) investigation of novel biomarkers in cancer cell lines, animal models and human tumor tissues for prostate cancer therapeutic targets and prediction. She has published more than 10 papers in peer-reviewed journals in cancer research area as the first author and co-author. In addition, Dr Hao was awarded several travel grants and one new investigator grant.

Dr Joseph Bucci received his MBBS, FRACP, FRANZCR and is a Senior Radiation Oncology staff specialist at the St George Hospital Cancer Care Centre in Sydney, Australia. Dr Bucci was originally trained in prostate brachytherapy at the British Columbia Cancer Agency in 2000–2001 in Vancouver. His main practice is in the radiation treatment of urological malignancies. With his colleagues he has also established the first publicly funded prostate seed brachytherapy program in Sydney. He has a keen interest in Quality Assurance in Brachytherapy and is involved in a number research projects related to this.

Dr Paul Cozzi is an Associate Professor at University of Notre Dame Australia, Senior Lecturer at the UNSW and Senior Staff Specialist at St George Public Hospital. A/Prof Paul Cozzi graduated from UNSW in 1990. He completed his urology training and obtained the FRACS in 1999. He has a major interest in clinical and laboratory based cancer research and completed a Masters in Surgery in 1998. He obtained 2 years of fellowship training in Urologic Oncology at Memorial Sloan Kettering Cancer Care Center in New York, USA. Paul's expertise in prostate cancer treatment includes the latest techniques pioneering nerve sparing surgery with open and robotic surgery to optimize cure rates whilst maintaining erectile function. Paul has published widely including several landmark papers in international journals of excellence and book chapters with more than 100 peer reviewed publications to date. He is very active in research, under-graduate and post-graduate teaching, and serves on the editorial board of several medical journals including the Australian and New Zealand Journal of Surgery.

Dr Yong Li received his MD and MSc in Medicine at Zhengzhou University, China in 1987 and 1992, and his PhD. degree in Faculty of Medicine in 2000 from the UNSW, Sydney, Australia. He is an Associate Professor at UNSW, NHMRC Career Development Fellow, and Principal Scientific Officer of SESLHD and the Head of Cancer Research Program at St George Hospital. A/Prof Li' research program is aimed at (a) to investigate the mechanisms of cancer metastasis and drug/radio-resistance associated with tumor microenvironment, cancer stem cell and signaling pathways; (b) to use targeted cancer therapy and combination therapy to control cancer therapeutic resistance and metastasis; (c) to investigate novel biomarkers from human body fluids, cancer cell lines and cancer animal models for cancer diagnosis and monitoring cancer progression. A/Prof Li' laboratory employs cell and molecular biology techniques, modern proteomic techniques and metastatic animal model development as well as IVISÒ Imaging System for animal monitoring. These studies will help to provide new insights into the mechanisms of cancer metastasis, chemo-/radioresistance and identify novel biomarkers, which may lead to the development of novel therapies for the treatment of cancer progression. He has published over 80 research papers and book chapters in peer-reviewed journals.

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