

Mini review

MOLECULARLY TARGETING THE PI3K-Akt-mTOR PATHWAY CAN SENSITIZE CANCER CELLS TO RADIOTHERAPY AND CHEMOTHERAPY

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Abstract: Radiotherapy and chemotherapeutic agents that damage DNA are the current major non-surgical means of treating cancer. However, many patients develop resistances to chemotherapy drugs in their later lives. The PI3K and Ras signaling pathways are deregulated in most cancers, so molecularly targeting PI3K-Akt or Ras-MAPK signaling sensitizes many cancer types to radiotherapy and chemotherapy, but the underlying molecular mechanisms have yet to be determined. During the multi-step processes of tumorigenesis, cancer cells gain the capability to disrupt the cell cycle checkpoint and increase the activity of CDK4/6 by disrupting the PI3K, Ras, p53, and Rb signaling circuits. Recent advances have demonstrated that PI3K-Akt-mTOR signaling controls FANCD2

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Abbreviations used: AMPK1 – AMP-activated protein kinase; ATM kinase – ataxia-telangiectasia mutated kinase; ATR – ataxia telangiectasia and Rad3-related; CDK4/6 – cyclin-dependent kinase 4/6; Chk1 – checkpoint kinase 1; Chk2 – checkpoint kinase 2; FA – Fanconi anemia; FANCD2 – Fanconi anemia group D2; FANCI – Fanconi anemia group I; HR – homologous recombination; ICL – DNA interstrand crosslinker; IGF1BP3 – insulin-like growth factor binding protein 3; IRS – insulin receptor substrate; MAPK – mitogen-activated protein kinase; mTOR – mammalian target of rapamycin; NER – nucleotide excision repair; PH – pleckstrin homology; PI3K – phosphoinositide 3-kinase; PIP2 – phosphatidylinositol 4,5-phosphate; PIP3 – phosphatidylinositol 3,4,5-trisphosphate; PTEN – phosphatase/tenascin homolog deleted on chromosome 10; Rb – retinoblastoma; Rheb – Ras-homolog enriched in brain; RNR – ribonucleotide reductase; RTK – receptor tyrosine kinase; TLS – translesion DNA synthesis; TSC2 – tuberous sclerosis complex-2

and ribonucleotide reductase (RNR). FANCD2 plays an important role in the resistance of cells to DNA damage agents and the activation of DNA damage checkpoints, while RNR is critical for the completion of DNA replication and repair in response to DNA damage and replication stress. Regulation of FANCD2 and RNR suggests that cancer cells depend on PI3K-Akt-mTOR signaling for survival in response to DNA damage, indicating that the PI3K-Akt-mTOR pathway promotes resistance to chemotherapy and radiotherapy by enhancing DNA damage repair.

Keywords: PI3K, Akt, Target of rapamycin, Ribonucleotide reductase, p53, FANCD2, Drug resistance, DNA damage response, Chemotherapy, Radiotherapy, ATM

THE PI3K-Akt-mTOR PATHWAY

The PI3K-Akt-mTOR pathway is the central regulator of cell survival, proliferation, growth, and metabolism [1–4]. PI3K is activated by receptor tyrosine kinase (RTK) and G-protein coupled receptor (GPCR). It converts the phosphatidylinositol 4,5-phosphate (PIP₂) to phosphatidylinositol 3,4,5-trisphosphate (PIP₃) in the cell membrane. Phosphatidylinositide-dependent kinase 1 (PDK1) and Akt (also called protein kinase B, PKB) bind PIP₃ through the pleckstrin homology (PH) domain [5]. PDK1 and the mammalian target of rapamycin complex 2 (mTORC2) activate Akt by phosphorylating it at Ser308 and Ser473, respectively [6]. Activated Akt promotes cell cycle progression, proliferation, and survival, and DNA damage repair by phosphorylating numerous downstream targets, including Bad, FRKH, GSK3, TSC2, Mdm2, PDK1, and IKK [7–9].

Most cancers have a deregulated PI3K-Akt-mTOR circuit. This makes it a major signaling pathway of interest in current research around molecular-targeted cancer therapy [10–12]. However, the mechanism by which deregulation of the PI3K-Akt pathway contributes to tumorigenesis and the sensitization of cancer cells to chemotherapy and radiotherapy is largely unknown.

PI3K-Akt SIGNALING CONTROLS CELL CYCLE PROGRESSION

Deregulation of cell cycle control is a hallmark of cancer cells [13, 14]. The PI3K-Akt pathway promotes cell cycle progression through multiple mechanisms [7–12]. Activating Akt leads to the phosphorylation and inactivation of the forkhead transcription factor FOXO3, which enhances the gene transcription of p27^{kip1} and p130^{Rb2} and suppresses cyclin D1. Protein 27^{kip1} is a potent inhibitor of the cyclin-dependent kinases Cdk2 and Cdk1 [15]. Transcription factors E2F1 through 3 promote the transcription of genes essential for G1/S phase transition and S phase progression [16]. Protein 130^{Rb2} is a negative regulator of G1/S phase transition, which inhibits the E2F family members [15, 16]. Thus, PI3K-Akt suppresses p27^{kip1} and p130^{Rb2} to promote cell-cycle progression.

Akt also enhances cell-cycle progression by phosphorylating and inactivating GSK3 kinase, which suppresses myc and cyclin D1 [9, 17]. The myc proto-oncogene is an important transcription factor for cell cycle progression. It is mutated in numerous cancers. Dysregulation of cyclin-dependent kinases Cdk4 and Cdk6 leads to malignant transformation. Cyclin D1 plays a vital role in the activity of CDK4/6. A wide range of cancer cells upregulate cyclin D1 via different mechanisms [15, 16]. Thus, deregulation of PI3K-Akt signaling promotes malignant transformation by enhancing unscheduled G1/S phase progression.

mTOR SIGNALING IS A CENTRAL INTEGRATOR AND PROCESSOR OF THE CELL GROWTH SIGNAL

mTOR kinase is a conserved member of the PI3K-related kinase (PIKK) family [1–4]. It was first identified in the budding yeast *Saccharomyces cerevisiae* by screening rapamycin-resistant mutants [18]. Yeast encodes two TOR kinases: TOR1 and TOR2. Together with LST8, KOG1, and TCO89, TOR1 or TOR2 form the TORC1 complex, which is a rapamycin-sensitive central regulator of cell growth and proliferation. TORC1 responds to environmental changes in the levels of nutrients, energy, and oxygen, and to other stresses. It also controls protein translation, autophagy, ribosome biogenesis, stress-induced transcription, and cell cycle transit into S-phase. TOR2 is essential for cell survival and can also form the rapamycin-insensitive TORC2 complex with LST8, AVO1, AVO2, AVO3, and BIT61 [1, 19]. TORC2 regulates the organization of the actin cytoskeleton, which is vital for cell mitosis, motility, and the maintenance of cell morphology [1]. The components and functions of the TOR signaling pathways are conserved from yeast to human cells.

Mammalian TORC1 dictates the rates of macromolecule synthesis and thus the cell growth, proliferation, and survival [1–4, 20, 21]. Cell growth and proliferation depend on both nutrients and extracellular growth factors. The position and number of any specific types of cell in the tissue of an organism is determined by growth factor signaling. The predominant growth-promoting signaling pathways are PI3K-Akt and Ras-MAPK, both of which converge on mTORC1. The intracellular oxygen concentration and energy status are transmitted to mTORC1 through LKB1-AMPK or Redd1/2 and LKB1-AMPK, respectively [22]. Wnt and p38MAPK signal to the mTORC1 network [23, 24]. Inflammation promotes mTORC1 signaling via the TNF α -IKK β pathway [25]. Moreover, cyclin B/CDK1 increases mTORC1 activity during the G2/M phase of the cell cycle [26], although the physiological function of this link is unknown. Most of these signals converge on mTORC1, via the upstream TSC1/2 complex, a GTPase-activating protein (GAP) that converts GTP-Rheb to GDP-Rheb. Rheb is a Ras-like GTPase that promotes the activation of mTORC1 kinase [21]. Amino acids are essential for mTORC1 activation via Rag [27]. Thus, mTORC1 controls cell growth and proliferation, and maintains tissue homeostasis [1–4, 20, 21].

An increasing volume of data shows that dysregulation of Akt-mTOR signaling leads to cancer [2–4]. There are numerous mechanisms that result in deregulation of Akt-mTOR signaling. Mutations of the upstream negative regulators including IGFBP-3, PTEN, TSC1, TSC2, LKB1, and AMPK1 result in the upregulation of mTORC1 [2, 3, 7]. Moreover, oncogenic mutations of the upstream positive regulators of mTORC1, such as overexpression or mutation of PI3K and growth factor receptors, activation of receptor tyrosine kinases (RTK) via the autocrine loop, or mutations of Ras and Akt, lead to sustained activity of the Akt-mTOR signaling pathway. The most important of these mutations are PTEN and Ras.

Oncogenic mutations of the downstream targets of mTORC1 have been found in many cancers. Among these mutations are 4E-BP and eIF-4E [12]. The PI3K and RAS pathways are altered in more than 70% of all cancer cases [5]. These are the two major signaling pathways for cancer drug development. Recent data indicate that inhibiting the RTK-mTOR or RAS-mTOR pathways sensitizes many cancer cells to chemotherapy and radiotherapy, but the molecular mechanism has yet to be determined [10, 11, 28, 29].

PI3K-Akt SIGNALING REGULATES THE FANCONI ANEMIA SIGNALING PATHWAY

The Fanconi anemia (FA) signaling pathway is activated by genotoxins, including DNA interstrand crosslinker (ICL). It plays an important role in ATM DNA damage and ATR intra-S phase checkpoint activation. Deficiencies in FA signaling result in genome instability and make cells hypersensitive to DNA-damaging agents [30–32]. FANCD2 is the key player in FA signaling. It coordinates translesion DNA synthesis (TLS), nucleotide excision repair (NER), and homologous recombination (HR) [33]. In response to ICL, the FA core E3 ubiquitin ligase complex monoubiquitinates FANCI and FANCD2. The monoubiquitinated FANCI-FANCD2 complex, together with endonucleases, cuts both sides of ICL to generate DNA strand breaks and promotes TLS, NER, and HR [32–35].

It was recently found that FANCD2 promotes early ATM-Chk2 activation in response to ICL-induced DNA lesions [36]. Accurate and complete genetic information is maintained by the ATM checkpoint [37]. These findings suggest that one of the mechanisms by which FANCD2 functions as a genome caretaker is by promoting timely ATM checkpoint activation. Most importantly, it was revealed that Akt-mTOR signaling maintains FANCD2 gene transcription by enhancing the activity of CDK4 and NF- κ B [36, 38], thus providing a mechanism by which molecular inhibition of PI3K-Akt-mTOR signaling sensitizes cancer cells to DNA damage agents, especially ICL-based chemotherapies (Fig. 1). Accordingly, inhibition of mTOR kinase sensitized rhabdomyosarcoma and leukemia to radiotherapy and chemotherapy [36, 39].

TOR SUSTAINS RIBONUCLEOTIDE REDUCTASE IN RESPONSE TO DNA DAMAGE

Ribonucleotide reductase (RNR) catalyzes the rate-limiting step in the production of dNTPs, and blocks DNA replication and repair. The protein levels and activity of RNR are tightly controlled in all organisms because higher than physiological levels of dNTPs lead to gene mutations and lower levels compromise cell viability [40–42]. It was reported that rapamycin inhibition of TORC1 enhanced the cytotoxicity of DNA damage agents and at the same time reduced the DNA damage-induced mutations through downregulation of RNR in budding yeast, suggesting that the TOR pathway and DNA damage checkpoint function in parallel to control RNR in response to genotoxin [43]. The DNA damage-induced increase of dNTP levels is conserved in mammalian cells as one of the small subunits of mammalian RNR, p53R2, is induced by p53 following DNA damage [44]. Moreover, it was recently discovered that DNA damage increases the main mammalian ribonucleotide reductase small subunit

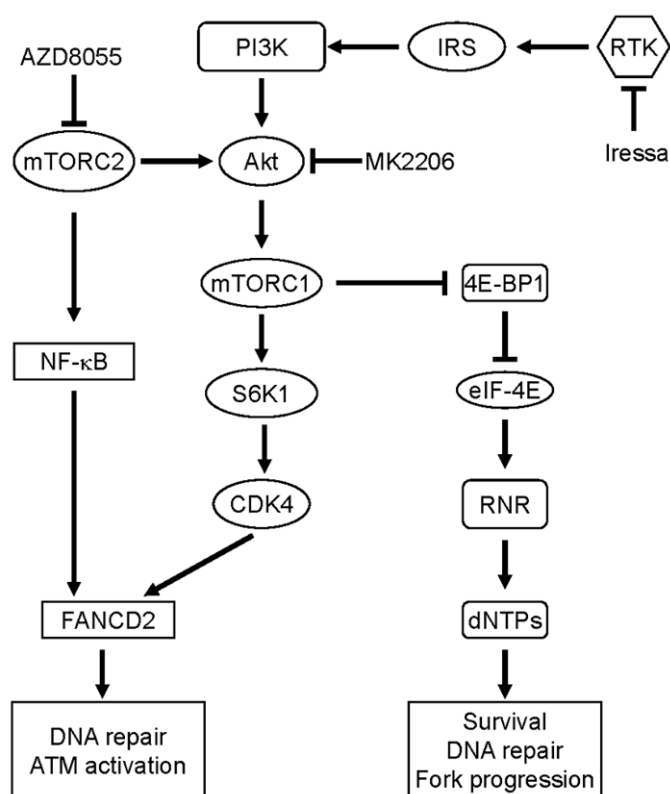


Fig. 1. Regulation of FANCD2 and RNR by the PI3K-AKT-mTOR signaling pathway. Downregulation of FANCD2 and RNR by targeting RTK-PI3K-AKT-mTOR would sensitize cancer cells to DNA damage agents. AZD8055 (AstraZeneca) is an mTOR kinase inhibitor; MK2206 (Merck) is an AKT kinase inhibitor.

M2 (RRM2) via ATR kinase [45]. In mammalian cells, the translation of both the ribonucleotide reductase large subunit M1 (RRM1) and the small subunit RRM2 is cap-dependent [46]. As cap-dependent translation is controlled by mTORC1 [12], deregulation of PI3K-Akt-mTOR signaling may promote tumorigenesis and maintain cancer cell survival via upregulation of RRM1 and RRM2 in response to DNA replication stress and damage (Fig. 1).

TARGETING PI3K-AKT-mTOR SENSITIZES CANCER CELLS TO CHEMOTHERAPY AND RADIOTHERAPY

PTEN is mutated in a wide range of cancer cells [47], so restoring PTEN will disrupt PTEN mutation-dependent cancer cell growth. Extensive efforts have been made in recent years to restore PTEN in cancer therapy. For example, the introduction of wild-type PTEN by viral vectors; the aerosol delivery of non-viral vector, urocanic acid-modified, chitosan-mediated PTEN; and the introduction of cell permeable, recombinant, wild-type PTEN into cells by fusing PTEN with a cell permeable protein transduction domain (PTD) demonstrated the possibilities to further develop these strategies [48–49].

Great advances have been also made in the development of molecularly targeted therapies targeting the kinases of the PI3K-Akt-mTOR network. The most common strategy is to inhibit the activities of the agonists upstream of the growth factor receptor tyrosine kinases (GF-RTK). Numerous GF-RTK-specific monoclonal antibodies have been developed, such as herceptin for Her2 and Cetuximab for EGFR [10, 11, 50, 51]. Recently, many small molecular inhibitors targeting intracellular kinases of the PI3K-Akt-mTOR pathway, such as MK2206 for Akt, and AZD8055 for mTOR, were developed (Fig. 1) [52, 53]. However, both preclinical and clinical trials clearly demonstrated the resistance of cancer patients to these molecularly targeted therapies, raising new challenges for eradicating human cancers [10, 11].

The major function of DNA damage checkpoints is to promote DNA damage repair and completion of DNA replication in response to genotoxins. Accordingly, a plethora of familial cancer cells derived from deficiency in one of genome surveillance or tumor suppressor genes, such as ataxia-telangiectasia syndrome with deficiency of ATM, Nijmegen breakage syndrome with deficiency of NBS, and Li-Fraumeni syndrome with deficiency of p53 or CHK2 are hypersensitive to DNA damage agents [37, 54].

As FANCD2 and RNR play important roles in the survival of cells in response to DNA damage agents, positive control of these DNA damage repair proteins by PI3K-Akt-mTOR signaling suggests that inhibition of this pathway sensitizes cancer cells to DNA damage-based cancer chemotherapy and radiotherapy.

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