Effective PI3K modulators for improved therapy against malignant tumors and for neuroprotection of brain damage after tumor therapy (Review)

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Abstract. Due to the key role in various cellular processes including cell proliferation and cell survival on many cell types, dysregulation of the PI3K/AKT pathway represents a crucial step of the pathogenesis in many diseases. Furthermore, the tumor suppressor PTEN negatively regulates the PI3K/AKT pathway through its lipid phosphatase activity, which is recognized as one of the most frequently deleted and/or mutated genes in human cancer. Given the pervasive involvement of this pathway, the development of the molecules that modulate this PI3K/AKT signaling has been initiated in studies which focus on the extensive effective drug discovery. Consequently, the PI3K/AKT pathway appears to be an attractive pharmacological target both for cancer therapy and for neurological protection necessary after the therapy. A better understanding of the molecular relations could reveal new targets for treatment development. We review recent studies on the features of PI3K/AKT and PTEN, and their pleiotropic functions relevant to the signaling pathways involved in cancer progress and in neuronal damage by the therapy.

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1. Introduction

Phosphatidylinositol 3-kinase (PI3K)/AKT pathway is been known as an important signaling pathway in a variety of human cancers (1-3), which also plays critical roles in normal cell survival and proliferation under physiological condition (4,5). For example, prostate cancer development is often associated with silencing of the tumor suppressor phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/AKT signaling pathway (6,7). The PTEN is a multi-functional enzyme inhibiting the PI3K/AKT signaling in the cytosol and stabilizing genomes in the nucleus. Various extracellular signals including growth factors and/or cell nutrients could act as modulators for the PI3K/AKT/PTEN signaling axis. Once activated PI3K recruits cellular protein kinases such as the serine/threonine kinase AKT that consecutively transduces a signal to several downstream molecules. In general, relationship of the intracellular signaling networks coordinates cellular function containing cell cycle progression, proliferation and cell protection. Mutation in some of the effectors may result in consequent activation and/or inhibition of the signaling.
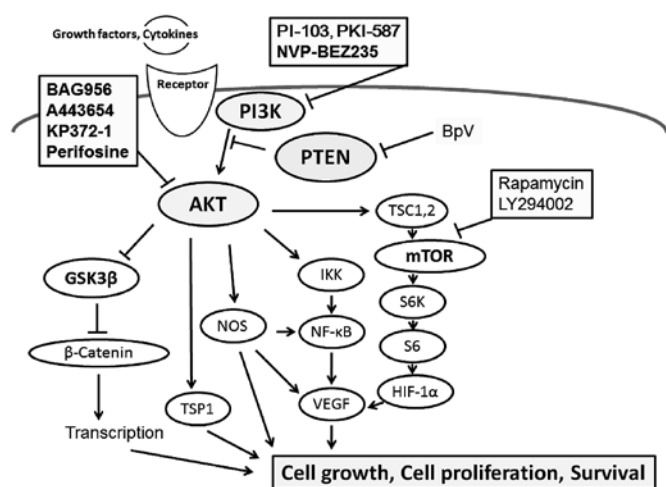
Figure 1. Schematic depiction and overview of PI3K/AKT/PTEN signaling, and example molecules known to act on the PI3K/AKT/PTEN pathway are shown. Several inhibitors linked to the PI3K/AKT/mTOR/PTEN signaling pathway are also presented. Arrowhead, indicates stimulation and hammerhead shows inhibition, suggesting implication of PI3K/AKT/mTOR modulators for pharmaceutical therapy of cancers. Note that some critical pathways have been omitted for clarity.

This dysregulation of the signal occurs commonly in many malignancies, thereby rendering the cancer cells proliferative and with survival advantage. Accordingly, both nuclear and cytosolic PTEN/PI3K/AKT activity should be reflected for correlation with clinicopathological parameters of cancer (8). In addition, the PI3K/AKT signaling has been shown to induce the gene expression of multidrug resistance protein that is considerably associated with cancer therapy-opposition (9). Development of this multidrug resistance seems the major obstacle for chemotherapy of cancers. Therefore, it seems a remarkable target for molecular therapy in various diseases including cancer and related diseases. To date, many pharmacological inhibitors acting on the PI3K/AKT pathway have been established (10).

Overall, cancer treatment could have secondary negative effects such as neurocognitive deficits, serious sequelae that follow the therapy used to treat patients especially with brain neoplasms (11,12). The pathogenesis of the neurocognitive deficits involves apoptosis of neurons and other neuronal cells in a region in brain for learning and memory. After and during the intensive cancer therapy, brain damage has emerged as an important clinical problem (13,14). In regards to this, some reports show that nuclear trafficking of PTEN following brain injury leads to neuronal survival (15), indicating hope for new treatment options. The present review focuses on the recent advance in PI3K/AKT/PTEN-mediated neuroprotection and neurogenesis after several cancer therapies, highlighting its potential molecular and cellular mechanisms on the therapeutic advantages.

2. PI3K/AKT/PTEN pathway is involved in cancer development

Increased proliferation and cell motility are common cellular consequences associated with the high levels of intra-cellular phosphatidylinositol 3,4,5-triphosphate (PIP3) that give

the metastatic characteristics to cancer (16). A feedback mechanism may increase the PIP3 further activating AKT and metastasis. Therefore, several studies have advocated that the PI3K/AKT signaling pathway is concerned with the progression and the prognosis of various types of cancer (17,18). Accordingly, suppression of PI3K and/or AKT inhibits proliferation and induces apoptosis in cancer cells (Fig. 1). On the contrary for example, dysregulation of the PI3K/AKT pathway seems to contribute to the malignant tumor activity with RET proto-oncogene mutations (19), which are involved in the pathogenesis of some forms of a neuroendocrine medullary thyroid cancer. In addition, it has also been shown that PI3K/AKT/mTOR signaling may play an important role in the biology of papillary tumors (20). Positive mTOR expression and PTEN loss may have a synergic effect on tumorigenesis and cancer cell proliferation (21). The evidence may lead to possible procedures of PI3K/AKT inhibitors in the therapy for patients with certain cancers (Fig. 1). In fact, targeting PI3K/AKT signaling pathway through specific inhibitors may represent an attractive potential therapeutic approach for the patients (19), actually exhibiting potent antitumor efficacy, providing rationale for clinical investigation of this inhibition in cancers of PI3K-mediated cells (22). Classically, wortmannin and LY294002 are the most characterized PI3K/AKT pathway inhibitors which prevent ATP from binding to the PI3Ks (23,24), both of which are cell-permeable and low molecular weight compounds. Wortmannin irreversibly inhibits PI3Ks, while the inhibition with LY294002 is reversible (10). Generally, PI3K inhibitors have been discovered to affect cell growth, proliferation and survival of cancer cells, as predicted before. The PI3K/AKT and its downstream inhibitors, when combined with other pharmacological agents would appear to be a more promising therapeutic modality. Particularly, PI3K/AKT inhibitors are prominently effective in PTEN null cells (25).

3. PI3K/AKT/PTEN pathway is involved in neurodegenerative disorders

ROS play a pivotal role in the pathogenesis both of neuro-inflammatory and of neuro-degenerative diseases (26). Inflammatory conditions generally lead to the chronic neurodegenerative disease such as Parkinson's disease, Huntington's disease and Alzheimer's disease (27). Studies have indicated that cancer therapy commonly induces ROS production, which accelerates blood-brain barrier disruption and the neuronal cell death (28). Cancer therapy may induce apoptosis both for cancer cells and for normal neuronal cells. In this meaning, reduction of ROS may have a high potential to diminish brain damage induced during cancer therapy. It has been demonstrated that upregulation of PTEN causes modulation of PI3K/AKT signaling pathway to reduce the ROS generation in cells (29). As described before, the *PTEN* is one of the most prominent tumor suppressor genes that is frequently deleted or mutated in a variety of human cancers (30). In addition, PTEN is highly expressed in neurons and it has been described to be related to critical neuroprotection (31,32). Recently, it has been shown that AKT activation may likely play a therapeutic role in neurodegenerative diseases (33,34). Schematic structures of the AKT and PTEN protein are shown in Fig. 2. Accordingly,
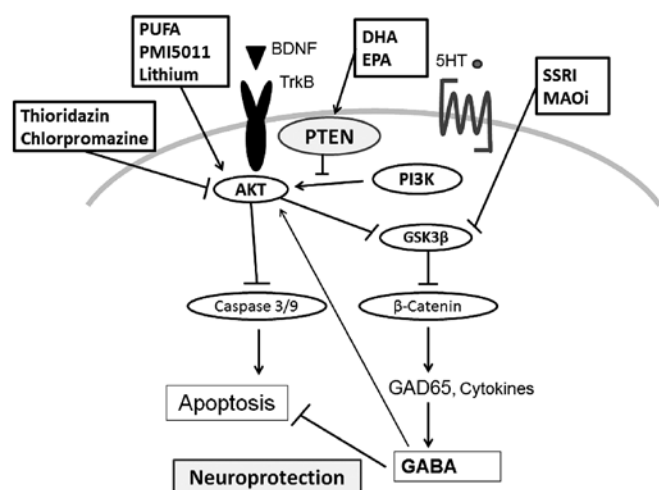
Figure 2. Potential molecular targets based on the predominant PI3K/AKT/GSK3β pathway, suggesting certain diets and medications may contribute to neuro-protection via modulating the function of AKT and GSK3β. Note that some critical events have been omitted for clarity. BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine, serotonin; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitors.

the tumor suppressor PTEN, which antagonizes the PI3K/AKT pathway, has been recognized to play a crucial role in neural functions. Neuroprotection by inhibiting PTEN has been reported by activating the PI3K/AKT pathway in primary neurons (35,36). Deletion of PTEN gene has been shown to result in cognitive impairment (37). Ischemic stroke induces rapid PTEN degradation in both neurons and astrocytes which play both protective and detrimental action to neurons in a spatiotemporal- and cell-type-dependent manner (38). Simultaneous deletion of PTEN promotes significant nerve regeneration after the crush injury with enhanced axon regeneration (39). However, there is somewhat controversy whether accumulation of the tumor suppressor PTEN protein under stress conditions such as trauma and stroke causes neuronal cell death. A number of studies have reported enhanced apoptosis in neurons possessing increased amount of nuclear PTEN, with the interpretation that its nuclear phosphatase activity leads to the reduction of survival AKT signaling activity. One interpretation is that brain trauma may modify the nucleo-cytoplasmic distribution of PTEN, resulting in the increased nuclear PTEN, but only in surviving neurons near the traumatic lesion (15,40).

4. Potential therapeutic approach for neuro-cellular protection via the modulation of PI3K/AKT/PTEN pathway

Cognitive failures after brain tumor and its treatments are appropriately consistent, although there is only a small worldwide body of research describing them (41). Chemotherapy against cancer is often associated with cognitive deficits which may remain after the end of the treatment (42). In the central nervous system, PI3K/AKT signaling modifies synaptic plasticity underlying the memory-processes suggesting that PI3K/AKT signaling contributes to improvement in the cognitive development. Inhibition of PTEN is expected to promote neural cell survival, neuroprotection and neurore-

generation, which can also promote myelination of axons through the AKT activation (43). Actually, a PTEN inhibitor reduces tissue damage, neuronal cell death and promotes the functional recovery (43). In addition, it has been shown that PTEN-induced putative kinase 1 (PINK1) induces mitophagy promoting neuroprotection on Huntington's disease (44). Furthermore, anti-depressants acting on serotonin neurotransmission generally activate AKT then inhibit the downstream GSK3β in neuronal cells. Several psychoactive medicines have been shown to modulate the activity of the PI3K/AKT signaling (45) (Fig. 2). AKT has downstream substrates such as the GSK3β (46). MAO inhibitors and SSRI antidepressants which promote serotonin synaptic transmission may inhibit the GSK3β activity (47). Atypical antipsychotics may inhibit the regulation of the GSK3β signaling (48). Similar results have been reported after the treatment with haloperidol (49,50). Chlorpromazine is a prominent antipsychotic agent initially developed to control several psychotic disorders, which also inhibits cell proliferation and cell survival by suppressing PI3K/AKT signaling pathway (51). Whereas AKT pathway is regulated by different types of psychiatric drugs in this way, lithium activates PI3K and PI3K-dependent downstream AKT signaling (52). These activities eventually protect neuronal cells against neuronal toxicity. Therefore, treatment with inhibitors of PI3K may exacerbate neuronal cell death after brain damage in the area of injury. On the contrary, inhibition of PTEN expression diminishes the neurological damage after brain injury. In addition, it has been revealed that pharmacological inhibition of PTEN protects against brain injury in a dose-dependent manner, whose protective effect might be induced via the upregulation of PI3K/AKT signaling (53,54). Furthermore, PTEN has some crosstalk effects with serotonin receptor signaling (55). By blocking dopamine D2 receptors, classic antipsychotics can prevent the inhibition of AKT signaling (56,57). In addition, reductions in AKT activation in neurons may increase excitability through decreases in GABA neurotransmission (58). It seems important to exploit the potential benefits of these optimal treatments and/or combination with the PI3K/AKT modulators for the actual neuroprotection against neurological damage.

5. Dietary regulation of PI3K/AKT signaling via the modified PTEN expression

The PI3K/AKT and PTEN signaling plays various cellular key roles under normal and/or pathological conditions. Activation of both pathways can impact functional consequences in cancer therapy and the subsequent multiple CNS disorders. Of course, pharmacological interference of signaling molecules provides convenient method. For example, bisperoxovanadium compounds inhibit PTEN signaling, and have been used for elevation of neuroprotection in many CNS damage studies (43,59,60). In addition, small molecules have prevalent use by means of experimental tools as well as therapeutics (61). Now, it is challenging to describe appropriate strategies to achieve cost effective benefits from easy diets to control the PTEN signaling molecules. Dietary and/or therapeutic interventions could not only contribute to the prevention of diseases but reduce the rate of its development. Actually, several herbs had been established to have characteristics
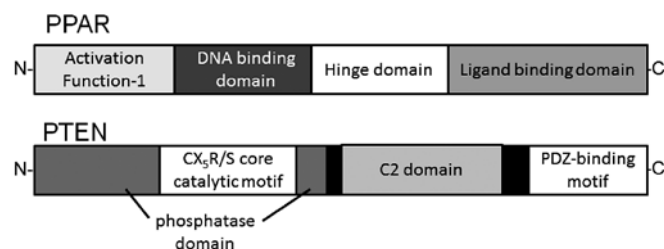
Figure 3. Schematic structures of human PPAR and PTEN protein. The predicted consensual domain structures for each protein are depicted. Note that the sizes of protein are modified for clarity. C2 domain, a structural domain involved in targeting proteins to cell membranes; PDZ, a common structural domain in signaling proteins (PSD95, Dlg, ZO-1).

for antitumor activity (62). In addition, dietary regulation of PI3K/AKT signaling via the modulating PTEN expression might be effective both for cancer inhibition and for a neuroprotection. For example, dietary intake of isothiocyanate sulforaphane, a dietary isothiocyanate derived from broccoli, modulates PTEN gene expression (63). Dietary exposure to the soy isoflavone such as genistein also induces PTEN expression at physiologically relevant concentrations (64). Phytoestrogen exposure might result in an increase in PTEN expression and the subsequent decrease in cellular responses including AKT phosphorylation. Accordingly, consumption of moderate levels of soy, vegetables, some fruits, and red wine can be protective against cancers. A high-fat diet raises circulating fatty acids, which also increases PTEN expression in prostate epithelial cells (65). In addition, dietary intake of indole-3-carbinol upregulates PTEN in an animal model (66). Indole-3-carbinol is a promising cancer-preventive phytochemical found in some vegetables such as broccoli. PTEN expression at the level of mRNA and protein is elevated in experimental animals fed with whey protein (67) which has been shown to possess multiple health benefits (67). In addition, it has been reported that DHA and EPA raise the level of PTEN in breast cancer cells, providing a mechanism for the beneficial effects of fish oils on breast cancer cells (68,69). Fish oil rich in polyunsaturated fatty acids may induce the PTEN expression by activation of peroxisome proliferator-activated receptor (PPAR) (68,69), which also attenuate neuron cellular damage after a brain ischemia and appear to play an important role in the activation of anti-apoptotic signaling (70). Schematic structures of human PPAR and PTEN are shown in Fig. 3. PUFA ethanolamides DHA and EPA induce autophagy through PPAR activation in cancer cells (68). In contrast, high fat diet attenuates the neuroprotection because of decreased survival of AKT signaling (71). A lignan Honokiol isolated from the bark of *Magnolia officinalis* could attenuate PI3K/AKT signaling by upregulation of PTEN expression (72), which is a potential antitumor compound. Honokiol has been reported to improve the learning and memory impairments in experimental animals (73). A food ingredient curcumin, derived from the root of the plant *Curcuma longa*, repairs PTEN expression (74). Curcumin inhibits cell proliferation in human osteoclastoma cells (75). Furthermore, curcumin is a potential therapeutic mediator for neuro-cognition (76). In contrast, certain component of rosemary herb decreases the expression of PTEN in K562 human myeloid cells (77).

Resveratrol, an ingredient in grapes, has been reported to exhibit anticancer activity, anti-inflammatory activity and cardiovascular protection property. Notably, resveratrol has been recently reported to have neuroprotective effect (78). Supplementation of these natural compounds may provide an innovative therapeutic approach to brain disorders after cancer therapy (31).

6. So what next?

Increasing evidence pointing to AKT pathway-modification in psychotic disorders offer a novel implication of the treatment mechanisms for rescuing brain damage after cancer therapy. Although PTEN has been discovered as a tumor suppressor, PTEN is also involved in several other diseases, and may be regulated at multiple levels including transcription, protein stability and phosphorylation. Potential synergy with other targeted inhibitors and/or with conventional chemotherapy may provide additional therapeutic options to optimize the therapeutic efficacy. In addition, abnormalities in the PI3K/AKT signaling pathway and in the cross-talk pathways provide a clear rationale for the development of signal transduction inhibitor-based approaches aimed for both cancer therapy and the subsequent neurological disorders. Understanding the important roles of the intracellular signaling and the intricate internetwork communication is an important direction for making effective and specific therapies. However, much more work is needed to effectively produce and validate therapies that target pathways. Particularly, it will be now a challenge to seek out how to use medicinal herbs for the correction in critical processes required for maintaining neuronal homeostasis linking to a brain injury characterized by cancer therapy. Current evidence, as described here, suggests that work toward understanding these complex signaling cascades is not only promising, but may be critical for achieving the goal of improved neurological outcome after brain and spinal cord damage. This relationship has similarities with another relationship between methotrexate (MTX) therapy and a leucovorin (LV) rescue (79). We think the order of the usage of medicine and/or compound for the treatment is the most important. Of course, precise understanding of these regulations is crucial for therapeutic intervention and the effective design of novel therapeutics. A comprehensive description of the PI3K/AKT signaling network has to be evolved. Studies may be ongoing to identify the most optimal inhibitors for cancer subtypes.

Acknowledgements

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