Pharmacological Research 93 (2015) 1–10

Contents lists available at ScienceDirect

Pharmacological Research

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

Review

Natural inhibitors of PI3K/AKT signaling in breast cancer: Emphasis on newly-discovered molecular mechanisms of action

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ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form 9 December 2014
Accepted 13 December 2014
Available online 19 December 2014

Keywords:
Breast cancer
Natural inhibitors
PI3K
AKT

Chemical compounds studied in this article:
Thymoquinone (PubChem CID:10281)
Wogonin (PubChem CID: 5281703)
Fenretinide: (PubChem CID: 5288209)
Isoliquiritigenin (PubChem CID: 638278)
BYL-719 (PubChem CID: 56649450)
Ascofuranone (PubChem CID: 6434242)
CDRI 85-287 (PubChem CID: 159508)
Quercetin (PubChem CID: 5280343)
Platycodin D (PubChem CID: 162859)

ABSTRACT

Epidermal growth factor receptor (EGFR) plays a critical role in the initiation and progression of a variety of human cancers, including breast cancer. An important signaling pathway downstream of EGFR is the PI3K/AKt pathway, which regulates cellular processes as diverse as cell growth, survival, proliferation and migration. Deregulated activity of this pathway may lead to uncontrolled cell growth, survival, migration and invasion, contributing to tumor formation. In this review, we evaluate natural compounds that, in vitro (breast cancer cell lines) and/or in vivo (animal model, clinical) studies, suppress breast cancer cells or tumors mainly by suppressing the PI3K/AKT signaling pathway. The effect of these compounds on cell cycle arrest, inhibition of cell migration and invasion, tumor angiogenesis and metastasis in breast cancer are discussed.

Contents

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http://dx.doi.org/10.1016/j.phrs.2014.12.004
1043-6618/

Introduction

Epidermal growth factor receptor (EGFR) is a member of the HER family of transmembrane receptors that regulate cellular processes as diverse as cell survival, cell proliferation, and apoptosis. Aberrant expression of this receptor on the cell surface or its enhanced activity may contribute to cancer [1,2]. Deregulated EGFR signaling causes cancer cells to be refractory to anticancer therapies, including immunotherapy, chemotherapy or radiotherapy [2–5]. Compared to other human cancers, breast cancers display more complex intracellular signaling involving receptors, such as for estrogen and progesterone, which are not found in other cancers. In addition, breast cancer cells can be either positive or negative for HER2 expression [6–8]. Such diversity in the receptor expression profile of breast cancer cells potentially contributes to additional complexity in intracellular signaling and influences the efficiency of treatment strategies. In this review, we consider natural compounds proven to exhibit significant potency against breast cancer cells via influencing the EGFR/PI3K pathway, and present recently discovered molecular mechanisms by which these compound suppress breast cancer.

Brief overview of EGFR downstream signaling pathways

EGFR activation upon ligand binding and dimerization triggers several signaling pathways within the cell, ultimately resulting in cell survival and proliferation. The main signaling pathways downstream of EGFR are PI3K/AKT, RAS/RAF/MEK/ERK, STAT, PLC/PKC, and nuclear signaling EGFR [2]. In this review, we specially focus on the PI3K/AKT pathway and discuss the natural compounds suppressing this pathway in breast cancer. The pathway is initiated by AKT phosphorylation and activation, which is mediated by two different kinases: phosphoinositide dependent kinase 1 (PDK1) and the mammalian target of rapamycin complex 2 (mTORC2). During several steps, the active AKT activates mTOR, a serine/threonine kinase having two substrates, 4E-BP1 and p70-S6 kinase 1. Phosphorylation of p70-S6 kinase 1 results in activation and initiation of protein synthesis via the S6 ribosomal subunit, and phosphorylation of 4E-BP1 results in the release of eIF4E, a translation initiation factor. Inside the nucleus, the pathway leads to transcription and expression of several genes involved in different cellular processes. The PI3K/AKT pathway is naturally attenuated by PTEN (phosphatase and tensin homologue deleted in chromosome 10), a tumor suppressor protein that dephosphorylates AKT (Fig. 1) [2,9].

Natural compounds inducing cell cycle arrest and/or apoptosis in breast cancer

Thymoquinone arrests the cell cycle at G1 by downregulating Akt-mediated cyclinD1 expression

Thymoquinone (TQ) (Fig. 2) is a bioactive constituent of black seed oil (*Nigella sativa*) whose efficacy has been demonstrated for treatment of a number of human diseases, including cancer. TQ suppresses the growth of cancer cells and induces apoptosis. This compound mediates its activity through multiple mechanisms, including: increase ofp53 and p21 expression, inhibition of Bcl-2, disruption of mitochondrial membrane potential, and activation of caspase proteins [10,11]. A recent study carried out on both estrogen-negative and estrogen-positive cancer cell lines (MDA-MB-468 and T-47D cell lines, respectively) indicated that TQ decreases the cyclin D1 mRNA level through decreasing the phosphorylated form of AKT. TQ decreases the expression levels of two mTOR-dependent proteins involved in translation initiation, p-4EBP1 and p-eIF4E, resulting in impairment of functional 5′cap formation on mRNA (Fig. 1). In addition, TQ prevents the phosphorylation of S6 Kinase and S6R (40S ribosomal subunit), resulting in inhibition of cyclin D1 translation initiation. Decreased expression of cyclin D1 leads to cell cycle arrest at G1 (Fig. 3). p27 has been found to decrease in MDA-MB-468 and T-47D cells following treatment with TQ. p27 is a cyclin-dependent kinase (CDK) inhibitor that arrests the cell cycle at G1. TQ also increases the Bax/Bcl-2 ratio, decreases the cyclin E expression, increases the p53 protein level, deactivates PDK and activates PTEN [12]. TQ exerts its anti-proliferative activity through suppression of AKT-mediated mTOR signaling as well as of translational machinery downstream of mTOR involved in cyclin D1 expression. Therefore, TQ can serve as an AKT suppressor to inhibit breast cancer growth or to overcome AKT-induced therapeutic resistance.

Tehranolide inhibits cell proliferation and induces G0/G1 arrest via affecting the PI3K/Akt/cyclin D1 pathway

Tehranolide is a natural sesquiterpene lactone isolated from *Artemisia annua*. Its anti-tumor activity has been proven in vitro. Studies on the cell line MCF-7 have indicated that tehranolide inhibits cell proliferation by affecting PI3K/AKT/cyclin D signaling. The compound downregulates the expression of phospho-Akt and phospho-PI3K, and significantly reduces the expression of cyclin D1and CDK4 (a cyclin-dependent kinase that forms a complex with cyclin D1) (Fig. 3). In addition, tehranolide increases the expression of the CDK inhibitor $p27^{kip1}$ [13]. Cyclin D/CDK complexes regulate the cell cycle progression from G1 to S phase [14]; therefore,