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Sphingosine-1-phosphate and estrogen signaling in breast cancer

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ABSTRACT

Breast cancer remains the most common malignant disease in women. The estrogen receptor-α (ERα) and its ligand 17β-estradiol (E_2) play important roles in breast cancer. E_2 elicits cellular effects by binding to ERα in the cytosol followed by receptor dimerization and translocation to the nucleus where it regulates gene expression by binding to ERE response elements. However, it has become apparent that E_2 also exerts rapid non-genomic effects through membrane-associated receptors. There is emerging evidence that this induces formation of the bioactive sphingolipid metabolite sphingosine-1-phosphate (S1P). S1P in turn has been implicated in many processes important in breast cancer progression. One of the enzymes that produce S1P, sphingosine kinase 1 (SphK1), is upregulated in breast cancer and its expression has been correlated with poor prognosis. This review is focused on the role of the SphK/S1P axis in estrogen signaling and breast cancer progression and will discuss new therapeutic approaches targeting this axis for breast cancer treatment.

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Abbreviations: ERα, estrogen receptor α; EGFR, epidermal growth factor receptor; ERE, estrogen response element; ERK, extracellular signal regulated kinase; E_2, 17β-estradiol; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; MAPK, mitogen activated protein kinase; PHB2, prohibitin 2; SphK, sphingosine kinase; S1P, sphingosine-1-phosphate; S1PR, S1P receptor; TNBC, triple negative breast cancer; TRAF2, TNF receptor-associate factor 2.

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1. Introduction

The estrogen receptor-α (ERα) and its ligand 17β-estradiol (E_2) play important roles in breast cancer. Most of the canonical genomic effects of binding of E_2 to ERα are mediated by nuclear transcriptional regulation. However, E_2 also exerts rapid non-genomic signaling through membrane-associated receptors many of them resulting from increased formation of the bioactive sphingolipid metabolite sphingosine-1-phosphate (S1P). S1P and sphingosine kinases (SphKs) that produce it have been implicated in many processes important in breast cancer progression. In this review, we discuss the role of the SphK/S1P axis in estrogen signaling and breast cancer progression and also some new therapeutic approaches to potentially target this axis for breast cancer treatment.

1.1. Formation and metabolism of S1P

It has long been known that sphingolipid metabolism generates metabolites with important functions. The best characterized are ceramide, the backbone of all sphingolipids, its breakdown product sphingosine, and S1P. S1P metabolism has been discussed in many reviews (Hannun and Obeid, 2008; Maceyka and Spiegel, 2014; Shamseddine et al., 2015) and is only briefly outlined here. Two sphingosine kinases, known as SphK1 and SphK2, catalyze the phosphorylation of sphingosine to S1P, which is irreversibly cleaved by S1P lyase to phosphoethanolamine and a fatty aldehyde or dephosphorylated back to sphingosine by several phosphatases which then can be reutilized for ceramide and sphingolipid formation. Tissue levels of S1P are thus determined by the balance between activity of SphKs and S1P lyase and phosphatases.

1.2. S1P signaling

1.2.1. S1P and its receptors

S1P has important roles in regulation of a wide variety of complex biological processes important for breast cancer progression (Carroll et al., 2015; Maceyka and Spiegel, 2014). Most of these actions are mediated by binding to a family of five specific cell surface receptors (S1PR1-5) (Maceyka and Spiegel, 2014). Numerous stimuli, including hormones such as estradiol (E_2), rapidly activate SphK1 and/or SphK2 to transiently increase intracellular S1P levels in specific pools. S1P produced mainly by activated SphK1 can then be secreted by Spns2, a member of the major facilitator superfamily of non-ATP-dependent transporters or by ABC transporters ABCA1, ABCC1, and ABCG2 (Nishi et al., 2014; Takabe and Spiegel, 2014). S1P in turn activates its receptors in an autocrine or paracrine manner known as 'inside-out' signaling of S1P (Hobson et al., 2001; Takabe et al., 2008). Physiological responses regulated by S1P depend on the spectrum of ubiquitously but differentially expressed S1PRs and the variety of G proteins they are coupled to. Thus, many signaling pathways downstream of S1PRs that have been linked to cancer progression have been shown to be activated depending on the cell type, including MAPKs, phospholipase C, adenylate cyclase, and Rac/PI3K/Akt, to name a few (Pyne et al., 2014; Takabe et al., 2008). Moreover, various types of cancer cells differentially express different sets of S1PRs, thus providing S1P with the ability to regulate numerous cellular processes important for breast cancer, including growth, survival, migration, invasion, inflammation, angiogenesis, and lymphangiogenesis (Nagahashi et al., 2014).

1.2.2. Intracellular actions of S1P

While it has long been suspected that S1P also has intracellular actions that are independent of S1PRs, only recently have several intracellular targets been identified that are likely to be important in the context of cancer. We found that S1P, but not dihydro-S1P, produced by SphK1 activated by TNF directly binds to and activates the E3 ubiquitin ligase activity of TNF receptor-associate factor 2 (TRAF2), an important component in NF-κB signaling (Alvarez et al., 2010). NF-κB regulates transcription of pro-survival or anti-apoptosis genes, thus identifying one of the mechanisms for the pro-survival actions of S1P in cancer progression. Interestingly, in contrast to SphK1, which is localized to the cytosol, SphK2 is mainly in the nucleus of most types of cells. We showed that nuclear S1P produced by ERK/MAPK-dependent activation of SphK2 is an endogenous inhibitor of histone deacetylases (HDACs) (Hait et al., 2009). Since SphK2 is present in repressor complexes together with HDACs in the nucleus of breast cancer cells (Hait et al., 2009), the S1P it produces inhibits HDAC activity resulting in enhanced transcription of specific target genes. This was the first indication that nuclear sphingolipid metabolism is involved in epigenetic regulation. Another link between nuclear S1P and gene expression was recently reported by Ogretmen and colleagues who discovered that S1P binds to hTERT and stabilizes telomerase at the nuclear periphery by allosterically mimicking hTERT phosphorylation. In murine xenografts, inhibitors of SphK2 decreased tumor growth and overexpression of wild-type hTERT in cancer cells, but not a hTERT mutant that was unable to bind S1P, restored tumor growth (Panneer Selvam et al., 2015). Their results suggest that S1P promotes telomerase stability and telomere maintenance important for cancer cell proliferation and tumor growth. In the mitochondria, SphK2 produces S1P that binds to prohibitin 2 (PHB2), a protein that regulates mitochondria assembly and function. Deleting SphK2 or PHB2 induced a mitochondrial respiration defect through cytochrome c oxidase (Strub et al., 2011) and may be important for the well-known Warburg metabolism of cancer cells. In this regard, it was suggested that SphK1, but not SphK2, functions to maintain the Warburg effect and cell survival (Watson et al., 2013).

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