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Review article

Role of sphingosine 1-phosphate receptors, sphingosine kinases and sphingosine in cancer and inflammation

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ABSTRACT

Sphingosine kinase (there are two isoforms, SK1 and SK2) catalyses the formation of sphingosine 1-phosphate (S1P), a bioactive lipid that can be released from cells to activate a family of G protein-coupled receptors, termed $S1P_{1-5}$. In addition, S1P can bind to intracellular target proteins, such as HDAC1/2, to induce cell responses. There is increasing evidence of a role for S1P receptors (e.g. $S1P_4$) and SK1 in cancer, where high expression of these proteins in ER negative breast cancer patient tumours is linked with poor prognosis. Indeed, evidence will be presented here to demonstrate that $S1P_4$ is functionally linked with SK1 and the oncogene HER2 (ErbB2) to regulate mitogen-activated protein kinase pathways and growth of breast cancer cells. Although much emphasis is placed on SK1 in terms of involvement in oncogenesis, evidence will also be presented for a role of SK2 in both T-cell and B-cell acute lymphoblastic leukemia. In patient T-ALL lymphoblasts and T-ALL cell lines, we have demonstrated that SK2 inhibitors promote T-ALL cell death via autophagy and induce suppression of c-myc and PI3K/AKT pathways. We will also present evidence demonstrating that certain SK inhibitors promote oxidative stress and protein turnover via proteasomal degradative pathways linked with induction of p53-and p21-induced growth arrest. In addition, the SK1 inhibitor, PF-543 exacerbates disease progression in an experimental autoimmune encephalomyelitis mouse model indicating that SK1 functions in an anti-inflammatory manner. Indeed, sphingosine, which accumulates upon inhibition of SK1 activity, and sphingosine-like compounds promote activation of the inflammasome, which is linked with multiple sclerosis, to stimulate formation of the pro-inflammatory mediator, IL-1β. Such compounds could be exploited to produce antagonists that diminish exaggerated inflammation in disease. The therapeutic potential of modifying the SK-S1P receptor pathway in cancer and inflammation will therefore, be reviewed.

Abbreviations: ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; DAMPs, danger associated molecular patterns; EAE, experimental autoimmune encephalomyelitis; HER2, human epidermal growth factor related receptor 2; ERK, extracellular signal regulated kinase; mTOR, mammalian target of rapamycin; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family, pyrin domain containing 3; IFNγ, interferon gamma; IL-1β, interleukin-1beta; PI3K, phosphoinositide 3-kinase; PP2A, protein phosphatase 2A; PP1, protein phosphatase 1; SK, sphingosine kinase; S1P, sphingosine 1-phosphate; S1P1, sphingosine 1-phosphate receptor-1; TH, T helper cells.

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1. Introduction

Formation of the bioactive lipid, sphingosine 1-phosphate (S1P) is catalysed by sphingosine kinase. There are two isoforms of sphingosine kinase (SK1 and SK2) which differ in their subcellular localisations, regulation and functions (Pyne et al., 2009). The S1P formed by these enzymes can either be exported from cells (through transporter proteins e.g. *Spns2*) and act as a ligand on a family of five S1P-specific G protein coupled receptors ($S1P_{1-5}$) (Blaho and Hla, 2014) or can bind to specific intracellular target proteins. For instance S1P formed by nuclear SK2 inhibits HDAC1/2 activity to induce *c-fos* and *p21* expression (Hait et al., 2009). Dephosphorylation of S1P is catalysed by S1P phosphatase and the sphingosine formed is then acylated to ceramide catalysed by ceramide synthase isoforms (Stiban et al., 2010). S1P can also be irreversibly cleaved by S1P lyase to produce (*E*)-2 hexadecenal and phosphoethanolamine (Degagné and Saba, 2014). The interconversion of ceramide to sphingosine and S1P has been termed the sphingolipid rheostat. In this model, shifting the balance toward ceramide induces apoptosis, while increased S1P formation promotes cell survival (Newton et al., 2015). For instance, ceramide activates protein phosphatase 2A (Dobrowsky et al., 1993), which dephosphorylates phosphorylated AKT (Zhou et al., 1998) and thereby alters BAD/Bcl2 regulation to induce apoptosis (Zundel and Giaccia, 1998). In contrast, S1P promotes cell survival, involving for instance, activation of the extracellular signal regulated kinase-1/2 (ERK-1/2) pathway (Pyne et al., 2009). However, the sphingolipid rheostat exhibits greater complexity, as certain ceramide species regulate processes other than apoptosis, such as autophagy and proliferation. This suggests temporal and spatial regulation, where the functionality of the sphingolipid rheostat is governed by compartmentalised signalling involving, for instance, ceramide synthase isoforms that produce different ceramide species with specific stress-dependent signalling functions that govern a defined cellular outcome e.g. apoptosis *versus* proliferation. The conversion of S1P to (*E*)-2 hexadecenal and phosphoethanolamine is also considered an exit point in the sphingolipid metabolic pathway, but (*E*)-2 hexadecenal has potential signalling functions (Kumar et al., 2011) and both (*E*)-2 hexadecenal and phosphoethanolamine can be further metabolised to produce phospholipids that have additional defined signalling functions in cells (Nakahara et al., 2012). Therefore, the regulation of the sphingolipid rheostat in different cellular compartments is likely to impact significantly on lipid signalling pathways that regulate cell context specific physiology and pathophysiology.

2. S1P receptors, sphingosine kinase and cancer

S1P has been implicated in regulating cellular processes, some of which underlie the hallmarks of cancer. First, over-expression of SK1 promotes the Ras dependent transformation of fibroblasts into fibrosarcoma (Xia et al., 2000). Second, S1P promotes neovascularisation of tumours (LaMontagne et al., 2006). Third, SK1 maintains the survival of cancer cells (a process termed 'non-oncogenic' addiction (Vadas et al., 2008)), promotes acquisition of replicative immortality and drives hormone-independent growth in prostate and breast cancer. Fourth, S1P induces inflammation involved in cancer progression. Thus, S1P enhances colitis associated cancer via an amplification loop involving SK1, $S1P_1$, NFκB, STAT3 and IL-6 (Liang et al., 2013; Pyne and Pyne, 2013; Nagahashi et al., 2014). Fifth, S1P binding to $S1P_1$/$S1P_3$ promotes growth and enhances migration of cancer cells (for review see Pyne and Pyne, 2010) and SK1 regulates microenvironmental interaction between cancer cells and tumour associated myofibroblasts to promote metastasis (Albinet et al., 2014; Pyne and Pyne, 2014). Sixth, inhibition/down-regulation of SK1 blocks the Warburg effect to which cancer cells are addicted for ATP production and anabolic metabolism (Watson et al., 2013).

From a clinical perspective, we have established that high tumour expression of SK1 is associated with reduced survival and decreased disease recurrance times in estrogen receptor (ER)-positive breast cancer patients (Watson et al., 2010; Long et al., 2010a; Ohotski et al., 2013). In addition, larger, more vascularised treatment resistant tumours are formed when cancer cells over-expressing SK1 are injected or implanted into mice (for review see Pyne and Pyne, 2010). There is also a substantial body of evidence to demonstrate a role for S1P receptors in cancer cell migration (for review see Pyne and Pyne, 2010). Moreover, we established that high $S1P_1$ and $S1P_3$ expression in tumours of ER positive breast cancer patients are associated with poor prognosis (Watson et al., 2010). We have also used a breast cancer cell line (MCF-7 cells) to demonstrate that S1P binding to $S1P_3$ stimulates the accumulation of phosphorylated ERK-1/2 into membrane ruffles/lamellipodia and the nucleus

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