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Review

S1P metabolism in cancer and other pathological conditions

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ABSTRACT

Nearly two decades ago, the sphingolipid metabolite sphingosine 1-phosphate was discovered to function as a lipid mediator and regulator of cell proliferation. Since that time, sphingosine 1-phosphate has been shown to mediate a diverse array of fundamental biological processes including cell proliferation, migration, invasion, angiogenesis, vascular maturation and lymphocyte trafficking. Sphingosine 1-phosphate acts primarily via signaling through five ubiquitously expressed G protein-coupled receptors. Intracellular sphingosine 1-phosphate molecules are transported extracellularly and gain access to cognate receptors for autocrine and paracrine signaling and for signaling at distant sites reached through blood and lymphatic circulation systems. Intracellular pools of sphingosine 1-phosphate available for signaling are tightly regulated primarily by three enzymes: sphinosine kinase, S1P lyase and S1P phosphatase. Alterations in sphingosine 1-phosphate as well as the enzymes involved in its synthesis and catabolism have been observed in many types of malignancy. These enzymes are being evaluated for their role in mediating cancer formation and progression, as well as their potential to serve as targets of anti-cancer therapeutics. In this review, the impact of sphingosine 1-phosphate, its cognate receptors, and the enzymes of sphingosine 1-phosphate metabolism on cell survival, apoptosis, autophagy, cellular transformation, invasion, angiogenesis and hypoxia in relation to cancer biology and treatment are discussed.

1. Introduction

Sphingolipids are structural membrane components and have also become widely recognized as the reservoir for a family of bioactive lipid mediators including ceramide, sphingosine, sphingosine 1-phosphate (S1P) and ceramide 1-phosphate derived from sphingolipid metabolism. S1P is the final common product of the sphingolipid degradative pathway and a bioactive molecule that mediates a diverse range of cellular processes. S1P acts extracellularly in paracrine and autocrine manner through five specific G protein-coupled receptors $S1P_1$–$S1P_5$ [1]. S1P circulates in blood and lymphatic systems and, thus, potentially gains access to receptors distant from its site of synthesis. There is some evidence that S1P may have direct intracellular functions, although this mechanism of action is poorly understood and remains controversial [2–4]. Since the first discovery of S1P's involvement in cellular proliferation in 1991 [5], numerous studies have revealed roles for S1P signaling in regulating conserved cell death pathways, cytoskeletal rearrangements, cell motility and vascular development [6–8]. Increased generation of S1P triggers signaling pathways that mediate cell survival and malignant transformation, and regulate apoptosis, invasion, angiogenesis, and hypoxia [9–11]. These fundamental biological processes are integral to cancer pathogenesis, thereby implicating S1P in cancer biology.

S1P homeostasis is tightly regulated by the balance between its synthesis and degradation via three enzymes (Fig. 1). These include sphingosine kinase (SphK), which generates S1P through phosphorylation of its precursor, sphingosine; S1P phosphatases (SPP1 and SPP2), which reversibly convert S1P back to sphingosine, and S1P lyase (SPL), which irreversibly degrades S1P to generate ethanolamine phosphate and hexadecenal, representing the last step in the sphingolipid degradation pathway [12]. Modulation of these enzymes affects S1P-mediated biology, and alterations of these enzymes have been observed in various pathological conditions, including cancer. This review focuses on our current understanding of how S1P signaling and the enzymes involved in S1P homeostasis impact cancer biology.

2. Alterations in S1P levels and related genes in cancer

Sphingolipid metabolism is often found to be dysregulated in cancer. Numerous studies have shown that Sphk1 acts as an oncogene [13] and is upregulated in a variety of human tumors, including lung, colon, breast, ovary, brain, stomach, uterus and kidney, compared with their healthy tissue counterparts [14–16]. Increased tumor Sphk1 expression correlated with a shorter survival for

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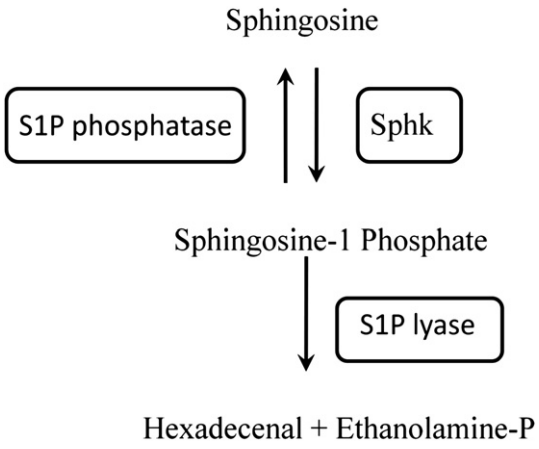

Fig. 1. S1P homeostasis is tightly regulated by the balance between its synthesis and degradation via three enzymes. (1) sphingosine kinase (SphK), which generates S1P through phosphorylation of its precursor, (2) S1P phosphatases (SPP1 and SPP2), which reversibly convert S1P back to sphingosine, and (3) S1P lyase (SPL), which irreversibly degrades S1P to generate ethanolamine phosphate and hexadecenal, representing the last step in the sphingolipid degradation pathway.

patients with glioblastoma multiforme [17]. Moreover, microarray analyses revealed a worse outcome for breast cancer patients with elevated Sphk1 expression, further supporting the notion that increased S1P generation confers a worse prognosis for cancer patients [18]. In a transgenic mouse model of erythroleukemia, increased Sphk1 expression and activity correlated with an increase in tumorigenic potential [19].

Consistent with the growth promoting effects of S1P in many tumors [20], S1P was found to be elevated in the plasma and malignant ascites of ovarian cancer patients [21,22]. Increased S1P levels and decreased SPL expression and enzyme activity were also observed in the polyps of the $Apc^{Min/+}$ mouse model of intestinal tumorigenesis compared to surrounding tissues [23]. The two enzymes responsible for S1P catabolism, SPP and SPL, were also downregulated in human colon cancer tissues compared to uninvolved colonic tissue [23]. These findings indicate that S1P metabolism is altered in neoplastic tissue, and that SPL and SPP could potentially function as anti-oncogenes [24]. In addition, SPL expression is downregulated in association with myc-mediated β-cell tumorigenesis in mice [25]. Significant downregulation of SPL was also observed in metastatic tumor tissues compared with primary tumors from the same patient, which suggests a role for SPL in tumor progression [26]. Conversely, SPL was found to be upregulated in ovarian cancer [27] and in ovarian tumors that were resistant to chemotherapy [28]. Whether SPL upregulation is a manifestation of tissue responses to elevated levels of S1P or is a causative factor remains to be determined.

3. S1P metabolism in relation to cell proliferation, transformation and conserved cell death pathways

A recent study demonstrated marked attenuation of tumor progression in murine xenograft and allograft models with the administration of a specific S1P-targeted monoclonal antibody that acts by interrupting S1P signaling [29]. This hallmark study illustrates the contribution of S1P signaling to tumorigenesis and the potential of targeting the S1P pathway for cancer treatment.

S1P acts as a mitogen and suppressor of apoptosis in most cell types [30,31]. S1P promoted cell growth and survival via extracellular signal-regulated kinase activation in human glioblastoma cells [32]. S1P upregulated myeloid cell leukemia-1 Mcl-1, an anti-apoptotic member of the bcl-2 family, and protected multiple myeloma cells and chronic myeloid leukemia cells from dexamethasone-induced apoptosis [33]. Although the mitogen effect of S1P in many tumors is well recognized [20], S1P has also been shown to exert an apoptotic effect in prostate cancer cell [34]. It has been speculated that the conversion of S1P to sphingosine by SPP or the accumulation of ceramide when the cells were stimulated with S1P may account for this finding. However, it is also possible that S1P may have anti-proliferative effects in certain cell populations. Intriguingly, S1P induced the expression of connective tissue growth factor CTGF, which possessed an anti-proliferative effect in Wilms tumor cells. The induction of CTGF is reported to be mediated by the $S1P_2$ receptor [35].

Some of the mitogenic and anti-apoptotic actions of S1P may be mediated independently of S1P receptors [4]. In the $Apc^{Min/+}$ mouse model, deletion of Sphk1 attenuated tumor formation, whereas the deletion of S1P receptors did not [36]. Redundancy of receptor signaling could be responsible for this observation. Alternatively, these findings could represent a role for sphingosine-mediated growth inhibition or a receptor-independent effect of S1P on the regulation of adenoma growth. S1P has been shown to mobilize calcium from internal stores [5,37] and activate phospholipase D [38] independent of $S1P_1$ receptor expression [4]. In addition, S1P-induced focal adhesion kinase phosphorylation was not affected by suramin, an inhibitor of S1P receptor–ligand interactions [39]. S1P inhibited changes in mitochondrial membrane potential and prevented cytochrome c release from mitochondria [40]. S1P signaling has also been shown to downregulate Bax, prevent its translocation to mitochondria and inactivate Bad in response to Fas-induced apoptosis [41]. To date, the precise intracellular targets of S1P remain elusive, and the role, if any, of receptor-independent S1P actions in tumorigenesis is unclear.

Besides regulating cell proliferation, S1P is able to trigger autophagy in cancer cells, which may experience nutrient starvation and rely on autophagy for survival. In human prostate cancer PC3 cells, S1P inhibited rapamycin signaling and induced autophagy through $S1P_5$ [42]. Nutrient deprivation stimulated both autophagy and SphK activity. Overexpression of Sphk1 in MCF-7 cells stimulated autophagy by increasing the formation of LC3-positive autophagosomes and the rate of proteolysis sensitive to the autophagy inhibitor 3-methyladenine. Conversely, knocking down Sphk1 diminished nutrient deprivation-induced autophagy [43].

Two isotypes of SphK (Sphk1 and Sphk2) have been identified. There is strong evidence supporting the importance of Sphk1 in tumorigenesis, whereas the role of Sphk2 in this process remains to be determined [44]. Sphk1 is activated to produce S1P by a variety of growth factors (epidermal growth factor, EGF and insulin-like growth factor-1, IGF-1), hormones (estradiol) and angiogenic factors (vascular endothelial growth factor, VEGF) implicated in mediating cancer progression [2]. Overexpression of Sphk1 in mouse fibroblasts resulted in H-Ras-mediated cellular transformation and tumor formation in nude mice, thereby revealing the oncogenic role of Sphk1 [13]. Promotion of tumor growth was also observed in xenograft studies using prostate cancer cells overexpressing Sphk1, whereas downregulating Sphk1 resulted in apoptosis and reduced cell growth [45,46]. Overexpression of Sphk1 in MCF-7 breast cancer cells elevated S1P levels, stimulated estrogen-dependent cell proliferation, promoted breast cancer growth in soft agar and enhanced tumorigenesis in mice [47], whereas silencing of Sphk1 resulted in growth arrest and apoptosis [48]. In $Apc^{Min/+}$ mice, knockdown of SphK resulted in reduction of adenoma size and attenuation of epithelial cell proliferation in the polyps, suggesting that Sphk1 plays a role in tumor progression [36]. Similarly, knockdown of Sphk1 in mice treated with azoxymethane led to reduction of crypt foci formation, indicating the importance of Sphk1/S1P pathway in colon carcinogenesis [16]. Importantly, SphK inhibitors