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Mini Review

Drug Resistance in Chronic Myelogenous Leukemia Caused by Sphingosine Kinases

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Abstract

Sphingosine 1-Phosphate (S1P) is a mitogenic lipid molecule formed by the enzymes, Sphingosine Kinase (SphK) 1 and 2. SphK1, which is commonly over expressed in malignant tumours, is recognized as a significant contributor to cancer cell survival and tumour angiogenesis, and is accordingly implicated in the pathogenesis of various types of cancer. Initial studies focused on non-haemopoietic malignancies; however a growing body of literature on the role of sphingolipid metabolism in haemopoietic malignancies is now emerging. In particular, Sphk1 is implicated in the resistance of Tyrosin Kinase Inihibitors (TKIs) in Chronic Myelogenous Leukemia (CML) Here, we discuss the roles of the SphKs in CML and the compounds currently available in order to develop new combinatorial therapeutic approaches.

Keywords: Chronic Myelogenous Leukemia (CML), Tyrosine kinase inhibitors (TKIs), Resistance, BCR-ABL, Sphingosine Kinase 1 (SphK1), Sphingosine Kinase 2 (SphK2)

Introduction

The molecular hallmark of CML is the Philadelphia chromosome leukemia results from the neoplastic transformation of Hematopoietic Stem Cells (HSCs) [1]. HSC is still able to differentiate into granulocytes during the Chronic Phase (CP) but this ability is lost during the Accelerated phase (AC) and/or a Blast Crisis (BC) characterized by the presence of several undifferentiated cells also in peripheral blood. The median duration of CP is 3-4 years. As the disease progresses, after the acquisition of additional genetic and/or epigenetic abnormalities, patients enter an accelerated phase followed by BC. This is the most aggressive phase and is characterized by a block of cell differentiation that results in the presence of 30% or more myeloid or lymphoid blast cells in peripheral blood or bone marrow [2]. The molecular hallmark of CML is the Philadelphia Chromosome (Ph), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22) (q11;q34)]. The Philadelphia chromosome contains a BCR-ABL hybrid gene that encodes an oncogenic fusion protein. The BCR-ABL protein has deregulated tyrosine kinase activity that promotes cell growth through phosphorylation of signaling proteins [3-7]. Depending on the precise breakpoints in the translocation and RNA splicing, different forms of BCR-ABL protein with different molecular weights (p185 BCR-ABL, p210 BCR-ABL and p230 BCR-ABL) can be generated in patients. Such protein is localized exclusively to the cytoplasm and is able to constitutively tyrosine phosphorylate a host of substrates. Importantly, due to autophosphorylation, there is increased phospho-Tyrosine (p-Tyr) on the BCR-ABL oncoprotein itself. Substrates of BCR-ABL can be grouped into three broad categories, depending on function: (1) adaptor molecules such as CrkL and p62Dok; (2) cell membrane and cytoskeleton related proteins such as talin and paxillin and (3) proteins with catalytic function such as Ras-GAP and Phospholipase Cg (PLCg) [8]. Tyrosine phosphorylation of these BCR-ABL substrates results in the constitutive activation of multiple cytoplasmic and nuclear signalling cascades, which are shared with cytokines known to regulate the proliferation, differentiation and survival of haemopoietic cells.

BCR-ABL inhibitors

Before 2000s, CML has been treated with hydroxyl urea and interferon therapy that provide temporary disease control but do not alter progression to advanced disease with a median survival ranging 45-55 months from diagnosis [9]. Therefore, the most effective treatment strategy was Allogeneic Stem Cell Transplantation (ASCT). The recognition of the BCR-ABL oncogene and the corresponding protein led to the synthesis of small-molecule drugs, designed to interfere with BCR-ABL tyrosine kinase activation [10]. The small molecule Tyrosin Kinase Inihibitors (TKIs) are the central line of treatment against CML. Over the past decade the development of TKIs that directly target the constitutive tyrosine kinase activity of BCR-ABL has resulted in significantly improved survival rates and disease management in CP CML patients. Nevertheless, it has to be noted that allogeneic transplantation remains the most effective long-term therapy for CML, particularly in the more aggressive stages of the disease. The first TKI to be discovered was imatinib which could specifically discriminate CML cells from their normal counterparts by directly targeting BCR-ABL [10]. Imatinib treatment of CML in CP is associated with an overall survival rate of 89% over a five-year clinical evaluation and a progression-free survival rate of 93%, which was much higher than earlier treatment strategies involving interferon-alpha (IFN-α) [11]. However, resistance to imatinib can arise as a result of mutations in the kinase domain that either make direct interactions with imatinib or are important in formation of the inactive BCR-ABL conformation that is required for drug interaction [12]. Therefore, two second generation TKIs were designed to overcome the observed imatinib resistance, which included nilotinib [13], a derivative of imatinib with ~30-fold higher strength, and dasatinib [14], with 300-fold higher potency than imatinib. In

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addition, other two second-generation oral, dual Src/Abl TKIs, has been shown to be more efficient than imatinib against CML cell lines such as Bosutinib (formerly SKI-606) [15]. Bafetinib (formerly INNO-406) [16,17]. The administration of second generation TKIs resulted in achieving a quicker response, significantly reduced progression to the later stages of the disease and increased overall survival. Nevertheless, BCR-ABLT315I is the most TKI-insensitive mutation which is referred to as the gatekeeper mutation that could not be targeted by second generation TKIs [18]. Therefore, there have been increased efforts to develop third generation TKIs that can target BCR-ABLT315I mutant, such as ponatinib [19] and DCC-2036 [20]. CML patients who have responded to therapy and are in a state of remission harbour a very suppressed clone of CML cells which is referred to as Minimal Residual Disease (MRD) or Leukemia Stem Cells (LSCs) [21,22]. LSCs are responsible for the relapse of CP CML after the withdrawal of TKIs and therefore, patients are kept on lifelong TKI treatment after achieving remission. In addition, the TKI resistance of LSCs is not associated with the BCR-ABL kinase domain mutations [22]. These observations indicate that TKI-insensitive LSCs and TKI-sensitive leukemic progenitor cells are biologically different, which leads us to believe that LSCs and more differentiated leukemic cells have different genetic mechanisms [23].

The sphingosine kinases

These kinases regulate the generation of Sphingosine 1-Phosphate (S1P), although many other enzymes are also involved in the dynamic metabolic network of this bioactive lipid. Hence, they emerge as an excellent therapeutic target for modifying the levels of S1P. Among the biological and pathological processes that involve S1P, cancer and inflammation are top candidates for therapeutic intervention by targeting S1P production by SphK. It is highly expressed in different human tumors [24]. To date, two human isoforms of SphK genes, SphKl and SphK2, have been identified and cloned from different chromosomes. It is evolutionary highly conserved from yeast to human, in that five conserved domains have been identified from these isoforms across several species [25,26].

Sphingosine kinase 1: There are three isoforms of SphK1 resulting from alternative splicing that differs only in their N-termini [27], however, little is known about their function in cancer. The oncogenic role of SphK1 was first defined with the demonstration that its over expression enabled non-transformed fibroblasts to form tumours in immunodeficient mice [28]. The connection between SphK1 and cancer was further recognized after the expression level of SphK1 in a diverse range of solid tumours was observed to be, on average, approximately 2-fold higher than in matched normal tissue [29]. Many tumour promoting factors, including Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor Beta (TGFβ), and Phorbol 12-Myristate 13-Acetate (PMA) are known to activate SphK1 [30]. This activation can be achieved by inducing SphK1 mRNA expression, as demonstrated by up regulated SphK1 mRNA expression following treatment with PMA in leukaemia cells [31], or EGF [32] and 17β-estradiol in breast cancer cells [33]. In addition to the long-term activation produced by transcriptional up-regulation, SphK1 can be activated immediately and transiently: oncogenic stimuli can promote phosphorylation of SphK1 at its Serine225 (Ser225) residue by activated Extracellular Signal-Regulated Kinase (ERK). This causes its translocation from the cytosol to the plasma membrane, and such translocation is known to be a crucial mechanism for the oncogenic role of SphK1 because it promotes proliferation and tumourigenicity of non-cancer cells by increasing production of S1P, especially extracellular S1P [34]. Extracellular S1P secreted from the cells signals in an autocrine manner through S1P receptors [35], resulting in ERK activation, a well-known signal for cancer cell proliferation and migration [36], as well as activation of Phosphatidylinositol 3-kinase/Aktivin, Protein Kinase B (PI3K-Akt) pathway, a well-established oncogenic survival pathway [37]. In addition, the autocrine signalling of S1P from activated SphK1 can transactivate various oncogenic receptor tyrosine kinases [38-40].

Sphingosine kinase 2: SphK2, the other SphK isoform, is a relatively newly discovered enzyme [41]. In contrast to SphK1, the involvement of SphK2 in cancer is much less well understood and only recently emphasized with a handful of literature reports suggesting that it may play an important role in cancer cell proliferation. The mechanism through which endogenous SphK2 activity promotes cancer cell proliferation and survival has not been thoroughly studied. Also noteworthy is that, in contrast to SphK1, SphK2 expression is not reported to be increased in any human cancer tissue. Whilst SphK1 over-expression promotes cell proliferation and oncogenic transformation, Sphk2 up-regulation has the opposite effect: inhibition of DNA synthesis cell cycle arrest [41], and induction of apoptosis [42]. This apoptotic role of SphK2 over expression was later shown to be due to increased SphK activity in intracellular membrane structures, specifically the Endoplasmic Reticulum (ER) [43-45]. These studies emphasise that the distinct localization of SphK may enable the specific cellular functions of the enzyme. SphK1 mainly resides in the cytosol with occasional encounters with membrane structures, presumably for its oncogenic actions in the plasma membrane, whereas SphK2 is often associated with intracellular membrane structures including the ER [43] and nucleus [41]. Since SphK2 may function as an apoptotic effectors in the intracellular membranes, the recently revealed role of SphK2 in proliferation may require its translocation. Comparable to the translocation of SphK1 from the cytosol to the plasma membrane, SphK2 is known to be translocated from the nucleus to the cytosol by external stimuli, including serum [46] and a cell growth promoting factor, PMA [47]. In addition, PMA increases SphK2 activity through ERK-mediated activation in breast cancer cells [48], indicating that the actions of SphK2 in the cytosol may act as a downstream effectors of various factors that promote cell proliferation and survival.

Sphingosine kinases and drug resistance

Many studies have implicated SphK1/S1P signalling in the process of drug resistance because this signalling protects cancer cells from chemotherapy-induced apoptosis. Considerable evidences indicate a deregulation of SphK1 in both acute and chronic myelogenous leukemia. Elevated levels of SphK1 have been identified in variety of leukemic cell lines, correlating with chemotherapeutic resistance [49], while high SphK1 expression appears to be integral for erythroleukaemic progression [50]. Furthermore, SphK1 expression has been shown to be up regulated by BCR-ABL gene fusion, with this event necessary for Myeloid cell leukemia-1 (Mcl-1)-expressing and enhanced cell survival in CML [51].

Tyrosine Kinase inhibitors of BCR-ABL have improved the treatment outcome for CML and different studies have clarified the apoptotic mechanisms induced by TKIs, showing that they kill the CML cells emploing pro-apoptotic protein BIM [52]. On the other hand, different mechanisms for TKIs resistance have also been identified both BCR-ABL-dependent and –independent pathway.

In addition, by activating various BCR-ABL-independent signaling pathways, quiescent CML-initiating cells are most likely insensitive to TKIs [53], while various components of Bone Marrow Microenvironment (BMME), i.e. leukemia niches, also protects CML cells from TKIs [54,55]. Recent studies elucidated the molecular mechanism by which SphK1 induces the acquisition of resistance to the anticancer agent imatinib in CML [56,57]. CML patients express the oncoprotein BCR-ABL, a constitutively active tyrosine kinase that activates multiple signaling pathways to promote cancer progression. Imatinib, a BCR-ABL inhibitor, is the mainstay therapeutic option for treatment of CML. SphK1 contributes to the resistance of CML cells to this anticancer agent as demonstrated by the finding that siRNA knock-down of SphK1 expression sensitizes resistant CML cells to imatinib whereas enforced expression of SphK1 prevents apoptosis in response to this drug in sensitive CML cells [56,58]. Salas and colleagues [57] demonstrated that S1P/S1P2 signaling regulates BCR-ABL stability in CML cells by inhibiting the activity of the protein phosphatase PP2A. This prevents the dephosphorylation of BCR-ABL and therefore its proteasomal degradation, resulting in the accumulation of the oncoprotein. Thus, inhibition of the SphK1/S1P/S1P2 pathway sensitizes CML cells to imatinib by restoring the PP2A-dependent dephosphorylation and subsequent degradation of BCR-ABL [57]. Evidence also exists that the SphK1/S1P/S1P receptors pathway enhances the expression and activity of drug efflux pumps in cancer cells, which are major contributors to the development of multidrug resistance in cancer [59]. This might represent an additional mechanism by which SphK1 contributes to chemotherapy resistance. SphK2 is also involved in resistance to chemotherapy. This is exemplified by the finding that siRNA knockdown of SphK2 expression enhances apoptosis induced by the anti-cancer agent doxorubicin in breast and colon cancer cells, an effect that was associated with a reduction in the expression of the cell-cycle regulator protein p21 [60].

Sphingosine kinase inhibitors

The rational for developing SphK inhibitors is based on two facts: 1) the catalytic product of SphK and S1P plays an essential role in promoting cell proliferation and migration via its receptors and downstream proteins; 2) and SphKs are the key enzymes that control the balance between mitogenic S1P and apoptotic ceramides, also known as the "sphingolipid rheostat". In other words, SphK inhibitors could include: a) kinase inhibitors that can suppress the catalytic function of SphK, which subsequently decreases the production of S1P at the extracellular, intracellular, and even b) specific sub-cellular compartment level. Based on the above observations, S1P signaling is implicated in cell proliferation, migration, angiogenesis, and autophagy; all processes that facilitate cancer progression. Therefore, blocking of S1P signaling may be a potential target for cancer therapy.

There are a number of pre-clinical studies examining the effect of FTY720 (fingolimod) a synthetic myriocin analogue (2-amino-2-[2-(4-octylphenyl) ethyl] propane-1, 3-dio) on hematological malignancies. FTY720 is phosphorylated *in vivo* by sphingosine kinase 2 and binds to all four of the currently known Sphingosine 1 Phosphate (S1P) receptors ($S1PR_1$, $S1PR_3$, $S1PR_4$, and $S1PR_5$) with high affinity. Upon binding of p-FTY720, the S1PRs are internalized from the cell membrane and degraded, resulting in the sequestration of lymphocytes in secondary lymphoid organs [61]. Moreover, FTY720 was recently shown to be therapeutically active against several solid tumors, Multiple Myeloma, Chronic Lymphocytic Leukemia (CLL) [62,63], Mantle Cell Lymphoma [64], murine cell line models of Acute Myeloid Leukemia (AML) with KIT mutations, and a rat model of Natural Killer-cell (NK) leukemia [64,65]. In light of the studies by Salas et al. [57] and Tonelli et al. [66], it is conceivable that FTY720-induced apoptosis in CML cells might be due not only to its direct action on PP2A but also to the inhibition of SphK1 activity and consequent disruption of the S1P/S1P2 signaling.

In a recent report, it has been demonstrated that FTY720 is able to induce apoptosis of leukemic cells via activation of both BIM and BID and can overcome various type of resistance to TKIs used in the treatment of CML. Kiyota M et al. have investigated the precise mechanisms underlying the apoptosis caused by FTY720, especially focusing on the roles of BH3- only proteins. Hence, FTY720 activates proapoptotic BH3 -only proteins: BIM, which is essential for apoptosis by BCR-ABL TKIs and BID, which accelerates the extrinsic apoptosis. Finally, these results provide the rationale that such drug, with its unique effect on BIM and BID, could lead to new therapeutic strategy for CML [68]. In another study, Neviani P. et al, have presented the investigation of FTY720 as novel therapeutic approach for patients with imatinib/dasatinib sensitive and -resistant advanced CML and Ph-positive Acute Lymphocytic Leukemia (ALL). FTY720 is able to induce marked apoptosis of CML-BC (Blast Crisis), Ph–positive ALL CD 34+ /CD 19+ patient cells by impairing –BCR-ABL activity [69]. Furthermore, in vivo long-term administration of pharmacologic FTY720 doses not induce adverse effects and significantly inhibits wild-type and T315I p210 and p190 BCR/ABL leukemogenesis in mice [70]. In particular, two recent reports have demonstrated that restoration of PP2A activity by FTY720 or its derivatives (*S*)-FTY720-OMe, (*S*)-FTY720-regioisomer are able to block the proliferation of Leukemia Stem Cells (LSCs) (derived by CML patients), but not of quiescent Hemapoietic Stem Cells (HSCs) (derived by healthy individuals) both in vitro and in vivo [71,72]. There are other inhibitors: threo-DHS (threo-dihydrosphingosine), a sphingosine competitive inhibitor of SphK1 [24] and Safingol (L-threo-DHS), a synthetic L stereoisomer of endogenous threo-dihydrosphinganine, that may be more suited to inhibit SphK1 [73]. In spite of the fact that it induces autophagy in colon carcinoma cells through inhibition of Protein kinase C (PKC) and the PI3K pathway [74], it entered clinical trials as an anticancer drug. In combination with cisplatin, it can be safely administered with reversible dose dependent hepatic toxicity [75]; however, no data from phase II clinical trial is reported. SphK1-1 (2R, 3S,4 E)-N -methyl-5-(4' -pentylphenyl)-2-aminopent-4-ene-I,3- diol) is a sphingosine analogue that is water-soluble and cell permeable [60]. It decreases growth and survival of human leukemia U937 and Jurkat cells, and enhances apoptosis and cleavage of Bcl-2 [76].

Conclusion

Due to the important roles of S1P in tumor genesis, targeting of

S1P signaling may potentially serve as an adjuvant for cancer therapy. Since S1P is generated from sphingosine by SphKs, the factors that regulate the balance of the ceramide-sphingosine-S1P rheostat towards ceramide and decreasing SphK activity may be candidates for anti-cancer drug development. In addition, the findings indicate that combination therapies of SphK1/SphK2 inhibitors with conventional anticancer agents might be a valuable option for the clinical management of therapeutic-resistant cancers.

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