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Addressing the Potential Role of Fingolimod in Cancer Therapy

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Abstract

Fingolimod is a well known immunomodulator used by oral route in relapsing multiple sclerosis patients. Upon phosphorylation by sphingosine kinase 2 (SPHK2), fingolimod binds to one or more of at least five G protein coupled receptors known as S1PR1-5, thus it causes S1PRs internalization and consequent sequestration of lymphocytes in lymphoid organs. Fingolimod also affects other signaling pathways. In particular, this drug is able to activate the serine-threonine protein phosphatase 2A (PP2A) which regulates multiple cell signaling cascades by virtue of its phosphatase activity. PP2A loss-of-function may represent one of the major events contributing to cancer development and progression. Hence, there is a need for therapeutic PP2A reactivation. In this regard, fingolimod is revealing a promising candidate for cancer treatment due to its ability to reactivate PP2A, reduce cell viability and promote apoptosis. However, the appropriate dosage and safety remain a challenge.

Keywords: Fingolimod; PP2A; Cytotoxicity; Apoptosis; Cancer

Introduction

Fingolimod (FTY720), a myriocin analogue structurally related to sphingosine, is a well known immunomodulator, currently used by oral route in relapsing multiple sclerosis patients [1,2]. Upon phosphorylation by sphingosine kinase 2 (SPHK2), fingolimod binds to one or more of at least five G protein coupled receptors known as S1PR1-5. S1PR1 couples to Gi to activate Ras/ERK and PI3-kinase/Akt pathways leading to mitogenic and survival signaling as well as cell migration [3]. S1PR2 couples with multiple heterotrimeric G proteins, including G12/13 which exerts a potent inhibitory effect on Rac GTPase with consequent inhibition of cell migration [3]. Although fingolimod has an initial agonist activity at S1PRs, it subsequently causes internalization and consequent reduction of receptor levels on the cell surface, thus interfering with immune cell trafficking between lymphoid organs and peripheral blood [4-6].

Although fingolimod exerts the immunosuppressive effects by modulating S1PRs signaling, thus leading to sequestration of lymphocytes in lymphoid organs, it also affects other signaling pathways. These non classical effects have been referred to as "*off-target*" since they are induced when fingolimod is used at concentrations higher than those required for its classical "*on-target*" action as a S1PR ligand [7]. As a sphingosine analogue, fingolimod influences other components of the sphingolipids pathway. In particular, it inhibits and reduces the expression of SPHK1 [8,9] and SPHK2 [10], is a competitive inhibitor of ceramide synthase [11,12] and an inhibitor of S1P lyase [13]. Of note, fingolimod is also able to activate the serine-threonine protein phosphatase 2A (PP2A) which regulates multiple cell signaling cascades by virtue of its phosphatase activity. For instance, PP2A counteracts most of the signals triggered by protein kinases, hence controls apoptotic pathways, translation of oncogenic proteins, and cell division [14]. PP2A loss-of-function may represent one of the major events contributing to cancer development and progression. Alterations of the regulatory and scaffold subunits as well as dysregulation of other binding partners of PP2A have been found in numerous malignancies [14,15]. Hence, there is a need for its therapeutic reactivation.

Is fingolimod tailored for cancer therapy?

The ability of fingolimod to activate PP2A seems to be independent from SPHK2 phosphorylation and S1PR1 interaction [16]. Fingolimod-induced activation of PP2A seems to be due to a direct effect on the PP2A heterotrimeric complexes with consequent Akt dephosphorylation independently from PI3-kinase inhibition [17]. However, fingolimod is able to inactivate the PI3K/Akt via inhibition of PI3K [18] or increase in the expression of PTEN (phosphatase and tensin homologue) which regulates PI3K activity [19]. Of note, the PI3K/Akt pathway could also be activated by S1P [7]. Therefore fingolimod could inhibit the PI3K/Akt pathway via S1P-dependent and –independent mechanisms.

Loss of PP2A function can be achieved through the aberrant expression of regulatory factors interacting with PP2A. Among them, CIP2A (cancerous inhibitor of PP2A) interacts with PP2A, thus inhibiting PP2A-dependent dephosphorylation of oncogenes such as c-Myc [20]. SET (I2PP2A, inhibitor 2 of PP2A) is an additional binding partner of PP2A with specific inhibitory activity [21]. Fingolimod interacts with SET/PP2A complexes and also reduces the expression of SET, thus leading to PP2A reactivation [22]. However, the mechanism underlying the anticancer property of fingolimod is more complex than one could expect on the basis of simple PP2A reactivation because of the extensive crosstalk among signaling pathways which participate in the regulation of cell metabolism, proliferation and survival.

Fingolimod is cytotoxic and reduces efficiently the viability of cancer cell lines *in vitro* with apparently minimal effects on normal cells [7]. The majority of studies have shown that cytotoxicity of fingolimod depends on the ability to promote apoptosis via activation of both extrinsic and intrinsic pathways [23-26] or even induce autophagy [27]. Apoptosis induced by fingolimod in several haematological cancer cells appears to be mediated by PP2A activation and consequent downstream dephosphorylation of ERK1/2. In fact okadaic acid, a selective PP2A inhibitor with tumor-promoting activity, is able to rescue these cells from fingolimod-induced death [28]. One of the most challenging aspect of the pharmacological profile of fingolimod is the ability to kill some cancer cells resistant to conventional chemotherapy [16,23,29-31] and sensitize cancer cells to radiation [9,32,33]. At cytotoxic concentrations, fingolimod induces G_1 phase cell cycle arrest by either down-regulating cyclin D1, cyclin E and cyclin-dependent

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kinases (CDK)2/4 or up-regulating the CDK inhibitors [18,19,26,34,35]. Fingolimod-induced cell cycle arrest and inhibition of cell proliferation appear to be mediated by both PP2A [29,36] and PTEN/PI3K/Akt signaling pathways [18,19]. Moreover, there is evidence that FTY720 is phosphorylated by SPHK2 in breast cancer cells and accumulates in the nucleus [37]. Nuclear FTY720-P is a potent inhibitor of class I histone deacetylases (HDACs) that enhance histone acetylation and regulate the expression of a restricted set of genes independently of its known effects on canonical signaling through S1PR1 [37]. In ERα-negative human and murine breast cancer cells, FTY720 reactivates expression of silenced ERα receptors and sensitizes them to tamoxifen [37]. These effects underline the potential benefit of fingolimod in the management of breast cancer resistant to conventional hormonal therapy.

Interestingly, at concentrations lower than those causing cytotoxicity, fingolimod exhibits anti-migratory and/or anti-invasive effects in different cancer cell lines in agreement with its ability to induce cytoskeletal disorganization [38]. Moreover, fingolimod suppresses lymph node and organ metastasis in *in vivo* cancer models [7]. The SPHK1/S1P/S1PR signaling pathway appears to play a key role in mediating the effects of fingolimod on migration/invasion and metastasis [30,39]. Notably, fingolimod is able to down-regulate the active form of small GTPases, such as RhoA and Rac, which are downstream effectors of the S1PRs and key regulators of cell mobility [37,40,41]. These properties make fingolimod a potential drug tailored for the management of late stage disease. Moreover, fingolimod has been shown to inhibit angiogenesis at low doses. In particular, it is able to revert the effects of S1P on the migration of human umbilical vein endothelial cells (HUVEC) and vascular smooth muscle cells (VSMC), and down-regulate VEGF [42-45].

Conclusions

The ability of fingolimod to target multiple signaling pathways suggests that this drug could be useful to fight against a wide range of malignancies with a larger benefit for late stage and/or chemotherapy-resistant disease. However, the toxicity profile of fingolimod deserves much attention. The main side effects reported in MS patients treated with higher doses of fingolimod can be ascribed to immunosuppression [46,47]. However, transient bradycardia, reversible cerebral vasoconstriction syndrome, acute lymphoblastic leukemia, lymphomatoid papulosis, melanoma, macular edema and retinal hemorrhage have been also reported [48-54]. On the other hand, it is difficult to actually predict the toxicity profile in cancer patients as the treatment schedule may differ substantially from that used in MS patients. *In vitro* studies indicate that the anticancer effect may be achieved using a dose range higher than that necessary to antagonize S1PR signaling. Since there are side effects associated with inhibition of S1P signaling, fingolimod derivatives lacking S1P signaling capability but retaining the cytotoxic property or derivatives with enhanced sphingosine kinase inhibition are arousing strong interest to pharmaceutical and biotechnology companies [7]. Moreover, single or dual antibody liposomal formulations for targeted delivery of fingolimod could represent a further strategy to reduce unwanted toxicity [7]. However, accurate evaluation of actual benefits of fingolimod and its derivatives in different cancer settings as well as clinical trials are needed before claiming this drug as a potential candidate for inclusion in the repertoire of anticancer therapy.

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