FTY720 for cancer therapy (Review)

LI ZHANG, HAN-DONG WANG, XIANG-JUN JI, ZI-XIANG CONG, JIAN-HONG ZHU and YUAN ZHOU

Department of Neurosurgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu 210002, P.R. China

Received July 29, 2013; Accepted September 16, 2013

DOI: 10.3892/or.2013.2765

Abstract. 2-Amino-2-[2-(4-octylphenyl)]-1,3-propanediol hydrochloride (FTY720) is a potent immunosuppressant which has been approved by the Food and Drug Administration (FDA) as a new treatment for multiple sclerosis. As an immunosuppressant, it displays its anti-multiple sclerosis, immunosuppressive effects by activating sphingosine-1-phosphate receptors (S1PRs). In addition to the immunosuppressive effects, FTY720 also shows preclinical antitumor efficacy in several cancer models. In most cases, phosphorylation of FTY720 is not required for its cytotoxic effect, indicating the involvement of S1PR-independent mechanisms which are starkly different from the immunosuppressive property of FTY720. In the present study, we reviewed the rapidly advancing field of FTY720 in cancer therapy as well as some molecular targets of the unphosphorylated form of FTY720.

Contents

1. Introduction
2. Anticancer effects of FTY720
3. Side-effects
4. Molecular targets of unphosphorylated form of FTY720
5. Conclusion

1. Introduction

2-Amino-2-[2-(4-octylphenyl)]-1,3-propanediol hydrochloride (FTY720), also known as fingolimod, is a synthetic compound produced by modification of a metabolite from Isaria sinclairii (1,2). FTY720 is a newly developed immunosuppressant. This drug selectively reduces the number of lymphocytes in the peripheral circulation, significantly prolongs the survival of experimental animals and transplanted organs without prejudice to the immune response to the virus and immune memory function (3-7). In addition, on September 22, 2010, FTY720 became the first oral disease-modifying drug approved by the Food and Drug Administration (FDA) to reduce relapses and delay disability progression in patients with relapsing forms of multiple sclerosis. The immunosuppressive activity of FTY720 has been suggested to be related to its phosphorylation by sphingosine kinase 2 (SphK2) and subsequent modulation of G protein-coupled sphingosine-1-phosphate receptors (S1PRs) (S1PR1, S1PR3, S1PR4, S1PR5) that induce lymphopenia by altering lymphocyte trafficking (8). In addition to the potent immunosuppressive effects, evidence suggests that FTY720 has antitumor efficacy in multiple types of cancer, including breast (9), glioblastoma (10), prostate (11), lung (12), ovarian (13) and hematopoietic malignancies (14). This antitumor activity of FTY720 is reportedly independent of the phosphorylation of FTY720, which is different from the immunosuppressive effects of FTY720 (15). In the present study, we described the latest progress of FTY720 in cancer therapy (Table I).

2. Anticancer effects of FTY720

In vitro therapeutic activity of FTY720

Caspase-dependent apoptotic pathway. During studies assessing the lymphopenic action of FTY720, it was revealed that FTY720 also induced apoptosis in peripheral lymphocytes. This observation led to investigations into the potential of FTY720 to act as an apoptosis-inducing anticancer agent (8). FTY720 was first reported to induce early apoptosis in an androgen-independent prostate cancer cell line dependent on caspase-3 activation (16). Subsequently, it demonstrated preclinical antitumor efficacy in various cancer models. The antitumor activity of FTY720 was reportedly attributed to different apoptotic pathways. Generally, there are two distinct pathways for inducing apoptosis, including the mitochondrial death pathway (intrinsinc pathway of apoptosis) and the death receptor pathway (extrinsic pathway of apoptosis). The mitochondrial death pathway is controlled by members of the Bcl-2 family, including Bcl-2, Bad, Bax, Bid and Baf proteins on the mitochondrial membrane. Death stimuli increase mitochondrial permeability and release cytochrome c and other factors from the mitochondria, resulting in caspase-3 activation and then apoptosis. By contrast, the death receptor pathway is mediated by Fas (CD95) and Fas-ligand. Binding of Fas and Fas-ligand induces activation of the caspase cascade via activation of caspase-8 and results in apoptosis through activation
of caspase-3 (17,18). It has been demonstrated that FTY720 could activate caspase-3, caspase-9 and poly (ADP-ribose) polymerase (PARP) in gastric cancer cells, however there was no obvious change in procaspases-8 and -10, and the cleaved products were not detected (19). In addition, FTY720 was shown to increase the levels of caspase-2 and -3 and apoptosis-promoting Bcl-associated proteins, Bad, Bax, Bid and Btf, and decrease the protein level of Bcl-2 in human renal cancer cells. However, there was no difference in the protein levels of caspase-8, Fas, FADD and TRADD, between cells treated with FTY720 and controls (20). These data indicate that FTY720 induces apoptosis through the intrinsic apoptotic pathways, instead of the extrinsic pathway of apoptosis. By contrast, in multiple myeloma cells, FTY720 triggered activation of caspase-8, -9, -3, PARP cleavage, induced alterations in mitochondrial membrane potential and Bax cleavage, and anti-Fas antibodies augmented anti-multiple myeloma activity induced by FTY720 (21), demonstrating that FTY720 enhances death signaling via both the extrinsic and intrinsic pathways. The difference may be due to the intricate connections between FTY720 and cell apoptosis, depending on cell types and stimulation manners. Furthermore, there exists a caspase-independent apoptotic pathway that is mediated by apoptosis-inducing factor (AIF) (22). However, no reports as yet have demonstrated that FTY720 could induce cell apoptosis through this pathway.

Caspase-independent cell death. Due to the differences among cell types, there are also reports showing that FTY720 induces cell death independent of apoptosis. For example, in mantle cell lymphoma, FTY720 mediated time- and

Table I. Effects of FTY720 on cancer.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>In vitro/in vivo</th>
<th>Molecular targets</th>
<th>Functions</th>
<th>(Ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>In vitro</td>
<td>ROS</td>
<td>Autophagic cell death and caspase-dependent apoptosis</td>
<td>(21,26)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Both</td>
<td>CD74, Cyclin D1, PKB</td>
<td>Lysosomal membrane permeabilization related cell death and prolonged survival in mouse</td>
<td>(23,28)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>In vitro</td>
<td>ROS</td>
<td>Caspase, PP2A-independent cell death</td>
<td>(25)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia and lymphoblastic leukemia/lymphoma</td>
<td>Both</td>
<td>PP2A, ERK1/2</td>
<td>Induce caspase-independent cell death and prolong survival in mouse models</td>
<td>(24)</td>
</tr>
<tr>
<td>Glioma</td>
<td>Both</td>
<td>FAK, ERK1/2</td>
<td>Induce caspase-dependent apoptosis, decrease invasion and inhibit tumor growth, increase survival time in mouse models</td>
<td>(35,36)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>Both</td>
<td>S1P, CXCR4</td>
<td>Antiangiogenic and reduce tumor size</td>
<td>(12,37,38)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Both</td>
<td>SphK2, AKT</td>
<td>Induce cell death and inhibited the growth of NB xenografts</td>
<td>(39)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>In vitro</td>
<td>p38MAPK, ERK1/2, FAK, SphK 1</td>
<td>Induce caspase-dependent apoptosis and sensitize cells to radiotherapy</td>
<td>(40-42)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Both</td>
<td>Rac, EPCs, CXCL10, VEGF</td>
<td>Suppress metastasis</td>
<td>(43,44)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Both</td>
<td>SphK1, JNK</td>
<td>Induce apoptotic cell death, prevent tumor growth, metastasis and prolong animal survival</td>
<td>(9,42,45,46)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Both</td>
<td>PTEN, p53, AKT</td>
<td>Induce caspase-dependent apoptosis and inhibit tumor growth</td>
<td>(19)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>In vitro</td>
<td>AKT</td>
<td>Induce caspase-dependent apoptosis, suppress invasion and migration</td>
<td>(47,48)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>In vitro</td>
<td>JNK</td>
<td>Antiproliferative</td>
<td>(46)</td>
</tr>
</tbody>
</table>

ROS, reactive oxygen species; PP2A, protein phosphatase 2A; CD74, cluster of differentiation 74; PKB, protein kinase B; ERK1/2, extracellular signal-regulated kinase; FAK, focal adhesion kinase; S1P, sphingosine 1-phosphate; CXCR4, C-X-C chemokine receptor type 4; SphK2, sphingosine kinase 2; p38MAPK, p38 mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; SphK1, sphingosine kinase 1; EPCs, endothelial progenitor cells; CXCL10, C-X-C motif chemokine ligand 10; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; p53, tumor protein 53.
Numerous studies have shown that FTY720 of autolysosomes and increased LC3-II and p62 levels, which characteristics of autophagy blockage, including accumulation in mantle cell lymphoma cells, FTY720-treated cells showed evident induction of autophagy was observed in these cells both MCF7 breast cancer cells and Huh7 hepatoma cells, no Although FTY720 induced caspase-dependent apoptosis in cancer and acute lymphoblastic leukemia cells (25). However, whether these adverse effects presented in nude mice with human gastric cancer cell xenografts, the tumor growth and cell proliferation in FTY720-treated mice were significantly suppressed; the apoptotic index was markedly increased in that of FTY720 groups (19). In addition, in mouse breast cancer models, tumor growth and metastasis, which were markedly evident in control mice, were significantly prevented in the FTY720-treated groups, resulting in a significant prolongation of animal survival (9). Moreover, FTY720 showed in vivo anticancer effects in glioblastoma (33), hepatic carcinoma (34), lung cancer (12), renal cancer (20), mantle cell lymphoma (23) and prostate cancer (35). Consequently, FTY720 has promising effects in cancer therapy both in vitro and in vivo.

3. Side-effects

In multiple sclerosis models, the used doses of FTY720 are <0.5 mg/day. However, the doses required for anticancer effects of FTY720 in animal models (5 or 10 mg/day) are higher than those used in multiple sclerosis models. Serious adverse events of FTY720 for multiple sclerosis include bradycardia, relapse, basal-cell carcinoma. Other adverse events include macular edema, cancer and laboratory abnormalities (36). In vivo studies of the effects of FTY720 on cancer are conducted only on mice. In animal cancer models, FTY720 treatment did not cause any severe side-effects at a dosage of ≤10 mg/kg/day in mouse renal cancer models. In this case, all mice survived with a healthy appearance and no loss of body weight during the follow up period when treatment was performed at a dosage of ≤10 mg/kg/day (20). Furthermore, FTY720 prevented tumor growth and metastasis of mouse breast (9) and bladder (37) xenografts in nude mice without causing detectable toxicity in vital organs. However, whether these adverse effects presented in multiple sclerosis would occur during human cancer treatment, or could be tolerated if the therapy is efficacious, remains to be determined.

4. Molecular targets of unphosphorylated form of FTY720

The ability of FTY720 to induce cell death in cancer cells appears largely independent of the phosphorylation of the drug. FTY720 was able to induce cell death in ovarian cancer (13) and acute lymphoblastic leukemia cells (25); however, the phosphorylated form of FTY720 (FTY720-P) failed to induce cell death, demonstrating that activation of S1PR5 is not sufficient for cell death. While the mechanisms mediating the cell death action of FTY720 have yet to be fully clarified, a number of molecular targets of unphosphorylated form of FTY720 have been proposed which may explain the biological effects of this drug (Fig. 1).

ROS. ROS are chemically reactive molecules containing oxygen. Examples include oxygen ions and peroxides. ROS form as a natural byproduct of the normal metabolism of oxygen
Zheng et al.: FTY720 for Cancer Therapy

ROS and have important roles in cell signaling and homeostasis (38). However, under oxidative stress conditions, excessive ROS can damage cellular proteins, lipids and DNA, leading to fatal lesions in cells that contribute to carcinogenesis.

In acute lymphoblastic leukemia cells, FTY720 increased ROS generation in a time-dependent manner, which then resulted in a caspase-independent cell death, and the antioxidant NAC could block the cell death induced by FTY720 (25). The same occurred in mantle cell lymphoma (23), indicating that ROS is an upstream of cell death induced by FTY720. However, in multiple myeloma cells, FTY720-induced ROS activity promoted autophagy, reduced the expression of Mcl-1, survivin, bcl-2 and increased cleavage of Bid, ultimately leading to apoptosis of multiple myeloma cells (26). Furthermore, in hepatic carcinoma cells, ROS generation induced by FTY720 culminated in protein kinase C (PKC) δ activation and subsequent caspase-3-dependent apoptosis (39). In these two cases, ROS generated by FTY720 promoted cell apoptosis rather than death. Thus, the difference demonstrates that ROS may be just a mediator between FTY720 and apoptosis or cell death. However, whether FTY720 induces apoptosis or cell death depends on cell types. Of note, OSU-2S, a non-immunosuppressive analogue of FTY720, increased ROS generation, suppressed cell growth in the same way as FTY720 in hepatocellular carcinoma (40), suggesting a direct effect on ROS of unphosphorylated form of FTY720.

Protein phosphatase 2A (PP2A). PP2A is a ubiquitous and conserved serine/threonine phosphatase with broad substrate specificity and diverse cellular functions. PP2A has been shown to be genetically altered or functionally inactivated in several types of solid cancer and leukemias, and is therefore a tumor suppressor. Changes in PP2A subunits or loss of phosphatase activity have been linked to cancer development and to non-neoplastic diseases (41).

Currently, several studies have demonstrated that the anticancer activity of FTY720 may depend on its ability to act as a potent PP2A activator. In ovarian cancer cells, FTY720 activated PP2A, decreased autophagy and increased cell death (42). In this case, autophagy acted in a protective role. In acute myeloid leukemia (AML), FTY720-induced PP2A activity resulted in a dose-dependent growth inhibition and a significant decrease in viable cells. The specific PP2A inhibitor OA partially rescued the cells from FTY720-induced apoptosis (43), indicating that PP2A activation is required for FTY720-induced apoptosis in AML cells. FTY720 also induced cell apoptosis in lung tumor (44), CML and Ph-positive B-ALL progenitors (45,46) potentially by disrupting SET-PP2A interaction, allowing PP2A activation. Furthermore, animal studies demonstrated that FTY720 has anticancer effects in vivo by activating PP2A. Reports highlighted the efficacy of FTY720 in animal models of AML, reporting restored PP2A activity, decreased clonogenicity, and suppression of disease (47,48). However, it is unclear whether the anticancer effects of FTY720 in some malignancies should be attributed to activation of PP2A or to other mechanisms (such as autophagy) (41). For example, although FTY720 induced PP2A activation and cell death in acute lymphoblastic leukemia cells, activation of PP2A is not required for FTY720-induced cell death (25).

Mitogen-activated protein kinase (MAPK) signaling pathway. MAPKs are serine/threonine-specific protein kinases belonging to the CMGC (CDK/MAPK/GSK3/CLK) kinase group (49). They regulate proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis in cancer cells. There are several members in the MAPKs family, among which the ERKs and c-Jun N-terminal kinases (JNKs) are the most important in regulating cell death and survival.

FTY720 has recently been shown to induce the activation of ERK1/ERK2 and JNK1/JNK2, but not p38 in breast and colon cancer cells, which may result in the anti-proliferative activity of FTY720 (50). Furthermore, FTY720 increased phosphorylation of ERK in mantle cell lymphoma (23), but decreased phosphorylation of ERK in glioblastoma (33) and renal cancer cells (20); notably, they all finally contributed to apoptosis of cancer cells. The mediators between FTY720 and
the MAPK signaling pathway have not been fully clarified, but recent literature indicated that ROS may be involved in the activation of the MAPK pathway. For example, curcumin induced phosphorylation of ERK1/2 and p38 MAPK, yet the curcumin-induced phosphorylation of ERK1/2 and p38 MAPK was attenuated in the presence of NAC, a scavenger of ROS (51). Furthermore, piperlongumine selectively killed glioblastoma cells via JNK and p38 activation, and these activations were blocked by NAC pre-treatment (52). Thus, FTY720 may also activate MAPK signaling pathway through ROS generation, but, to date, how FTY720 mediates MAPK has not been studied. Although the relationship between FTY720 and MAPK signaling pathway remains unclear, the MAPK signaling pathway may be a pivotal target of FTY720 in cancer therapy.

**PI3K/AKT/mTOR signaling pathway.** PI3K/Akt/mTOR is another important intracellular signaling pathway in regulating cell survival and death. The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase which works downstream of protein kinase B (Akt). Once activated, mTOR triggers the phosphorylation of the downstream target p70S6K1, enhances the transcription of certain mRNAs, and increases the expression of proteins associated with proliferation (53-55). It has been reported that the PI3K/Akt/mTOR signaling pathway is overactivated in several types of cancer, such as non-small cell lung cancer (56,57), breast cancer (58), colorectal cancer (59) and cholangiocarcinoma (60). Therefore, some experimental cancer drugs aim to inhibit the signaling sequence at some point (61-63).

FTY720 could also facilitate PI3K/AKT signaling pathway to induce cell death. In gastric cancer cells, FTY720 induced apparent decrease of phosphorylation of AKT (473) level, followed by a concentration-dependent reduction of Bel-2, a concomitant increase of Bax, cleavage caspase-3, -9, PARP, resulting in significant apoptosis in cancer cells (19). Moreover, FTY720 induced p-AKT downmodulation in mantle cell lymphoma, which then caused cell death (23,28). In addition, in prostate cancer (64), neuroblastoma (65) and glioma (10,66) cells, FTY720 also showed anticancer effects by downregulating the phosphorylation of AKT.

**Cyclin D1.** Cyclin D1 belongs to the highly conserved cyclin family. It functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition. This protein has also been shown to interact with tumor suppressor protein Rb and the expression of cyclin D1 is regulated positively by Rb. Mutations, amplification and overexpression of this protein, which alters cell cycle progression, are frequently observed in a variety of tumors and may contribute to tumorigenesis. Cyclin D1 has been reported to be involved in tumorigenesis in breast cancer (67), prostate cancer (68), colorectal cancer (59,69), ovarian carcinoma (70), non-small cell lung cancer (71) and gastric carcinoma (72) cells.

Recently, studies showed that in mantle cell lymphoma (23,28), human hepatoma cells (14), rat glomerular mesangial cells (73) and mouse skin transplantation models (74), FTY720 reduced the protein level of cyclin D1, induced G1 phase cell cycle arrest, eventually inhibited cell proliferation and induced cell death. Meanwhile, recent data have also indicated a role for cyclin D2 and cyclin D3 in the pathogenesis of cancer (75-81); however, no reports have studied the effects of FTY720 on cyclin D2 or cyclin D3 and, thus, remains to be explored.

**Phosphatase and tensin homolog (PTEN).** PTEN is a protein that, in humans, is encoded by the PTEN gene (82). It is one of the most commonly lost tumor suppressors in human cancer. During tumor development, mutations and deletions of PTEN occur that inactivate its enzymatic activity leading to increased cell proliferation and reduced cell death. Frequent genetic inactivation of PTEN occurs in glioblastoma (83,84), endometrial cancer (85), and prostate cancer (86), and reduced expression is found in numerous other tumor types such as lung (87) and breast cancer (88).

However, studies on the effects of FTY720 on PTEN are few and only one reported that FTY720 induced obvious PTEN expression, consistent with a substantial decrease in p-Akt and MDM2, finally inhibiting gastric cancer cell proliferation, inducing G1 phase cell cycle arrest and apoptosis. Suppression of PTEN expression with siRNA significantly activated Akt, resulting in decreased apoptosis and increased cell survival (19). Thus, whether the anticancer activity of FTY720 in some malignancies is related to downmodulation of PTEN remains to be clarified.

**Sphingosine kinase (SphK).** SphK is a conserved lipid kinase that catalyzes formation sphingosine-1-phosphate (S1P) from the precursor sphingolipid sphingosine. There are two forms of SphK, SphK1 and SphK2.

SphK1 is a lipid enzyme with oncogenic properties that converts the proapoptotic lipids ceramide and sphingosine into the antiapoptotic lipid S1P and activates the signal transduction pathways that lead to cell proliferation, migration, the activation of the inflammatory response, and the impairment of apoptosis (89). There is compelling evidence that SphK1 activation contributes to tumorigenesis in prostate cancer (90), colorectal cancer (91) and breast cancer (92) cells. However, until recently, the absence of clinically applicable SphK1 inhibitors limited the translation of these findings into patients (89). Recent studies shed further insight into the mode of action of FTY720 by demonstrating that it directly inhibits SphK1 activity both in vitro and in vivo. For instance, FTY720 could re-sensitize human colorectal cancer to cetuximab by inhibiting SphK1 both in vitro and in vivo, with inhibition of tumor growth, interference with signal transduction, induction of cancer cell apoptosis, and prolongation of mouse survival (91). In addition to directly inhibiting SphK1 activity, FTY720 has been demonstrated to induce SphK1 degradation via ubiquitination and subsequent proteasomal processing (93); however, the precise mechanism has not been defined.

There exist two mammalian isoforms of SphK, SphK1 and SphK2, which share a considerable degree of sequence similarity, but differ in their developmental expression, subcellular localization and ability to phosphorylate artificial substrates (94). Moreover, FTY720 becomes phosphorylated mostly by SphK2. In neuroblastoma, FTY720, but not P-FTY720, induced neuroblastoma cell death, inhibited the growth of neuroblastoma xenografts and enhanced the tumor-suppressive effect of topotecan both in vitro and in vivo. Notably, FTY720 significantly decreased SphK2 mRNA and
protein expression instead of SphK1, disrupted the ceramide-sphingosine-1P balance (65). This may be due to the fact that neuroblastoma predominantly expresses SphK2 (95) and overexpression of SphK2 in neuroblastoma cells promoted tumor growth and cell proliferation.

Thus, FTY720 appears to target SphK via multiple mechanisms. With the well described role of SphK in oncogenesis, such effects of FTY720 on this enzyme provide a mechanistic explanation for its anticancer properties.

14-3-3. 14-3-3 proteins are a family of conserved regulatory molecules expressed in all eukaryotic cells. 14-3-3 proteins have the ability to bind a multitude of functionally diverse signaling proteins, including kinases, phosphatases and transmembrane receptors. For example, 14-3-3 interacted with both the dynein intermediate chain (DIC) and an Hsp70 co-chaperone Bcl-2-associated athanogene 3 (BAG3), thereby recruiting chaperone-associated protein cargos to dynein motors for their transport to aggresomes (96). Through binding to apoptosis signal-regulating kinase-1 (ASK-1), 14-3-3 negatively regulated the kinase activity of ASK-1, thereby blocking activation of stress-activated protein kinases (SAPK) such as p38 and JNK (97).

It was recently shown that FTY720 straightly bound to 14-3-3 proteins to render them phosphorylatable on Ser58 (in 14-3-3ζ) at the dimer interface. Phosphorylation of 14-3-3 induced by FTY720 could facilitate, at least in part, the apoptotic activity of this drug, as cells expressing non-phosphorylatable 14-3-3 exhibited attenuated apoptosis in response to FTY720 (98). Therefore, 14-3-3 proteins are key intermediates linking FTY720 and mitochondria, apoptotic commitment.

5. Conclusion

FTY720 was originally developed as an immunosuppressive agent and is currently undergoing multiple clinical trials, including prevention of kidney graft rejection and treatment of relapsing multiple sclerosis. However, over the past ten years, FTY720 has emerged as a key player in cancer therapy. FTY720 has shown preclinical antitumor efficacy in cancer models, including those of breast, bladder, glioblastoma, ovarian, prostate, lung, liver and hematopoietic malignancies. In these malignancies, the anticancer effects of FTY720 are reportedly attributed to its cytotoxicity towards cancer cells through caspase-dependent, caspase-independent or autophagic cell death pathways. Moreover, in most instances, phosphorylation of FTY720 is not required for its cytotoxic effect. To date, numerous molecular targets have been proposed for the unphosphorylated form of FTY720, including ROS, PP2A, cyclin D1, SphK1 and 14-3-3. These downstream targets appear to be associated with the ability of FTY720 to suppress cell growth and/or induce cell death. These observations make FTY720 an attractive therapeutic drug for developing alternative treatment protocols, and, possibly, for combining with other anticancer drugs to overcome drug resistance and achieve better outcomes. Thus, it is clear that further studies are required to elucidate the full spectrum of direct and downstream cellular targets of this FTY720. Ultimately, novel molecular targets will be found and may hold promise for clinical cancer therapy.

Acknowledgements

The present study was supported by grants from the Key Subject of Jiangsu Province (X4200722).

References


