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New tricks for human farnesyltransferase inhibitor: cancer and beyond†

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Human protein farnesyltransferase (FTase) catalyzes the addition of a C₁₅-farnesyl lipid group to the cysteine residue located in the COOH-terminal tetrapeptide motif of a variety of important substrate proteins, including well-known Ras protein superfamily. The farnesylation of Ras protein is required both for its normal physiological function, and for the transforming capacity of its oncogenic mutants. Over the last several decades, FTase inhibitors (FTIs) were developed to disrupt the farnesylation of oncogenic Ras as anti-cancer agents, and some of them have entered cancer clinical investigation. On the other hand, some substrates of FTase were demonstrated to be related with other human diseases, including Hutchinson–Gilford progeria syndrome, chronic hepatitis D, and cardiovascular diseases. In this review, we summarize the roles of FTase in malignant transformation, proliferation, apoptosis, angiogenesis, and metastasis of tumor cells, and the recently anticancer clinical research advances of FTIs. The therapeutic prospect of FTIs on several other human diseases is also discussed.

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1. Introduction

The post-translational modification of mammalian proteins by isoprenoid lipids, also known as prenylation, regulates the cellular localization and activity of many proteins that have crucial functions in biological process.¹ Protein prenylation, widely existed in the eukaryotic cells, is comprised of farnesylation and geranylgeranylation. Human protein farnesyltransferase (FTase, EC 2.5.1.58), one of the three enzymes in the prenyltransferase family, catalyzes the chemical reaction between farnesyl diphosphate and protein-cysteine during the post-translational modifications. Potential FTase substrates include the small GTPase Ras, Rheb, and RhoB, the phosphatases PRL1, 2 and 3, the chaperone protein DnaJ, the cytoplasmic dynein adaptor Spindly, as well as nuclear lamins.^{2–5} These proteins generally contain a CAAX (C = cysteine, A = aliphatic amino acids, and X = a variable amino acid) motif at their carboxyl terminus which can be recognized by FTase. Generally, farnesylation modification between a lipid farnesyl group and the Ras CAAX motif is comprised of four steps. In the initial step, FTase covalently link a 15-carbon farnesyl isoprenoid lipid from farnesyl pyrophosphate (FPP) to the cysteine of the CAAX motif *via* a thioether bond, which act as the rate-limiting step. Subsequently, the prenylated protein is inserted into the endoplasmic reticulum (ER) and the AAX amino acids of Ras are removed by Ras-converting CAAX

endopeptidase 1 (RCE1). Then, the carboxyl group of the farnesylcysteine in Ras will undergo an isoprenylcysteine carboxyl methyltransferase (ICMT)-catalyzed carboxymethylation process. Finally, palmitoyltransferase catalyzes the addition of two palmitoyl long-chain fatty acid groups to the upstream cysteine of the farnesylated carboxyterminal cysteine to obtain a hydrophobic tail that has affinity for membranes⁶ (Fig. 1).

The farnesylation of Ras is the first- and most critical-modification for the maturing of Ras into its biologically active form, and FTase is of intense interest as a potential tumor therapeutic target.⁷ Inhibition of FTase activity can prevent the Ras activation, thereby inhibiting the downstream signaling that related to human tumor initiation and progression. In addition to cancer therapeutics, inhibition of FTase has shown promise for the treatment of Hutchinson–Gilford progeria syndrome, and chronic hepatitis D in clinical trials.⁸ In this review, we focus on the molecular mechanisms by which FTase inhibitors (FTIs) achieve their therapeutic effects in cancer and other human diseases.

2. The development of FTIs

FTIs have been developed for cancer treatment for more than twenty years, many preclinical studies demonstrated that FTIs can effectively suppress tumor growth with little toxicity through blocking several pivotal signaling pathways. Various skeletons, including imidazoles, thiazoles, pyridine analogues, piperidines, tricyclics, polycyclics, benzoheterocyclics, benzophenones, aliphatic hydrocarbons, phenothiazine derivatives, indolizine–chalcones, 3-arylthiophene 2-carboxylic acids, indolizine derivatives, benzoylated *N*-ylides, have been

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Fig. 1 The farnesylation modification of Ras protein. FTase links a 15-carbon farnesyl isoprenoid lipid to cysteine of the CAAX motif, and enable the proteins insert into the ER. Then the AAX amino acids of Ras are removed by ER by RCE1, and a carboxymethyl is attached to the terminal cysteine by ICMT. Finally, palmitoyltransferase catalyzes the addition of two palmitoyl long-chain fatty acid groups to the upstream cysteine of the farnesylated carboxyterminal cysteine to obtain a hydrophobic tail that has affinity for membranes.

developed as FTIs^{9–16} (Fig. 2). Five compounds have entered into clinical investigation, including antroquinol (1), tipifarnib (2), lonafarnib (3), BMS-214662 (4) and L778123 (5) (Table 1). The development of FTIs started from the C terminal CVIM-tetrapeptide of K-Ras as the pharmacophore model, which served as the alternative substrate for FTase, and then experienced several generations in which aminomethylbenzoic acid and 2-phenyl-4-aminobenzoic acid were used to replace the “VI” dipeptide. After that, new stages of non-peptide mimetic of CAAX and non-thiol FTIs emerged to resolve the low *in vivo* efficacy of peptidomimetic FTIs and the adverse drug effects, respectively.¹⁷ A great number of compounds have been tested *via* cell proliferation, liquid scintillation or a fluorescence assay, which is based on the change of fluorescence and the accompanying shift to lower wavelength emission maximum of certain fluorophores,^{18,19} and some showed low micromolar, even nanomolar IC₅₀ values.^{11,12,20–22} Also, natural products are significant sources of enzyme inhibitors,^{23,24} such as antroquinol (1), which has inhibitory activity on FTase.²¹ Furthermore, computer-aided drug design makes use of the structural knowledge of either the target (structure-based) or known ligands with bioactivity (ligand-based) to facilitate the discovery of promising candidate drugs.^{25,26} In our previous studies, a panel of active FTIs have been reported using structure based virtual screening and medicinal chemical endeavor, and some of them displayed outstanding inhibition activities with low nanomolar IC₅₀ values^{27,28} (Table 2).

Among the developed FTIs, tipifarnib (2), the most widely investigated FTI, has entered phase III clinical trials on can-

cers, although the results were unsatisfactory until now. The underlying reason may be the existence of alternative resistant pathways, like geranylgeranylation of activated K-Ras.²⁹ Intriguingly, FTIs maybe still effective on cancers driven by oncogenic H-Ras, since the absence of alternative prenylation. And the presented comforting preclinical investigations and ongoing clinical trials for H-Ras mutant cancer will bring new avenues to the clinical development of FTIs.²⁹

3. FTase and cancer

Cancer is a serious disease characterized by self-sufficiency in growth signals, evading apoptosis, insensitivity to anti-growth signals, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis.³⁰ Among the proteins undergo farnesylation, Ras proteins are found mutated in ~30% of human cancers, especially at G12, G13 and Q61, leads to sustained activation and the subsequently stimulation of growth.³¹ Ras proteins are small G proteins that cycle between active GTP-bound state and inactive GDP-bound state, and they require membrane association *via* farnesylation for their biological activities. Oncogenic mutations of Ras proteins fail to cycle “off” from the active GTP-bound state to the resting GDP-bound state, resulting in constitutive Ras signaling.³² Generally, Ras proteins are involving in regulating downstream Raf-MEK-ERK and PI3K-Akt-mTOR signaling pathways, and are important targets in cancer therapy, especially in cancers with Ras mutations.^{33–35} Moreover, other substrates of FTase, such as Rho, RheB and Spindly, are also related to tumor initiation and progression, and a

Fig. 2 FTIs mentioned in this review. *The structure of PD169541 (**12**) is unavailable.

Table 1 A summary of clinical trials for FTIs

Compound	Clinical trials			Possible substrate
	Phase ^a	Diseases ^a	Combination ^a	
Antroquinonol (1)	I	Non-small cell lung cancer	— ^b	Ras, Rho
Tipifarnib (2)	I	Glioblastoma multiforme	Radiation therapy and temozolomide	Ras
	I/II	Non-disseminated intrinsic diffuse brainstem gliomas	Radiation therapy	Ras
	III	Acute myeloid Leukemia	—	Ras
	I/II	Stage IIB–IIIC breast cancer	Sequential weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide	Ras
Lonafarnib (3)	II	Non-small cell lung cancer	Gemcitabine and cisplatin	Ras
	II	Chronic hepatitis D infection	—	LHDAG
	II	Advanced metastatic urothelial cancer	Gemcitabine	Ras
	II	Chronic myelogenous leukemia	—	Ras
	II	Hutchinson–Gilford progeria syndrome	Zoledronic acid and pravastatin	Progerin
BMS-214662 (4)	I	Unspecified solid tumor	—	Ras
	I	Acute leukemias, myelodysplastic syndromes (RAEB and RAEB-T) and chronic myeloid leukemia	—	Ras
L-778123 (5)	I	Refractory solid malignancies	—	Ras

^a These data are obtained from <https://clinicaltrials.gov>. ^b Not available.

wealth of studies in recent years have demonstrated that these proteins are all enrolled in crucial signaling pathways that regulate the malignant transformation, proliferation, apoptosis, invasion of tumor cells and tumor angiogenesis.

3.1. Malignant transformation

Malignant transformation is the complex process by which cells acquire the properties of cancer. Transformed cells have several traits that set them aside from normal cells, including extended life or immortality, and rapid division and proliferation. This may occur in normal tissue as a primary process, or in a previously existing benign tumor. One of the causes of primary malignant transformation is genetic mutations, which includes Ras mutations. Normally, certain genes control cell division, growth, maturation, and death. The 3 RAS genes in humans (HRAS, KRAS, and NRAS) are the most common oncogenes in human cancer, and Ras proteins are upstream activator of some important kinase cascade.³⁶ Early experimental evidences have indicated that oncogenic Ras mutation result in malignant transformation in NIH3T3 cells.³⁷

Since the significance of farnesylation to Ras membrane association, this transformation can be reversed by FTIs. According to experimental validation, FTIs can selectively inhibit Ras-dependent cell transformation *in vitro*³⁸ and regress tumor growth *in vivo*.³⁹ Moreover, Ras^{V12} has recently been shown to mediate oncogenic transformation through epigenetically inactivating the Ras-related associated with diabetes (RADD) gene, which then downregulate RRAD and increase the glucose uptake.⁴⁰ K-Ras-PAK1-Crk pathway is also brought forward as a prominent pathway in the oncogenesis of K-Ras mutant lung cancer in a recent study.⁴¹ Accordingly, FTIs can selectively suppress Ras-dependent malignant transformation specifically in the following aspects.

3.2. Cell proliferation and cell cycle

Infinite proliferation is one of the hallmarks of cancer, and it is regulated by multiple pathways associated with growth factor-mediated gene regulation, such as Raf-MEK-MAPK. Meanwhile, cancer cells are characterized by continuous mitosis and have disordered cell cycle, which partially contributes to dysregulated cell proliferation. FTase targets Ras, CENP-E, CENP-F and Spindly are involved in modulating the pivotal regulatory molecules of cell proliferation and cell cycle. Ras, served as transducer that couple cell surface receptors to intracellular effector pathways, can enhance proliferation by inducing the transcription and the secretion of mature form of many growth factors, such as heparin-binding EGF-like growth factor (HB-EGF), transforming growth factor α (TGF α), amphiregulin (AREG).⁴² Simultaneously, oncogenic Ras can alter the expression of growth factor receptors. Furthermore, oncogenic proteins like Ras upregulate many transcription factors, including c-fos, serum response factor (SRF), c-Jun, nuclear factor- κ B (NF- κ B), the ETS domain-containing transcription factor ELK1 and activating transcription factor 2 (ATF2), which are in connection with cell cycle entry and progression and in turn trigger the expression of cyclin D1.⁴³ A recent study showed that inhibition of FTase may reduce cell proliferation, which is correlated with a reduction of cyclin D1 levels.⁴⁴ Importantly, oncogenic Ras can also trigger the initiation of DNA replication and promote cell cycle progression by deregulating anti-growth signaling pathways through the suppression of cyclin-dependent kinase inhibitors (CKIs), including p27 kinase inhibitory proteins (p27Kip1 or p27) and p21.⁴⁵ Meanwhile, to counteract DNA damage, which can impede proliferation, oncogenic Ras modulates the activation of the ATR/Chk1 DNA damage checkpoint and upregulates mediators of DNA damage repair mechanisms such as BER and alt-NHEJ pathways.⁴⁶

Table 2 A summary of recently identified potent FTIs

Number	Structure	IC ₅₀		Ref.	Original name
		Tumor cell proliferation (μM)	FTase activity inhibition (nM)		
1		3.24 (A549)	2986.00 ^a	21	Antroquinonol
15		— ^b	49.00	11	
16		—	9.00	12	
17		>10 (A431)	860.00 ^c	22	N-Benzyl-aclacinomycin A
18		—	65.00	20	Tecomaquinone I
19		—	2.90	27	
20		14.28 (MCF-7)	48.90	28	

^a KD value determined by SPR. ^b Not available. ^c The IC₅₀ value of compound 17 are measured with FTase that are purified from tumor cells EC17.

Besides, the farnesylation of cytoplasmic dynein adaptor Spindly and outer kinetochore protein CENP-E is crucial during the congression of chromosome and Spindly localization to kinetochores.^{2,47} Moreover, Rheb (Ras homologue enriched in brain) is a farnesylated small GTPase that positively regulates mTOR (mammalian target of rapamycin) signaling, is not a substrate for alternative prenylation.^{48,49}

FTIs inhibit cell proliferation by blocking the farnesylation of Ras. José Mendes *et al.* have reported the antiproliferative effect of L744832 (6) in non-Hodgkin lymphoma (NHL) cells.⁵⁰ FTI-276 (7) can inhibit the processing of H- and N-Ras in Calu-1 cells and A549 cells, and block the tumor growth in nude mice of a human lung carcinoma and in nude mice of A549 and Calu-1 xenografts.^{51,52} FTI-277 (8) can also inhibit tumor cell growth, such as human liver cancer cell lines, HepG2 and Huh7, with increased expression of p27Kip1 and Bcl-2, and altered association between Ras, Raf-1 and Bcl-2.⁵³ Other FTase substrates may also contribute to the anti-proliferation capacity of FTIs. For instance, FTI lonafarnib (3) can affect cell cycle by blocking the farnesylation of CENP-E, CENP-F and Spindly, and altering the association of CENP-E with the microtubules.² FTI can also inhibit cell proliferation and induce G0/G1 phase arrest through RhoB and p21.⁵⁴

3.3. Apoptosis

Apoptosis is a complex process which results from balanced molecular actions that are associated with a diverse range of pathways, and from both positive and negative modulators.⁵⁵ Apoptotic cell death is a significant defense mechanism which can remove aging or abnormal cells and prevent diseases including inflammatory response and cancer. However, cancer cells generally show damaged apoptotic functions and the abnormality of the apoptotic machinery.

Mechanistically, oncogenic Ras, the well-known FTase target, perform its anti-apoptotic function through several effector pathways, including the RasPI3K pathway, which leads to the upregulation of the inhibitors of apoptosis (IAPs) through the activation of NF- κ B and the downregulation of the pro-apoptotic protein BAK1, and the Ras-Raf pathway, which downregulates the pro-apoptotic transcriptional repressor prostate apoptosis response 4 (PAR4; also known as PAWR) and upregulates the anti-apoptotic proteins BCL-2, BCL-X_L, and apoptosis repressor with caspase recruitment domain (ARC; also known as NOL3). Both the Ras-PI3K-AKT and the Ras-Raf-MAPK pathways have been shown to phosphorylate the pro-apoptotic protein BCL-2-associated agonist of cell death (BAD) on serine 136 and serine 122 and inactivating BAD. Additionally, oncogenic Ras also induces the epigenetic silencing of the pro-apoptotic CD95 (APO-1/Fas) gene through an unknown mechanism.⁴³ K-Ras with a phosphomimetic residue at position 181 induces apoptosis *via* a pathway that requires Bcl-X_L⁵⁶ and FTI can induce DNA degradation and cell death in a BCL-X_L-dependent manner which is associated with substratum attachment.⁵⁷

FTIs can restore apoptosis in cancer cells *via* damaging biological functions of oncogenic Ras, thereby inhibit tumor growth. In human myeloma cell lines (HMCLs) XG-2, LP-1 and U266, FTI tipifarnib (2) can induce a significant and dose-dependent growth inhibition, and a significant apoptosis *via* blocking the Ras-MAPK and JAK-STAT pathways.⁵⁸ In Jurkat, H1299, MCF-7 and A293 cells, FTI lonafarnib (3) can completely suppress the NF- κ B activation and NF- κ B-regulated gene expressions induced by several factors, and upregulate apoptosis.⁵⁹ Besides, Jiang K. *et al.* have demonstrated FTI-277 (8) can inhibit PI3K-AKT2-mediated growth factor- and adhesion-dependent survival pathways and induces apoptosis.⁶⁰ In colon cancer cell line OS187, FTI tipifarnib (2) can promote cell senescence and apoptosis with the help of p53.⁶¹ Pelaia G. *et al.* suggested that FTI tipifarnib (2) may exert a pro-apoptotic and anti-proliferative activity, which appears to be mediated by inhibition of the Ras-Raf-MEK-ERK signaling cascade.⁶² Recently, manumycin A (9) was demonstrated to inhibit PI3K-AKT activation and lead to ROS accumulation and caspase-9 activation resulting in cell apoptosis.⁶³

Besides targeting Ras, FTI tipifarnib (2) may induce apoptosis by the inhibition of Rheb-induced the serine/threonine kinase mTOR signaling followed by dose-dependent upregulation of Bax and Puma in acute myelogenous leukemia.⁶⁴ Moreover, FTIs manumycin A (9), FTI-276 (7), and lonafarnib (3) induce autophagy in human cancer cell lines, which can act as the partner of apoptosis to induce cell death in a coordinated fashion.⁶⁵

3.4. Angiogenesis

Pathological angiogenesis stimulates tumor growth, invasion and metastasis by providing nutrients and oxygen and serving as ducts for tumor cells. On the flip side, oncogenic Ras in tumor cells can promote the angiogenic process by increasing the transcriptional activation of genes that control angiogenesis through a number of effector pathways, or stabilizing mRNA and, possibly, enhancing initiation of their translation.^{66,67}

Firstly, oncogenic Ras can activate multiple signaling cascades, including adaptor protein Raf-Shc, the PI3K-Akt pathway and the Raf-MEK-MAPK pathway, to stabilize the pro-angiogenic transcription factor hypoxia-inducible factor 1 α (HIF-1 α) which has the potential to activate the vascular endothelial growth factor A (VEGFA) promoter,^{68–71} and subsequently upregulate the level of VEGFA—the key player in the induction of endothelial cell proliferation and the sprouting of new blood vessels.⁴³ Besides, oncogenic Ras can upregulate VEGFA level by enhancing the cyclic AMP-dependent transcription of VEGFA *via* activating the pro-angiogenic enzyme cyclooxygenase 2 (COX2).⁶⁷ Through COX2, oncogenic Ras can also promote other endothelial growth factors-mediated endothelial cell spreading and migration, including the basic fibroblast growth factor (bFGF or FGF2) and the platelet-derived growth factor (PDGF).⁷²

Moreover, oncogenic Ras may upregulate the expression of some pro-inflammatory cytokines, such as interleukins (IL-8 and IL-6) and the chemokine growth-regulated oncogene 1 (GRO-1), which then recruit immune cells to produce angiogenic growth factors, at the transcriptional level.^{73,74} Furthermore, oncogenic Ras may upregulate the matrix metalloproteinases (MMP2 and MMP9) and urokinase-type plasminogen activator (uPA),⁶⁷ which can break down the extracellular matrix (ECM) to liberate those pro-angiogenic growth factors, such as VEGFA and FGF2,^{75,76} and downregulate the negative regulators of neo-vascularization, such as thrombospondins (TSP1 and TSP2),^{67,70,77} which can inhibit angiogenesis through direct effects on endothelial cell migration and survival, and through indirect effects on growth factor mobilization.^{78,79}

Taken as a whole, oncogenic Ras takes pro-angiogenic effect in above manners, hence FTIs can inhibit oncogenic Ras and play the anti-angiogenic function. FTI lonafarnib (3) appears to inhibit angiogenic activities by decreasing hypoxia- or insulin-like growth factor 1 (IGF1)-stimulated HIF-1 α expression and to inhibit VEGFA production by inhibiting HIF-1 α binding to heat shock protein 90 (HSP90), resulting in the proteasomal degradation of HIF-1 α .⁸⁰ FTI L744,832 (6) can reduce hypoxia in tumor expressing activated H-Ras while tipifarnib (2) can reduce hypoxia and MMP2 expression in human glioma xenograft, which both affect angiogenesis.^{81,82} FTI LB-42708 (10) can inhibit VEGF-induced tumor angiogenesis by blocking Ras-dependent MAPK and PI3K-Akt signal pathways in tumor-associated endothelial cells.⁸³ Besides, FTIs are demonstrated to inhibit

Fig. 3 The versatile roles of FTase targets in tumor. The FTase substrate, Ras, can promote cancer development by suppressing apoptosis, inducing angiogenesis, accelerating metastasis and altering cell cycle, through PI3K-Akt, Raf-MAPK-MEK and other signaling pathways. Meanwhile, other FTase substrates, including RhoB, Rheb, Rac1, Spindly, CENP-E and CENP-F, are also involved in the regulation of apoptosis and cell cycle in tumor cells.

angiogenesis by directly acting on endothelial cells in recent years.⁸⁴

3.5. Cell invasion and metastasis

Metastasis of tumor cells is one of the most threatening and lethal aspects of cancer, whereby the cells can spread to other distant organs. The progression is from pre-malignant lesions to invasive carcinomas and distant metastases, and oncogenic Ras endows cells with metastatic potential during the processes from depolarization to invasion, migration and intravasation through multiple cellular processes.^{85,86}

To begin with, oncogenic Ras could disrupt the polarization of epithelial cells, which allows them to detach from the primary tumor. During the development of carcinomas, epithelial cells may lose their polarity and acquire a 'de-differentiated' spindle-shaped fibroblastoid morphology, which is generally referred to as epithelial-mesenchymal transition (EMT).^{85,87} Moreover, cellular invasion is related with matrix metalloproteinase-1 (MMP-1) and MMP7, the secretion of these proteins is prenylation sensitive.^{88,89} Oncogenic Ras targets the calcium-dependent E-cadherin receptor and its associated cytoplasmic protein β -catenin, which maintain intercellular adhesion junctions, through Ras-Raf-MEK-MAPK pathway to disturb the interactions between cells.^{85,90} For this effect, oncogenic Ras upregulates the E-cadherin transcriptional repressors Snail and Slug, stimulates the proteolytic degradation of E-cadherin and induce the methylation of E-cadherin promoter. Meanwhile, oncogenic Ras can also induce the destabilization of E-cadherin- β -catenin complexes and the relocalization of β -catenin to weaken the interaction through the transforming growth factor- β (TGF β) signaling.⁸⁵ Signaling by TGF β can cooperate with activated Ras to induce epithelial de-differentiation.⁸⁵ Besides, the expression of oncogenic Ras can downregulate integrin subunits that facilitate the maintenance of stable adhesion complexes, while increasing the expression of receptors that may play a role in metastasis, and interfere the interaction between cell and matrix, so that the tumor cells can break out of the constrain of ECM and invade to elsewhere.⁴³ Also, the FTI targets Ras and Rho family small GTPases are involved in the integrin-receptor tyrosine kinase (RTK) signaling, which is crucial to tumor invasion and metastasis.^{91,92}

Taken together, oncogenic Ras, the most commonly FTI target, plays a significant role in promoting tumor metastasis. We can speculate that FTIs may be effective to prevent tumor cells from migration. For instance, lonafarnib (3) has multiplicity of anti-invasive effects in human head and neck cancer including the blockade of the IGF-1 receptor pathway, the induction of IGF binding protein 3 and reduction of the expression and activity of the uPA and MMP-2.⁹³ FTI-277 (8) can activate functioning of the E-cadherin-mediated cell adhesion system in human cancer cells, which is associated with suppression of cancer cell metastasis,⁹⁴ and FTase inhibition by FTI-277 (8) may be an effective strategy for targeting Ras-mediated proliferation, migration and invasion of breast

cells.⁹⁵ In recent studies, FTI moverastin (11) is demonstrated to inhibit H-Ras-dependent PI3K-Akt pathway and subsequent cell migration through the inhibition of FTase.⁹⁶ More recently, FTIs are suggested to be capable of ameliorating the aggressive phenotype of triple-negative breast cancer (TNBC) by suppressing the HIF-1 α -Snail pathway (Fig. 3).⁹⁷

3.6. Prospect of H-Ras targeting

Due to the geranylgeranylation of activated K-Ras which can also make oncogenic K-Ras insert in to ER and exert biological activities, many FTIs failed to be effective in clinical cancer therapy. Intriguingly, cancers with H-Ras mutation are not disturbed by this alternative pathway. H-Ras mutations are present in approximately 3.3% of human cancers.⁴⁵ In general, patients with these cancers have poor prognosis and limited options for treatment. H-Ras mutations are the second most common type of Ras mutation found in thyroid cancer. And are also associated with tumors of skin and of head and neck, which have relatively high incidence rate.⁹⁸

In recent preclinical studies, lonafarnib (3) only inhibit tumor development in H-Ras mutant cell lines, among cell lines harboring H-Ras, N-Ras and K-Ras.⁹⁹ This phenomenon made lonafarnib (3) have limited inhibitory activity and tend to be studied in combination therapy of cancer for many years.¹⁰⁰ Tipifarnib (2) has been demonstrated to block H-Ras farnesylation and membrane localization, consequently inhibiting the growth and proliferation of H-Ras mutant thyroid cancers. The selection of clinical tumors patients with H-Ras mutations may represents a promising strategy to discover those patients most likely to benefit from FTIs. Thus, in 2015, FTIs were reevaluated as targeted agents for H-Ras-driven cancers, which bring new clinical trials for urothelial carcinoma, and squamous head and neck cancer. Remarkably, the molecularly targeted therapy for the patient with H-Ras mutation tumor is in line with the trend of precision medicine for cancer cure.

4. Hutchinson–Gilford progeria syndrome

Progeria, also known as the Hutchinson–Gilford progeria syndrome (HGPS), is a rare, fatal, severe genetic premature aging disorder that characterized by multiple disease phenotypes, including failure to thrive, sclerodermatous changes of the skin, alopecia, abnormal in bone, and vascular disease.^{101,102} It has been proven that the mutations in lamin A (LMNA) cause this disorder. The mutant prelamin A, progerin, undergoes farnesylation before targeting to the nuclear rim to cause misshapen nuclei, so that we can inhibit its adverse function *via* interfering with FTase (Fig. 4).^{103,104}

As for preclinical assessment, exposure to FTI PD169541 (12), caused a significant improvement in the nuclear morphology of cells expressing GFP-progerin and in HGPS cells from patients.¹⁰⁴ Furthermore, treatment with the FTI ABT-100 (13) increased adipose tissue mass, improved body

weight curves, reduced the number of rib fractures, and improved bone conditions in $Lmna^{HG/+}$ mice, which exhibited phenotypes similar to those in human HGPS patients.^{105,106} The promising results from the *in vitro* and *in vivo* models promoted a clinical trial of FTIs in progeria and results from the phase II clinical treatment trial for children with HGPS provide preliminary evidence that lonafarnib (3) may improve vascular stiffness, bone structure, and audiological status.¹⁰⁷ Moreover, a combination therapy with pravastatin and zoledronic acid may bring additional bone mineral density benefit.¹⁰⁸

5. Chronic hepatitis D

Chronic hepatitis D is the most severe form of viral hepatitis, affecting ~20 million HBV-infected people worldwide. The causative agent, hepatitis delta virus (HDV) has been reported that its reassembly requires FTase. Inhibition of FTase suppresses large hepatitis delta antigen (LHDAg) prenylation thereby prevents its formation of virus-like particles (VLPs) with the HBV surface antigen (HBsAg) in HBV-infected cells, which then secret and increase infection.¹⁰⁹ Obviously, use of FTIs may be effective to interfere the further infection (Fig. 4).

Previously, FTI-277 (8) and FTI-2153 (14) are proved to be highly effective at clearing HDV viremia in the mouse-based model of HDV infection. And FTI-277 (8) had been demonstrated to prevent the production of complete, infectious HDV genotype I virions and HDV genotype III virions.¹¹⁰ After *in vivo* studies, a successful phase 2A trail has been completed in 2015, which indicates that treatment of chronic

hepatitis D with lonafarnib (3) significantly reduces virus levels.¹¹¹ Meanwhile, there are still many ongoing clinical trials, which may provide further evidence for the efficacy of FTIs in chronic HDV.

6. Cardiovascular diseases

Cardiovascular diseases (CVD) are the leading cause of death globally¹¹² and is one of the leading causes of morbidity and mortality among patients with chronic kidney disease (CKD) and diabetes,¹¹³ especially atherosclerosis and vascular calcification. The mevalonate pathway may play a role in this vascular pathology because of its implication in cholesterol synthesis, and in the activation of several key cellular proteins such as the Ras GTPases, which are involved in the modulation of many cellular signaling, differentiation, proliferation, adhesion, migration, cytokine production, and apoptosis.^{114,115} Besides, the small GTPase Rho and its downstream effector Rho kinase contribute to GPCR-agonist-induced vascular contraction *via* Ca^{2+} sensitization.¹¹⁶

FTIs prevent post-translational prenylation of GTPases such as Rho, Rheb, Rac and Ras, and interrupt the signaling in the vascular pathology. Igor G. Nikolov *et al.* have shown that the FTI tipifarnib (2) is effective in slowing the accelerated progression of atherosclerosis and vascular calcification since it leads to a decrease in oxidative stress and inflammation *via* both systemic and direct local effects on the vessel wall, probably involving Ras-Raf pathway.¹¹⁴ A Ponnusamy *et al.* also demonstrated that FTI-277 (8) inhibits vascular smooth muscle cells (VSMC) mineralization in vascular calcification, at least in part, by activating downstream PI3K-Akt

Fig. 4 Roles of FTIs in HGPS and chronic hepatitis D. In HGPS cells, inhibition of FTase blocks the farnesylation of the mutant prelamin A, progerin, which subsequently target to the nuclear rim to cause misshapen nuclei. In chronic hepatitis D, inhibition of FTase suppresses the prenylation of large hepatitis delta antigen (LHDAg) thereby prevents its formation of virus-like particles (VLPs) with the HBV surface antigen (HBsAg) in HBV-infected cells, which then secret and increase infection.

Fig. 5 Roles of FTIs in cardiovascular diseases. a) FTIs are effective in slowing the accelerated progression of atherosclerosis and vascular calcification since it leads to a decrease in oxidative stress and inflammation via both systemic and direct local effects on the vessel wall. b) FTIs may inhibit VSMC mineralization in vascular calcification by activating downstream PI3K-Akt signaling and preventing apoptosis of VSMC. c) FTIs may inhibit neovascularization in atherosclerosis via disturbing their motility by significantly impairing centrosome reorientation toward their leading edge and interrupting the interaction between FTase and the cytoskeletal protein.

signaling and preventing apoptosis of VSMC.¹¹⁷ FTI-276 (7) might attenuate myocardial fibrosis and partly improve cardiac remodeling in spontaneously hypertensive rats through suppression of the activation of Ras and ERK1/2 phosphorylation pathway.¹¹⁸ FTI lonafarnib (3) inhibits neovascularization in atherosclerosis via directly targeting endothelial cells and disturbing their motility by significantly impairing centrosome reorientation toward their leading edge and interrupting the interaction between FTase and the cytoskeletal protein.¹¹⁹ Moreover, FTI manumycin A (9) can also prevent the development of mature atherosclerosis with concomitant alleviation of oxidative stress in apolipoprotein E (apoE)-deficient mice (Fig. 5).¹²⁰

7. Other diseases

By inhibiting Rho GTPase and Ras activation, FTIs have the potential to attenuate leukocyte recruitment to the CNS in neuroinflammatory diseases and treat a neurodegenerative disorder, such as Parkinson's disease, Alzheimer's disease (AD), schizophrenia, myasthenia gravis, multiple sclerosis, and so on.^{121,122} Shaowu Cheng *et al.* suggested that specific inhibition of protein farnesylation could be a potential strategy for effectively treating AD.¹²³ Suboptimal axonal regeneration contributes to the consequences of nervous system trauma and neurodegenerative disease and FTIs combined with GGTIs are recently identified as potent promoters of axon outgrowth.¹²⁴

FTase signaling plays a significant role in acute pancreatitis by blocking neutrophil infiltration and tissue injury via regulating the neutrophil expression of macrophage-1 anti-

gen in neutrophil, and FTI-277 (8) can ameliorate disease phenotypes of pancreatitis.¹²⁵ Besides, FTIs have effect on acute liver failure. Tipifarnib (2) prevented protein farnesylation in the liver and markedly attenuated liver injury and mortality in galactosamine (GalN)-lipopolysaccharide (LPS)-challenged mice by inhibiting GalN-LPS-induced caspase 3 activation, inflammatory cytokine production and c-Jun N-terminal kinase (JNK) phosphorylation in the liver, upregulating anti-apoptotic protein Bcl-xL, and protecting primary hepatocytes from GalN/tumor necrosis factor- α (TNF- α)-induced cell death.¹²⁶

8. Conclusion

FTIs have been developed as anticancer agents for several decades, and five of them (antroquinonol (1), tipifarnib (2), lonafarnib (3), BMS-214662 (4), and L778123 (5)) have experienced clinical trials on various kinds of tumors. Interestingly, in recent years, an increasing number of preclinical and clinical studies have demonstrated that FTIs also have therapeutic efficiencies on other human diseases, such as progeria, hepatitis, cardiovascular diseases, as well as neurodegenerative disorders. In this review, we summarize the targets and pathways involved in FTIs' therapeutic functions on cancer, and discuss the effects of FTIs on cancer cell proliferation, cell cycle, apoptosis, angiogenesis, and metastasis. Importantly, recent advances and prospective identification of key mechanisms regulating the functions of mutant H-Ras by FTase in cancer are seem to lead to new therapeutic strategies with higher potency and improved selectivity of action, and several clinical trials are promoting a pipeline of

precision medicines for the treatment of locally advanced tumors that carry H-RAS mutations by using FTIs. Also, we explore the targets and mechanisms of FTIs in Hutchinson–Gilford progeria syndrome, chronic hepatitis D, cardiovascular diseases, neurodegenerative diseases, acute pancreatitis, and acute liver failure.

Although a large quantity of studies has revealed the therapeutic potential and mechanism of action of FTIs in the treatment of cancer and other human diseases, there are several important issues that need to be resolved. (1) The observation that some types of cancers, including certain haematological malignancies, are sensitive to FTIs in preclinical and clinical experiments demonstrating that farnesylated proteins are pivotal to the proliferation and survival of some human tumors. Thereby, more study was needed to reveal the FTase substrate proteins which are critical for the malignant transformation of some human tumors. (2) The effectiveness of FTIs that target K-Ras or N-Ras farnesylation modification has been thwarted by activation of alternative resistant pathways that limit their efficacy as single agents. Therefore, the drug combinations of FTIs and other targeted agents, such as prenylation inhibitors (such as GGTIs) and kinase inhibitors (such as erlotinib), needs to be investigated further. (3) FTIs show promise for the treatment of progeria and hepatitis in clinical trials. A major problem for future development of FTIs is a lack of available biomarkers which can effectively predict and reflect the clinical response. The identification of these biomarkers will enable us to improve clinical effectiveness and avoid toxicity in patients. (4) Medicinal chemistry campaigns for the development of more specific FTIs is needed, as certain FTIs were found as multi-target inhibitors.¹²⁷ Notably, allosteric modulators offer a couple of distinct advantages over traditional competitive inhibitors: improved selectivity, skeleton novelty and pharmacological uniqueness.^{128,129} The development of allosteric modulators of FTase should translate into hopeful new drug candidates for a wide range of diseases.

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