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SHORT COMMUNICATION

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FK228 (depsipeptide): a HDAC inhibitor with pleiotropic antitumor activities

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Abstract *Purpose*: The fundamental role of epigenetic events in carcinogenesis has resulted in the evolution of epigenetic targeting as a new paradigm in anticancer therapeutics. Aberrant histone deacetylase (HDAC) activity has been documented in many human malignancies resulting in the repression of tumor suppressor genes and promotion of tumorigenesis. FK228, also known as depsipeptide, is a novel, natural, bicyclic tetrapeptide with significant antitumor properties which are mostly mediated by inhibition of HDACs. *Results*: FK228 induces the expression of genes linked to the inhibition of cell growth, induction of cell differentiation, promotion of apoptotic cell death and inhibition of angiogenesis. *Conclusion*: Its multitargeting properties, its ability to act on non-histone targets, its clinical activity and its acceptable side-effect profile render FK228 a very promising novel anticancer agent.

Keywords Epigenetics · Histone deacetylase inhibitors · FK228 (depsipeptide) · Antitumor activity · Multitargeting

Introduction

FK228, also known as depsipeptide, is a novel, natural, bicyclic tetrapeptide (molecular formula $C_{24}H_{36}N_4O_6S_2$). Formerly named FR901228, FK228 bears the molecular structure of depsipeptides, namely sequences of alternating amino- and hydroxy-carboxylic acid residues. FK228 is [(*E*)-(1*S*,4*S*,10*S*,21*R*)-7[(*Z*)-ethylideno]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8,7,6]-tricos-16-ene-3,6,9,22-pentanone] and its chemical structure is depicted in Fig. 1. FK228 was isolated from a broth culture of *Chromobacterium violaceum* and was able to reverse the transformed morphology of Ras-1 cells (Ha-ras transformants). Moreover, it exhibited prominent antitumor activities against murine and human tumor cell lines in vitro and human tumor xenografts and murine tumors in vivo [1, 2].

Most of FK228 cytotoxic effects are mediated by potent inhibition of histone deacetylases (HDACs). Epigenetic gene regulation involves methylation at the carbon-5 position of cytosine bases located 5′ to a guanosine in a CpG dinucleotide ('cytosine methylation code') and post-translational covalent modifications of the amino-terminal residues of histones within the nucleosome ('histone code'). The histone code is an array of post-translational modifications which include acetylation, phosphorylation, methylation, sumoylation and ubiquitination of the amino-terminal tails of core histone proteins. These characteristic modification patterns occupy a central role in gene regulation through changes in chromatin structure and condensation. Post-translational acetylation of core histone proteins neutralizes the positive charge on lysine residues at their amino-terminal tails, allowing unfolding of the associated DNA which becomes accessible to transcription factors leading ultimately to transcriptional activation.

Epigenetic modifications of nucleosomes due to deregulated acetylation by HDACs have a fundamental role in the process of carcinogenesis. Aberrant HDAC activity has been documented in many human malignancies resulting in the repression of tumor suppressor genes and promotion of tumorigenesis [3]. Eighteen HDACs, which belong to three distinct classes, have been identified in humans [4]. Class I HDACs (HDAC-1, -2, -3 and -8) are ubiquitously expressed small nuclear

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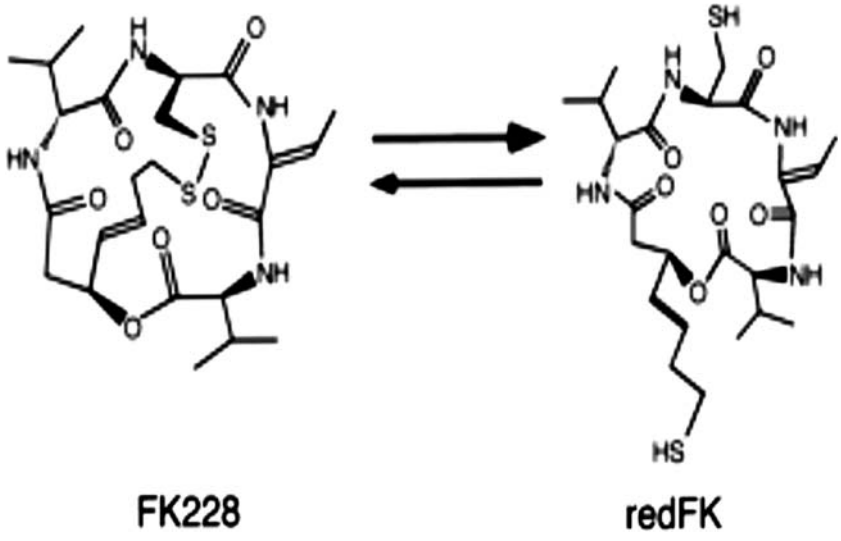

Fig. 1 Chemical structure of FK228 and its reduced form, redFK

proteins [5]. Class II HDACs (HDAC-4, -5, -6 and -7) are larger proteins which shuttle between the cytoplasm and the nucleus. Class I and class II HDACs are structurally similar particularly across the active site, and their enzymatic activity is zinc dependent. Limited information is available for class III HDACs (also known as SIRT family because of the similarity to yeast sirtuins). Their enzymatic activity is zinc independent and they have an absolute requirement for NAD. To date there have been seven class III members characterized [6]. HDACs are recruited by transcriptional repressor proteins such as Sin-3a, NCOR and MECP-2 to promoter regions and downregulate gene expression by core histone deacetylation [4]. HDAC inhibitors have a zinc-chelating group such as hydroxamate or sulfhydryl group, which interacts with the zinc atom in the active site pocket of HDACs abrogating catalytic activity [7].

Mechanisms of FK228 action in tumor cells

FK228 is a pro-drug, which is activated upon cell entry [8]. More specifically FK228, due to its stable molecular hydrophobic structure, may readily penetrate the tumor cell membrane and enter the cytoplasm, where it is activated through reduction by glutathione. FK228 has an internal disulfide bond which is reduced by intracellular glutathione yielding two free sulfhydryl groups capable of chelating the zinc in the HDAC active site. Reduced FK228 (redFK; Fig. 1) is the active drug but is hydrophilic and unstable in vivo. Increased intracellular glutathione is associated with multidrug resistance by serving as a cofactor in MRP-1 (multidrug resistance associated protein)-mediated drug transport out of the tumor cells [9]. Therefore FK228 may potentially be more effective in tumor cells with glutathione-mediated drug resistance. However, FK228 is a substrate for P-glycoprotein (Pgp) which plays a pivotal role in FK228 efflux. Reversible Pgp upregulation is a major mechanism for acquired FK228 resistance [9].

FK228 exhibits a considerably stronger direct inhibition in class I HDACs as compared to class II [8]. Depsipeptide has nanomolar inhibitory HDAC activity which is reversible. The macrocyclic peptide portion of the inhibitor binds with high affinity to the rim or opening of the channel to the active site and the sulfhydryl-containing aliphatic group enters the active site and binds to the active site zinc and water molecules. On the other hand, minor indirect suppression of class II HDAC activity by FK228 may be mediated through FK228 inhibition of mitogen-activated protein (MAP) kinase signaling and extracellular signal-regulated kinase 1/2 (ERK1/2) activity (see below), which normally activate class II HDACs [10].

FK228 is able to cause cell-cycle arrest via increased expression of cyclin-dependent kinase inhibitors $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ [11, 12]. By preventing deacetylation of histones, FK228 transcriptionally induces $p21^{WAF1/CIP1}$ expression in a p53-independent but ataxia-telangiectasia mutated (ATM) protein-dependent manner. $P21^{WAF1/CIP1}$ is known to inhibit both G1 and G2 cyclin/cyclin-dependent kinase (CDK) complexes leading to a retinoblastoma (Rb) hypophosphorylated state and G1 and G2 cell-cycle arrest [2]. On the other hand, $p27^{KIP1}$ is a cyclin E/CDK2 inhibitor which arrests cell cycle in G1 phase. Interestingly, $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ are reportedly downregulated in melanoma cell lines [13]. FK228-mediated G1 phase arrest is $p21^{WAF1/CIP1}$ dependent, while G2/M phase arrest is $p21^{WAF1/CIP1}$ independent and more cytotoxic than G1 phase cell-cycle arrest. FK228 causes mitotic arrest through the formation of aberrant mitotic spindles, probably by interfering with chromosome attachment, but does not affect mitotic microtubules [12]. This effect may account for the higher cytotoxicity of FK228 and trichostatin A (TSA) in comparison to other HDAC inhibitors (i.e., SAHA among the hydroxaminic acids).

FK228-mediated HDAC inhibition induces the expression of genes involved in cellular differentiation. It has been demonstrated that FK228 enhances the expression of sodium iodide symporter in poorly differentiated thyroid carcinoma cells [14]. HDAC inhibitors synergize with retinoic acid (RA) to stimulate leukemia cell differentiation in acute promyelocytic leukemia (APL) [15]. The t(11;17) translocation creates a fusion protein which includes retinoic acid receptor (RAR) and promyelocytic leukemia zinc-finger protein (PLZF). This translocation leads to a form of APL which is characteristically insensitive to pharmacologic doses of RA, as opposed to the common APL t(15;17) translocation which is sensitive to pharmacologic doses of RA. Treatment of patients with t(11;17) translocation with FK228 and RA leads to the dissociation of HDAC repressor complex from PLZF, transcriptional activation of the RAR-targeted genes and induction of differentiation of the leukemic cells.

Acetylation is a pivotal mechanism in the modulation of the stability and function of cell-cycle regulatory proteins. HDACs can cause deacetylation of non-histone substrates such as transcription factors (p53, E2F), cell-cycle proteins (Rb) and chaperone proteins Hsp90 (heat shock protein), accounting for some of their antitumor effects that cannot be attributed solely to histone acetylation [16]. Thus, FK228 increases post-translational acetylation of wild-type p53 [16]. Specifically, in non-small cell lung carcinoma (NSCLC) cell lines, acetylation of tumor suppressor protein p53 increases its stability, inhibits its murine double minute 2 (MDM2)-mediated ubiquitination and enhances its sequence-specific binding to DNA. Furthermore, FK228 enhances the acetylation of Rb protein, thus abrogating its phosphorylation by CDKs, which in turn results in cell-cycle arrest.

It has also been demonstrated that FK228 depletes mutant p53 in cancer cell lines and that this depletion is preceded by induction of p53-regulated transcription [17]. Either by restoring or mimicking p53 *trans*-functions, FK228 can initiate degradation of mutant p53. This is very important since sudden restoration of p53-like functions is highly cytotoxic to cells with mutant p53, which can explain the selectivity of FK228 cytotoxicity for cancer cells [17].

In NSCLC cell lines FK228 promotes acetylation of Hsp90 [16]. Hsp90 chaperone proteins are actively involved in cell signaling, proliferation and survival such as mutant p53, ErbB1, ErbB2, platelet-derived growth factor (PDGF), Raf-1 and CDK-4. Hsp90 acetylation inhibits the assembly of Hsp90 multichaperone complexes and thereby leads to the depletion of these oncogenic client proteins in tumor cells. FK228-mediated depletion of ErbB1, ErbB2 and Raf-1 oncoproteins decreases the kinase activity of ERK1/2 and thus blocks signal transduction via the MAP kinase (MAPK) pathway. MAPK activation is implicated early in the progression of melanomas [18]. FK228 also inhibits Raf-1 signaling which mediates mitogenic and anti-apoptotic cues emanating from receptor tyrosine kinases through the Ras/Raf-1/MEK/ERK pathway [19]. Deregulation of the MAPK signaling pathway by FK228 also leads to decreased *cyclin D1* gene transcription and thus contributes to G1 phase cell-cycle arrest [11]. Importantly, in NSCLC cell lines most of FK228 cytotoxic effects are attributed to inhibition of Raf-1 signaling (depletion of Raf-1 as stated above) [16].

FK228 bears significant pro-apoptotic activity. FK228 treatment of uveal melanoma cell lines induced upregulation of pro-apoptotic *Fas* and *FasL* gene transcription [20]. The Fas/FasL system constitutes the major extrinsic apoptotic pathway in normal and malignant cells. Fas and its ligand, FasL, are transmembrane proteins that belong to the tumor necrosis factor (TNF) family of receptors and ligands. Depsipeptide-mediated apoptosis involves the extrinsic apoptotic pathway which activates caspase-8, followed by activation of the effector caspase-3. C-FLIP, inhibitor of caspase-8 activation, is downregulated by FK228 in CLL cells [21]. The intrinsic, mitochondria-dependent apoptotic pathway (bax/cytochrome c/caspase-9) does not seem to be involved in FK228-mediated apoptosis in uveal melanoma and CLL cells. On the other hand, increased phosphorylation of Bcl-2 has been documented in human breast cancer cell lines treated with FK228, which implicates the intrinsic apoptotic pathway in the FK228-mediated apoptosis [22]. Unphosphorylated Bcl-2 inactivates bax and prevents the initiation of the intrinsic apoptotic cascade.

Aberrant expression of H-Ras is associated with increased susceptibility to FK228. The stress-activated protein kinase p38 pathway plays a pro-apoptotic role in FK228-induced apoptosis, while the ERK pathway plays an anti-apoptotic role in non-transformed cells and a pro-apoptotic role in Ras-transformed cells (in response to FK228). It is postulated that ERK pathway contributes to the pro-apoptotic role of oncogenic H-Ras to FK228 treatment via the procaspase-3 to caspase-3 pathway [23].

Microarray analysis in human esophageal squamous cell cancer lines treated with FK228 revealed that peroxiredoxin 1 (Prdx1), a member of the peroxiredoxin family of antioxidant enzymes with cell-growth suppression activity, was activated. FK228 induced the accumulation of acetylated histones H3 and H4 in *Prdx1* promoter and inhibited cell growth by induction of apoptosis [24].

It is important to note that FK228 contributes to the augmentation of radiation-induced apoptosis. FK228 radio-sensitized human gastric MKN45 and colorectal DLD1 adenocarcinoma cells by inducing the expression of pro-apoptotic BH3-only Bim proteins [25].

Many studies indicate that FK228 has anti-angiogenic effects. Angiogenesis is a multistep process, modulated by oppositely acting factors that induce or suppress endothelial cell proliferation and migration. Hypoxia, a stimulus for angiogenesis, also induces HDAC activity. Increased HDAC activity suppresses

anti-angiogenic genes like *p53* and von Hippel Lindau (*VHL*) and induces angiogenic genes like vascular endothelial growth factor (*VEGF*) and hypoxia inducible factor-1a (*HIF-1a*). FK228 blocks hypoxia-induced angiogenesis through the transcriptional induction of VHL and neurofibromin-2 (NF-2) and the transcriptional repression of HIF-1a, VEGF and VEGF receptor (FLK-1 or FLT1) [26, 27]. FK228 induces the potent inhibition of breast carcinomas and melanomas that require neovascularization to sustain their growth.

FK228 therapy has shown several immunomodulating effects such as presentation of tumor antigens. Through HDAC inhibition, FK228 enhances the expression of the cancer testis antigens MAGE-3 [28] and NY-ESO-1 [29] in cancer cells, which facilitates their recognition by specific cytolytic T lymphocytes. Moreover, FK228 increases the cellular responsiveness to the interleukin-6 (IL-6) family of cytokines—leukemia inhibitory factor (LIF), oncostatin M (OSM) and IL-6 [30]. This effect is mediated by the transcriptional induction of the cytokine receptor subunits LIFRalpha, OSMRbeta, gp130 or of the transcription factor STAT3. FK228 induction of LIFRalpha occurs independently of de novo protein synthesis and cell proliferation and is partly mediated by the CBP/p300 coactivator. IL-6-type cytokines lead to growth arrest of human A375 melanoma cells through activation of STAT3 transcription factor. In addition, IL-6-type cytokines enhance $p27^{KIP1}$ gene expression in a STAT3-dependent fashion.

Clinical trials and perspectives

The activity of FK228 has been evaluated in multiple phase I and II clinical trials in US. In phase I trials, FK228 exhibits significant activity against cutaneous T cell lymphoma and is generally well tolerated [31]. FK228 is now progressing through phase II trials for cutaneous T cell lymphoma. The dose-limiting toxicities (DLTs) were fatigue, nausea, vomiting and transient thrombocytopenia and neutropenia. Whereas cardiac toxicity was anticipated based on preclinical data, there was no evidence of myocardial damage. The maximum tolerated dose (MTD) of depsipeptide given on a day-1 and -5 schedule every 21 days was 17.8 mg/m^2 [32]. Phase II studies of FK228 alone or in combination with other agents are also underway in solid malignancies.

In conclusion, the fundamental role of epigenetic events in carcinogenesis has resulted in the evolution of epigenetic targeting as a new paradigm in anticancer therapeutics. Chromatin-modulating agents such as HDAC inhibitors are already playing an instrumental role in these strategies. FK228 induces the expression of genes linked to the inhibition of cell growth, induction of cell differentiation, promotion of apoptotic cell death and inhibition of angiogenesis. It also seems to enhance antigen expression in tumor cells. Its multitargeting properties, its ability to act on non-histone targets (thereby affecting multiple key survival and proliferative pathways of cancer cells), its clinical activity and its acceptable side-effect profile render FK228 a very promising novel anticancer agent.

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