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Largazole as a Promising Treatment for Angiogenic Diseases

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Abstract

Largazole is a macro cyclic depsipeptide, which is isolated from the marine cyanobacterium Symploca sp. Hydrolysis of Largazole leads to the production of Largazole thiol, a highly selective class I histone deacetylase (HDAC) inhibitor and an anti-proliferation agent. This review highlights the current understanding of Largazole in various vascular complications and its mechanism of action and discusses the challenges and future directions of Largazole-based therapeutics.

Keywords: Largazole; Eye; Angiogenesis; Proliferation; VEGF; Cell cycle inhibitors

Introduction

Marine organisms, especially cyanobacteria, serve as a rich source of novel biologically active compounds due to their ability to survive in different biotopes. Many of these bioactive compounds are modified peptides or peptide-polyketide hybrids. Largazole is a natural cyclic depsipeptide which is isolated from the marine cyanobacterium Symploca sp. Marine secondary metabolites containing thioester groups are rare and largazole is one of them. Since its first report in 2008, extensive research has been carried out to investigate its chemical structure, biological activity, and mechanism of action.

Structural and Chemical Properties

Largazole contains a unique thiazoline-thiazole ring system and a lipophilic thioester side chain [1]. Following the hydrolysis of the thioester, a secondary metabolite, Largazole thiol, is produced. Pharmacokinetics analysis of Largazole thiol in rats indicates a half-life of 30 minutes and it is rapidly eliminated from the systemic circulation within 2 hours, following a 10 mg/kg bolus injection. The swift clearance of Largazole thiol may indicate its rapid tissue distribution and/or biotransformation [2].

Largazole thiol is capable of coordinating to the catalytic Zn^{2+} ion of class I histone deacetylase (HDAC) [1] and leads to its inhibition [3]. HDACs are enzymes that catalyse the deacetylation of histone lysine residues and control a multitude of biological processes, such as cell differentiation, proliferation, angiogenesis, and apoptosis [4]. Extensive research has been performed using Largazole as a potential scaffold for new drug development. This leads to the development of different synthetic analogues of LargazoleFor example,modificationon the 16-membered macro cyclic depsipeptide moiety of Largazole was commonly used to achieve further selectivity for HDACs [5]. However, extra care should be taken when modifying the common side-chain unit as it usually leads to the loss of activities through changing the chain length and the stereo-configuration of the double bond and the secondary alcohol, as well as the Zn^{2+}-binding group [6,7]. Structure–activity relationships (SAR) of Largazole have been widely studied that aid in the design of novel compounds with improved HDAC inhibitory profiles, anticancer activity, and pharmacokinetic properties [5]. It has been demonstrated that the four-atom linker between the macro cycle and octanoyl group in the side chain and the (S)-configuration at the C17 position are critical to repression of HDAC activity. Yet, the valine residue in the macro cycle can be replaced with alanine without significantly causing any loss of activity.

Largazole is a Potent Anti-Angiogenic Factor

Abnormal blood vessel formation is a characteristic feature of many blinding eye diseases, such as retinopathy of prematurity (ROP), proliferative diabetic retinopathy (PDR), and neo vascular age-related macular degeneration (AMD) [6]. The incidence of PDR increases substantially in patients with prolonged diabetes [7]. The overall prevalence of PDR in type 2 diabetes patients is 6%, while the prevalence of PDR in DR patients is 17% [6]. Angiogenesis is a complex process and is regulated by the balance between pro-and anti-angiogenic factors, under physiological conditions [8]. However, this fine balance is disrupted under the pathological condition, leading to the formation of tortuous and leaky blood vessels [9]. Targeting abnormal neovascularization is considered an attractive strategy

to control ocular angiogenic diseases. Current treatment for this devastating group of diseases is dominated by vascular endothelial growth factor (VEGF)-blocking agents, which are effective in preventing abnormal neovascularization and leakage [7]. However, a substantial number of patients are not responsive or may develop resistance to the treatment over time [2]. Drugs that are complementary or alternative to anti-VEGF agents may offer a better treatment outcome. Largazole was previously shown to inhibit the proliferation, migration, and tube formation of human micro vascular endothelial cells (HEMC-1) and attenuate inflammatory corneal neo-vascularization in a mouse model of alkali-induced corneal injury [10]. Recently, these observations were confirmed in human retinal micro vascular endothelial cells (HRMEC) [11]. The same group also showed that Largazole inhibits sprouting angiogenesis from murine embryonic metatarsal bones at the Nano molar concentration [11]. It is noteworthy that Largazole at this concentration doesn't affect pericyte viability or recruitment to the newly formed blood vessels, suggesting possible fewer unwanted side effects. The potent inhibitory effect of Largazole on the activation of endothelial cells of different tissue origins makes it a potential drug to treat different types of vascular complications.

Largazole as a Potent al Treatment for Other Vascular Diseases

Angiogenesis plays a critical role in tumour development and progression. Similar to angiogenic endothelial cells, tumour cells are highly proliferative. Studies showed that Largazole selectively inhibits the proliferation of different types of tumour cells over normal cell lines [12-15]. The strong anti-cancer properties of Largazole against colon cancer, lung cancer, and bone osteosarcoma elicit particular interest in its value as a potential cancer chemotherapeutic. Recent research extends the application of Largazole to the treatment of brain cancer and neurodegenerative disorders due to its good selectivity and brain penetration [16]. Asides from cancer, Largazole was found to ameliorate the development of liver fibrosis by inhibiting the viability and extracellular matrix production of hepatic stellate cells (HSCs) and angiogenesis [17]. Again, Largazole has no significant influence on the proliferation of normal human hepatocytes [17]. Therefore, treatment with Largazole may cause fewer unwanted sides effects.

Discussion

The mechanism of act on of largazole

VEGF is one of the most prominent regulators of angiogenesis. It regulates specific endothelial responses such as cell survival, proliferation, migration, invasion, vascular permeability, and vascular inflammation, primarily via the ERK and PI3K/Akt pathways [18,19]. Largazole was previously demonstrated to suppress the VEGF-induced activation of Akt by inhibiting the expression of VEGF and VEGF receptor 2 (VEGFR2) as well as the VEGF-induced activation of P38MAPK in HSC. The Largazole-mediated inhibitory effect on VEGFR2 has also been observed in HRMEC. Besides VEGF, Largazole has been shown to modulate the expression of other proangiogenic factors and antiangiogenic factors, including b-FGF, Tsp-1, Tsp-1, and ADAMTS-1 in LPS-treated HMEC-1 [10]. In colon cancer, Largazole effectively inhibits tumour growth by modulating the expression levels of cell cycle regulators, such as p21, CDK6, and Cyclin D1, epidermal growth factor receptor, and insulin receptor substrate 1 [13]. Consistent with this observation, the promoting effect of Largazole on cell cycle inhibitor P21 has also been reported in HRMEC [19]. In addition, Largazole has been shown to exert its effect by inhibiting the activity of HDAC, leading to cell cycle arrest and apoptosis. Protein ubiquitination is a tightly regulated process that regulates the cell cycle, endocytosis, signal transduction, apoptosis, DNA damage repair, transcriptional regulation, and many other biological processes. Mechanistic studies have revealed the role of Largazole as a potent antagonist of the ubiquitin-activating enzyme; E1 was reported [20]. In comparison to HDAC inhibition, ketone and ester analogues of Largazole can actively block the ligation of ubiquitin onto E1. This finding suggests a differential mode of inhibitory activity since the formation of a thiol metabolite is necessary for E1 inhibition [20]. The ability of Largazole to target multiple growth factors and signalling pathways simultaneously suggests a potential use of Largazole to treat multi-factorial disorders that are resistant to targeted therapeutics.

Conclusion

Taken together, this review highlights the potential of Largazole as a novel treatment for vascular complications as well as other diseases involves active cell proliferation. In comparison to other clinical and preclinical HDAC inhibitors which are limited by isoform selectivity and metabolic instability, Largazole is attractive in that it is highly potent and stable in its free form. It leads to strong inhibition of cell growth and angiogenesis at the Nano molar concentrations. It is also highly selective to hyper proliferative cells over normal cells; therefore, fewer unwanted sides effects are expected following Largazole treatment. One of the underlying mechanisms of drug resistance to current anti-VEGF therapy is the activation of alternative angiogenic pathways in the presence of VEGF blockade. Considering the ability of Largazole to target multiple angiogenic signalling pathways and its impact on cell cycle regulators, Largazole may offer an alternative or complementary treatment to current anti-VEGF agents. Indeed, a collaborative effect was demonstrated between Largazole and an approved anti-VEGF drug, Aflibercept, in preventing angiogenesis. Future studies to evaluate the *in vivo* efficacy of Largazole on ocular angiogenesis, either on its own or in combination with VEGF inhibitors, is highly desired. In addition, the oral bioavailability of Largazole highlights the advantage of the thioester functionality as a pro-drug strategy. Finally, more structural studies on the molecular scaffold of Largazole could be carried out to design and synthesize isoenzyme-specific inhibition of HDAC, and there remains a need to study the pharmacodynamics and toxicological profile of Largazole in order to evaluate its safety and efficacy.

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