Cancer Letters 400 (2017) 47–60

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Original Article

In vitro and *in vivo* anti-uveal melanoma activity of JSL-1, a novel HDAC inhibitor

Yun Wang [a], Maoxing Liu [a], Yanli Jin [a], Sheng Jiang [b], Jingxuan Pan [a, *]

[a] Jinan University Institute of Tumor Pharmacology, College of Pharmacy, Jinan University; State Key Laboratory of Ophthalmology, Sun Yat-Sen University Zhongshan Ophthalmic Center, Guangzhou, China
[b] Laboratory of Medicinal Chemistry, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form
8 April 2017
Accepted 14 April 2017

Keywords:
Uveal melanoma
Epigenetics
HDAC inhibitor
Migration and invasion
β-catenin
Cancer stem-like cells

ABSTRACT

Uveal melanoma (UM) is the most common intraocular malignant neoplasm in adults. Despite the availability of enucleation, radiation and chemotherapy, the prognosis of patients with metastasis remains poor. Therefore, novel effective therapies for patients with metastatic UM are urgently needed. In the present study, we demonstrated that JSL-1, a novel HDAC inhibitor, effectively inhibited the proliferation. JSL-1 induced apoptosis with increased expression of proapoptotic BH3-only protein BIM in UM cells. JSL-1 suppressed migration and invasion of UM cells with MMP-2 decreased. Furthermore, JSL-1 blocked the canonical Wnt/β-catenin pathway, impaired self-renewal capacity and decreased percentage of $ALDH^+$ cells, thereby reflecting elimination of UM cancer stem-like cells (CSCs) which are believed seeds of metastasis. Importantly, JSL-1 potently inhibited the growth of uveal melanoma xenograft in NOD-SCID mice. These results suggested that JSL-1 may be a promising therapeutic agent for UM.

Introduction

Uveal melanoma (UM) is the most common primary intraocular tumor in adults [1], which can be classified into the choroid, ciliary body and iris melanoma according to its origin, with the choroid as the most common location of the disease [2]. The main clinical options for patients with UM are enucleation, photodynamic therapy, radiotherapy and chemotherapy [3]. They are, however, not effective for UM patients harboring metastatic foci. Approximately 50% of the patients develop liver metastasis [4] with the median overall survival of only 2–15 months [5]. Therefore, novel effective targeted therapies are urgently needed for metastatic UM.

In addition to abnormal genetic alternations, the dysregulation of epigenetic modifications is involved in tumor development and progression [6]. Histone acetylation is one of the important forms of epigenetic modifications. The balance between acetylation and deacetylation of histone proteins was regulated by the reciprocal functions of histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively [7]. HDACs remove the acetyl group of histone lysine residues, resulting in a condensed chromatin structure against transcription of genes, most of which are tumor suppressor such as p53 [8]. On the contrary, histone acetylation at the lysine residues regulated by HATs is more easily bound by the transcriptional factors to activate expression of genes involved in cell growth, differentiation and apoptosis [7].

Previous studies revealed that HDACs are overexpressed in multiple types of tumors. For example, HDAC1 and HDAC6 are overexpressed in liver cancer [9,10], and HDAC2 is highly expressed in lung cancer [11]. Increasing evidence has shown that HDAC inhibitors (HDACis) exert potently anti-tumor activities *in vitro* and *in vivo* [12]. pan-HDACi suberoylanilide hydroxamic acid (SAHA, Vorinostat) and class I-selective HDACi Romidepsin (FK-228) have been approved by the FDA to treat patients with cutaneous T cell lymphoma [13,14], which encourages development of novel HDACis.

Abbreviations: UM, uveal melanoma; HDAC, histone deacetylase; HDACi, HDAC inhibitor; HAT, histone acetyltransferase; CSCs, cancer stem-like cells; ALDH, aldehyde dehydrogenase; PI, propidium iodide; AIF, apoptosis-inducing factor; MMP-2, matrix metalloproteinase 2; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular regulating kinase 1/2; PEI, polyethylenimine.

* Corresponding author. Jinan University Institute of Tumor Pharmacology, College of Pharmacy, Jinan University; State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, 54 South Xianlie Road, Guangzhou, 510060, China.
E-mail address: panjx2@mail.sysu.edu.cn (J. Pan).

http://dx.doi.org/10.1016/j.canlet.2017.04.028
0304-3835/

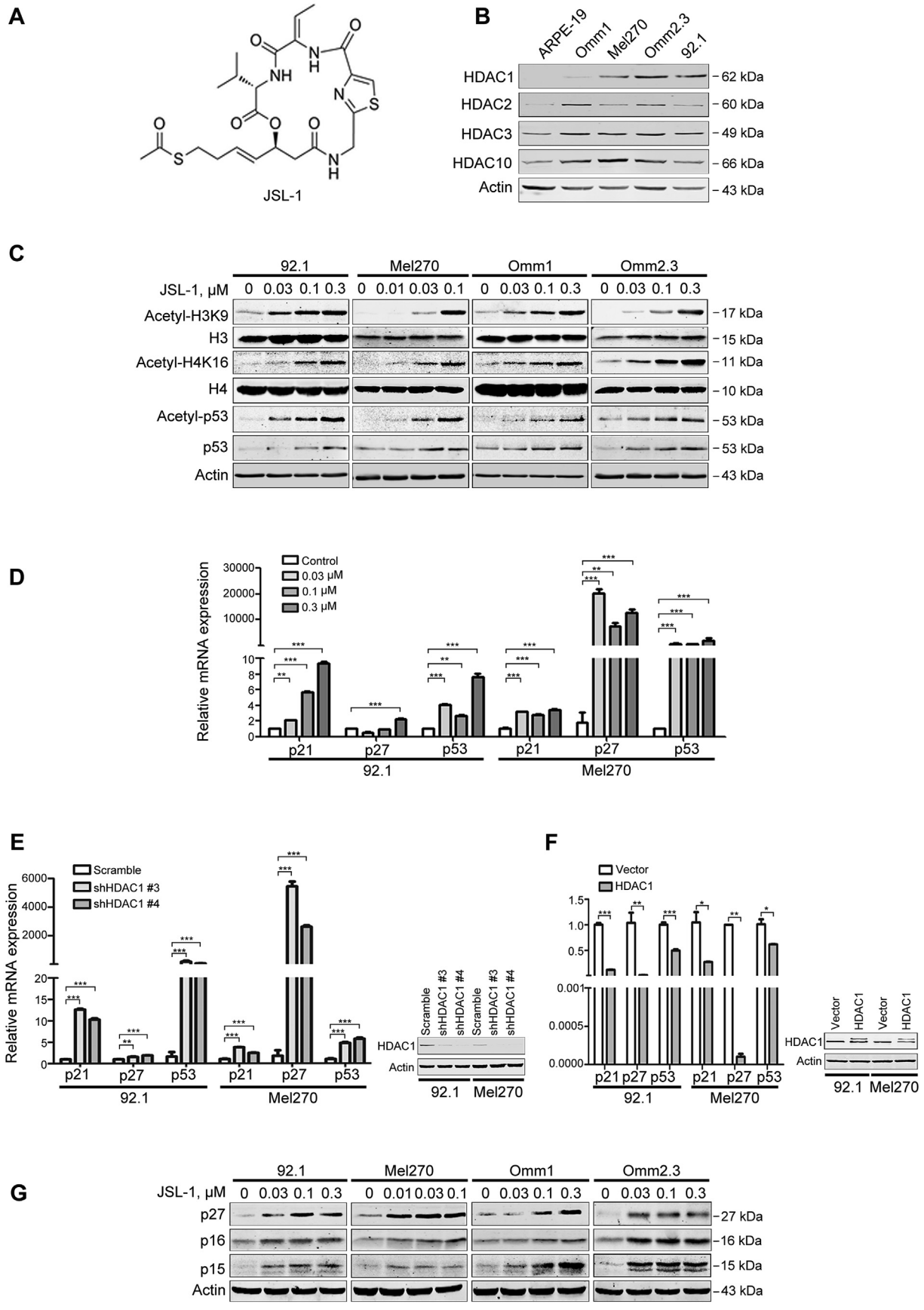

Fig. 1. JSL-1 inhibits HDAC activities in uveal melanoma cells. (A) Chemical structure of JSL-1. (B) Basal levels of HDAC1, 2, 3 and 10 were detected by Western blotting analysis. (C) JSL-1 induced acetylation of histone proteins H3, H4 and non-histone protein p53 in uveal melanoma (UM) cells. After treated with the indicated concentrations of JSL-1 for 48 h,