Title: Overcoming the resistance mechanisms of Smoothened inhibitors

Authors: Xiaochun Dong, Chenglin Wang, Zhongjian Chen, Weili Zhao

PII: S1359-6446(17)30365-3
DOI: https://doi.org/10.1016/j.drudis.2018.01.012
Reference: DRUDIS 2145

To appear in:

Received date: 18-10-2017
Revised date: 15-11-2017
Accepted date: 4-1-2018

Please cite this article as: Dong, Xiaochun, Wang, Chenglin, Chen, Zhongjian, Zhao, Weili, Overcoming the resistance mechanisms of Smoothened inhibitors.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.012

Overcoming the resistance mechanisms of Smoothened inhibitors

Xiaochun Dong[1], Chenglin Wang[1], Zhongjian Chen[2], and Weili Zhao[1]

[1]Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai, China
[2]Shanghai Dermatology Hospital, Shanghai, China
Corresponding authors: Chen, Z. (aajian818@163.com); Zhao, W. (zhaoweili@fudan.edu.cn)

Highlights

- The possible mechanism of acquired resistance to Smo inhibitors was reviewed.
- Development of second–generation inhibitors is critical to combat Smo resistance.
- Gli inhibition could benefit to patients with Smo–inhibitor resistant tumors.
- The Hh–associated oncogenic signaling pathways represent potential therapeutic targets.

Smoothened (Smo), the main transducer of the Hedgehog (Hh) signaling pathway, is a promising target for anticancer therapy. Although vismodegib and sonidegib have demonstrated effectiveness for the treatment of basal cell carcinoma (BCC), their clinical use has been associated with mutation-related drug resistance. In this review, we outline the resistance mechanisms of Smo inhibitors and point the way for future endeavors. We focus in particular on the development of second-generation Smo inhibitors based on co-crystal structures, inhibition of downstream components, and the regulation of other interacting pathways or mediators that could compensate for the inhibitory activity of upstream inhibitors.

Keywords: Hedgehog signaling pathway; Smoothened; resistance; cancer therapy.

Teaser: How should we deal with the emergency of mutation-related resistance during treatment with marketed Smo inhibitors? A better understanding of resistance mechanisms is essential for improving therapeutic strategies to obtain durable responses to such targeted therapies.

Introduction

The Hh signaling pathway, an evolutionarily conserved signaling axis, is essential for proper embryonic development and postembryonic tissue repair, as well as stem cell regulation [1]. The Hh signaling cascade is initiated by the binding of the Hh protein ligand to its cellular membrane receptor, Patched (Ptch), which relieves Ptch-mediated repression of the seven-transmembrane (7TM) protein Smo. Activated Smo transduces the signal to the GLI family of transcription factors, which translocate to the nucleus to regulate numerous gene products involved in tissue patterning and cell differentiation [2,3]. Inappropriate activation of the Hh signaling pathway in a ligand-dependent or independent manner is linked to a range of cancers, such as BCC, medulloblastoma, leukemias, bladder, colorectal, lung, pancreatic, prostate, and stomach cancers [1,3]. Therefore, inhibition of aberrant Hh signaling represents a promising approach for novel anticancer therapy [3,4].

Smo is the main transducer of the Hh signaling pathway. Accordingly, Smo inhibitors have received intense research attention since the identification of cyclopamine (a natural steroidal alkaloid) as the first Smo antagonist, which acts by blocking the Hh signaling pathway [5]. Notably, vismodegib (GDC-0449, **1**) and sonidegib (LDE225, **2**) were approved by the US Food and Drug Administration (FDA) for the treatment of BCC in 2012 and 2015, respectively [6,7]. Several other Smo inhibitors have also moved into various stages of clinical trials [8]. Unfortunately, the clinical use of Smo inhibitor(s) has also been associated with adverse effects, as well as instances of mutation-related drug resistance. Here, we review the mechanism of acquired resistance to Smo antagonists and discuss the possible strategies that could be used to overcome such resistance.

Mechanism of acquired resistance to Smo inhibitors