molecules

MDPI

Review

Current Development Status of MEK Inhibitors

Ying Cheng and Hongqi Tian *

Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin 300192, China; chengying624@163.com

* Correspondence: tianhongqi@irm-cams.ac.cn; Tel.: +86-186-0261-3300

Received: 9 August 2017; Accepted: 12 September 2017; Published: 26 September 2017

Abstract: The current development status of mitogen-activated protein kinase kinase (MEK) inhibitors, including the preclinical data and clinical study progress, has been summarized in this review. Different MEK inhibitors, possessing specific physicochemical properties and bioactivity characteristics, may provide different options for patients seeking treatment for cancer. Moreover, the combination of the MEK inhibitors with other therapies—such as chemotherapy, targeted therapy, and immunotherapy—may be a promising approach for clinical use.

Keywords: MEK inhibitors; targeted therapy; combination; approved drug; clinical study; preclinical study

1. Introduction

The mitogen-activated protein kinase (MAPK) signaling pathway plays critical roles in the regulation of diverse cellular activities, including cell proliferation, survival, differentiation, and motility [1]. Dysregulation of the MAPK pathway occurs in more than one-third of all malignancies. The classical MAPK pathway consists of Ras (a family of related proteins which is expressed in all animal cell lineages and organs), Raf (a family of three serine/threonine-specific protein kinases that are related to retroviral oncogenes), MEK (mitogen-activated protein kinase kinase), and ERK (extracellular signal-regulated kinases), sequentially relaying proliferative signals generated at the cell surface receptors into the nucleus through cytoplasmic signaling. The MEK inhibitor targets the Ras/Raf/MEK/ERK signaling pathway, inhibiting cell proliferation and inducing apoptosis. It hence has potential in clinical use for cancer treatment, especially for those cancers induced by RAS/RAF dysfunction [2].

Owing to the widespread activation of this pathway in numerous neoplasms, MEK inhibitors have been in the process of development and study as a type of monotherapy or combination therapy with other targeted and cytotoxic drugs in a variety of clinical situations. More recently, the combination with the use of immune checkpoint inhibitors has emerged as an efficacious treatment for some cancers, expanding the efficacy of this class of agent [3].

This review summarized the recent progress of MEK inhibitors, complementary to an earlier review [4–15] but with a greater focus on those compounds that have been approved or are in clinical stages of development. We also give a brief summary of compounds in the preclinical phase.

2. Ras/Raf/MEK/ERK Pathway and MEK Inhibitors

Signal transduction occurs when an extracellular signaling molecule activates a specific receptor located on the cell surface. In turn, this receptor triggers a biochemical chain of events inside the cell and creates a response. The Ras/Raf/MEK/ERK pathway is one of the critical pathways involved in signal transduction, which results in the control of cell proliferation, survival, and differentiation [16,17] and plays a role in the development of multiple cancers including melanoma, non-small cell lung

IJC
International Journal of Cancer

A benzoxazole compound as a novel MEK inhibitor for the treatment of RAS/RAF mutant cancer

Ying Cheng[1,2], Xingkai Wang[3], Xiangying Xia[3], Wei Zhang[2] and Hongqi Tian[1]

[1]Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China
[2]Center for Marine Bioproducts Development, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia
[3]Binjiang Pharma, Inc., Tianjin, China

Mutations in RAS/RAF occur in large portion of malignancies and are associated with aggressive clinical behaviors and poor prognosis. Therefore, we developed a novel benzoxazole compound (KZ-001) as a highly potent and selective MEK 1/2 inhibitor. Our efforts were focused on enhancing the activity of the known MEK inhibitor AZD6244 and overcoming the shortcomings existing in current MEK inhibitors. Here we show that compound KZ-001 exhibits approximately 30-fold greater inhibition against BRAF- and KRAS-mutant tumor cells than that of AZD6244. These results were also demonstrated using *in vivo* xenograft models. Furthermore, pharmacokinetics (PK) analysis was performed for KZ-001, and this compound showed good orally bioavailability (28%) and exposure ($AUC_{0-\infty}$ = 337 ± 169 ng h/mL). To determine its potential clinical application, the synergistic effect of KZ-001 with other agents was investigated both *in vitro* and *in vivo* (xenograft models). KZ-001 exhibited synergistic anti-cancer effect in combination with BRAF inhibitor vemurafenib and a microtubule-stabilizing chemotherapeutic agent docetaxel. In addition, KZ-001 inhibited the MAPK pathway like known MEK inhibitors. In summary, KZ-001, a structurally novel benzoxazole compound, was developed as a MEK inhibitor that has potential for cancer treatment.

Introduction

The RAS/RAF/MEK/ERK signaling pathway plays a critical role in cancer cell proliferation and apoptosis. RAS is a family of related proteins that is expressed in all animal cell lineages and organs. Once RAS is activated in normal cells, it interacts with RAF (A-RAF, B-RAF and C-RAF) and serine/threonine kinases, leading to the activation of downstream targets. RAF is a family of three serine/threonine-specific protein kinases that are related to retroviral oncogenes. Activated RAF phosphorylates and activates MEK1 (mitogen-activated protein kinase kinase) and MEK2 kinases, leading to downstream phosphorylation and activation of extracellular signal-regulated kinases, ERK1 and ERK2. This activation further triggers downstream activation of nuclear and cytoplasmic targets associated with transcription, cell proliferation, differentiation and metabolism.[1,2]

Members of the RAS/RAF/MEK/ERK pathway, in particular KRAS (proto-oncogene corresponding to the oncogene first identified in Kirsten rat sarcoma virus) and BRAF (a member of RAF), are frequently deregulated in several cancers, including melanoma, colorectal, non-small cell lung cancer (NSCLC) and pancreatic cancer.[1,3–5] Oncogenic mutations in the *RAS* gene, most commonly in *KRAS*, are detected in approximately 30% of human cancers.[6] The effort to directly target RAS including KRAS, has proven to be challenging,[7,8] hence therapeutic development has focused on the inhibition of downstream kinases, particularly MEK.[9] MEK is a central component that lies downstream of RAS and RAF, and is critical for transducing signals to ERK.[10] MEK inhibitors target the RAS/RAF/MEK/ERK signaling pathway to block cell proliferation and induce apoptosis, thus these inhibitors can be

Key words: benzoxazole compound, MEK inhibitor, RAF/RAS mutant cancer, synergism, high potency
Additional Supporting Information may be found in the online version of this article.
Disclosure of Potential Conflicts of Interest: No conflicts of interest were disclosed by the authors.
Grant sponsor: CAMS Innovation Fund for Medical Science from the Chinese Academy of Medical Sciences & Peking Union Medical College; **Grant number:** CIFMS, 2017-I2M-3-019; **Grant sponsor:** Fundamental Research Fund for CAMS & PUMC; **Grant number:** 2016ZX310199; **Grant sponsor:** Innovation Team Funding from the Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College; **Grant number:** 1649
DOI: 10.1002/ijc.32119
History: Received 18 Sep 2018; Accepted 20 Dec 2018; Online 10 Jan 2019
Correspondence to: Hongqi Tian, Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 238 Baidi Road, Nankai District, Tianjin 300192, China, Tel.: +86-22-65378920, Fax: 022-65378920, E-mail: tianhongqi@irm-cams.ac.cn

Supporting Information

A Benzoxazole compound as a novel MEK inhibitor for the treatment of RAS/RAF mutant cancer

Ying Cheng[1,3], Xingkai Wang[2], Xiangying Xia[2], Wei Zhang[3], and Hongqi Tian[1]

Authors' affiliations: [1]Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin 300192, China.
[2]Tianjin Binjiang Pharma, Inc., Tianjin 300192, China
[3]Center for Marine Bioproducts Development, College of Medicine and Public Health, Flinders University, Bedford Park, Adelaide, SA, 5042, Australia

Running title: A novel potent Benzoxazole MEK inhibitor.

Keywords: Benzoxazole compound; MEK inhibitor; Synergism; High potency.

Financial support: This work was supported by the innovation team funding (1649) from the Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, and Fundamental Research Fund for CAMS&PUMC (2016ZX310199), CAMS Innovation Fund for Medical Science (CIFMS, 2017-I2M-019) from the Chinese Academy of Medical Sciences & Peking Union Medical College.

Corresponding author: Hongqi Tian, Adress: No.238 Baidi Road, Nankai District, Tianjin, China. ZIP Code: 300192; Phone: 18920797117; Fax: 022-65378920; Email: tianhongqi@irm-cams.ac.cn,

Received: 19 September 2018 | Revised: 17 December 2018 | Accepted: 24 December 2018

DOI: 10.1111/jcmm.14159

ORIGINAL ARTICLE

WILEY

The protective effects of XH-105 against radiation-induced intestinal injury

Ying Cheng[1,2] | Yinping Dong[1] | Qinlian Hou[1] | Jing Wu[1] | Wei Zhang[2] | Hongqi Tian[1] | Deguan Li[1]

[1]Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin, China

[2]Center for Marine Bioproducts Development, College of Medicine and Public Health, Flinders University, Bedford Park, Adelaide, South Australia, Australia

Correspondence
Hongqi Tian and Deguan Li, Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Science and Peking Union Medical College, Tianjin, China.
Emails: tianhongqi@irm-cams.ac.cn; lideguan@irm-cams.ac.cn

Funding information
Fundamental Research Fund for CAMS & PUMC, Grant/Award Number: 2016ZX310199; CAMS Innovation Fund for Medical Sciences, Grant/Award Number: CIFMS, 2017-I2M-3-019; National Natural Science Foundation of China, Grant/Award Number: 81573094

Abstract

Radiation-induced intestinal injury is one of the major side effects in patients receiving radiation therapy. There is no specific treatment for radiation enteritis in the clinic. We designed and synthesized a new compound named XH-105, which is expected to cleave into polyphenol and aminothiol in vivo to mitigate radiation injury. In the following study, we describe the beneficial effects of XH-105 against radiation-induced intestinal injury. C57BL/6J mice were treated by gavage with XH-105 1 hour before total body irradiation (TBI), and the survival rate was monitored. Histological changes were examined, and survival of $Lgr5^+$ intestinal stem cells $Ki67^+$ cells, $villi^+$ enterocytes and lysozymes was determined by immunohistochemistry. DNA damage and cellular apoptosis in intestinal tissue were also evaluated. Compared to vehicle-treated mice after TBI, XH-105 treatment significantly enhanced the survival rate, attenuated structural damage of the small intestine, decreased the apoptotic rate, reduced DNA damage, maintained cell regeneration and promoted crypt proliferation and differentiation. XH-105 also reduced the expression of Bax and p53 in the small intestine. These data suggest that XH-105 is beneficial for the protection of radiation-induced intestinal injury by inhibiting the p53-dependent apoptosis signalling pathway.

KEYWORDS
apoptosis, DNA damage, p53, small intestine, total body irradiation

1 | INTRODUCTION

The small intestine is one of the most sensitive organs for ionizing radiation. The main symptoms of radiation-induced intestinal damage include anorexia, vomiting, diarrhea, dehydration, systemic infection, and in extreme cases, septic shock and death.[1] Radiation-induced intestinal damage seriously affects the treatment of patients with abdominal or pelvic tumours, reducing the quality of life of patients. However, there is no specific treatment for radiation enteritis in the clinic. Therefore, the development of efficient radiological intestinal damage protectors is an important area in radiation protection.

Natural anti-oxidation agents exist widely in herbs and fruits and mainly include flavonoids and polyenes that could be used as radioprotectors.[2-5] Both of these agents have advantages of low toxicity and moderate efficacy, but display poor stability and bioavailability.[6] Aminothiols emerge as the most promising compounds, especially after amifostine was discovered and approved by the Food and Drug Administration. Although amifostine is currently used clinically, its drug toxicity, limited times of protection and unfavourable routes of administration[7] limit the utility of the drug in non-clinical settings. The most probable protective mechanisms of aminothiols are that the aminothiol radioprotectors donate a H atom, scavenge hydroxyl

Ying Cheng and Yinping Dong contributed equally to this work.