Bioorganic & Medicinal Chemistry Letters 25 (2015) 192–197

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Role of the ERK1/2 pathway in tumor chemoresistance and tumor therapy

Qing-Hua Liu [a,b,†], Mei-Lin Shi [a,†], Chao Sun [a], Jin Bai [a,*], Jun-Nian Zheng [a,c,*]

[a] Jiangsu Key Laboratory of Biological Cancer Therapy, Xuzhou Medical College, 84 West Huaihai Road, Xuzhou 221002, Jiangsu Province, China
[b] School of Pathology, Xuzhou Medical College, Xuzhou, Jiangsu, China
[c] The Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu, China

ARTICLE INFO

Article history:
Received 27 August 2014
Revised 14 November 2014
Accepted 27 November 2014
Available online 5 December 2014

Keywords:
ERK1/2
Ras
Raf
MEK
Tumor chemoresistance
Tumor therapy

ABSTRACT

Chemotherapy is one of the important methods for treatment in tumors. However, many tumor patients may experience tumor recurrence because of treatment failure due to chemoresistance. Although many signaling pathways could influence chemoresistance of tumor cells, the extracellular signal-regulated kinase 1 and 2 (ERK1/2) pathway has gained significant attention because of its implications in signaling and which has crosstalk with other signaling pathways. Extensive studies conclude that ERK1/2 pathway is responding to chemoresistance in many kinds of malignant tumors. The aim of this review is to discuss on the role of ERK1/2 pathway in chemoresistance and therapy of tumors. A comprehensive understanding of ERK1/2 pathway in chemoresistance of tumors could provide novel avenues for treatment strategies of tumors.

Chemoresistance remains the main obstacle to cancer therapy and which has different mechanisms. Understanding the mechanisms of chemoresistance is very important for finding novel therapeutic approaches for cancer therapy. The molecular mechanisms of chemoresistance in tumor are very complex and not very clear, which include high expression levels of adenosine triphosphate-binding cassette transporters, an active DNA repair capacity, slow rate of self-renewal, cancer stem cells and tumor microenvironment, etc.[1–3] Recently, ERK1/2 pathway has gained significant attention in tumor chemoresistance and tumor therapy. ERK is a downstream component of ERK1/2 pathway that is activated by serine/threonine kinase, Ras, Raf and MEK. This signaling pathway has been reported to be activated in numerous physical or pathological progresses due to varieties of stimuli and this pathway plays a critical role in the transmission of signals from growth factor receptors to nucleus for regulating downstream gene expression. The activation of the downstream components ranges from stimulation of cell differentiation, cell senescence, cell apoptosis and cell survival, etc. In this review we will focus on its biochemical importance in tumor chemoresistance and tumor therapy.

ERK 1/2 are important components in the Ras-Raf-MEK-ERK signaling pathway cascade. ERK1 (44kDa) and ERK2 (42kDa) are homologous subtypes of ERK family, which share the same substrate-specificities.[4] These 44- and 42-kDa proteins can phosphorylate a multitude of protein substrates and they have nearly 85% amino acid identity with much greater identity in the core regions and express in almost all tissues.[5] The activation of ERK1/2 cascade is mostly initiated by protein kinase C or Ras (Fig. 1).

Ras is a small GTP-binding protein firstly was found in murine sarcoma virus Harvery and the offspring of murine sarcoma virus Kirsten in 1981.[6] When Ras is activated, it then undergoes from Ras-GDP to Ras-GTP.[7] This change could induce a series of intracellular phosphorylations, which will transmit the signal by activating Raf.[8] When Raf is normally activated by a complex series of events including Ras, it can activate its downstream molecules, MEK and ERK.[9] The C-terminal region of activated Raf can bind to MEK and activate MEK by phosphorylating threonine and serine which located in the catalytic region of MEK.[10] When MEK is activated, it can phosphorylate both regulatory Thr and Tyr residues of ERK1/2.[11] Only the phosphorylated ERK1/2 is active.

ERK1/2 are cDNA sequences of one kind of a protein kinase isolated and identified by Boulton et al. in the early 1990s, the molecular weight are 44 kDa and 42 kDa.[5,12] Under resting conditions, ERK1/2 anchor in the cytoplasm by associating with MEK and after being phosphorylated (p-ERK1/2), they will transit to nucleus and regulate the activities of some transcription factors, such as: c-fos, c-Jun, Elk-1, STATs, c-myc and NF-κB, etc.[13–15] These transcription factors continually regulate their target genes, cause the change of

* Corresponding authors.
E-mail addresses: bj@xzmc.edu.cn (J. Bai), jnzheng@xzmc.edu.cn (J.-N. Zheng).
† Qing-Hua Liu and Mei-Lin Shi contributed equally to this Letter.

http://dx.doi.org/10.1016/j.bmcl.2014.11.076
0960-894X/

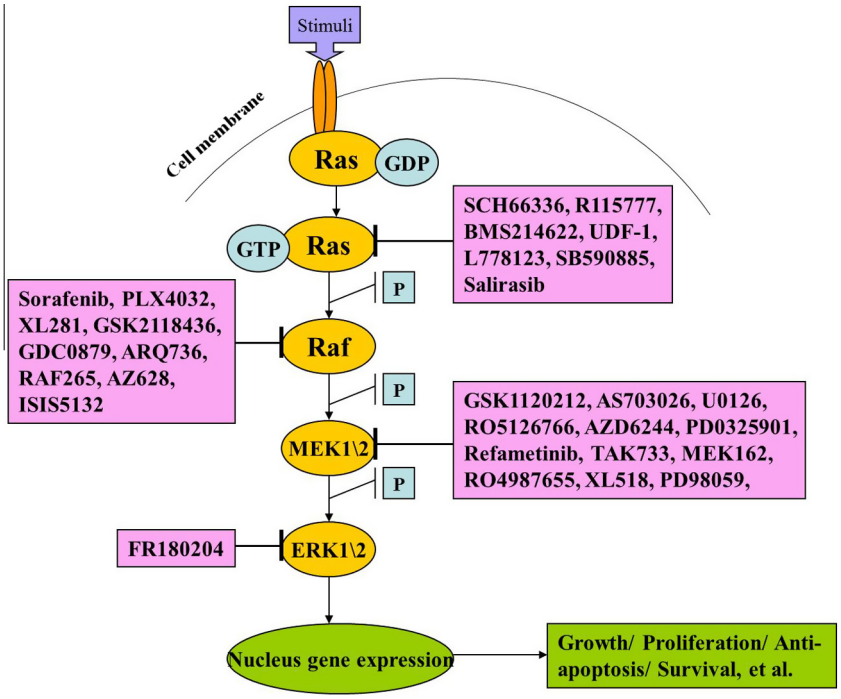

Figure 1. The ERK1/2 pathway is shown along with inhibitors for treatment. Activation of this pathway can occur by varieties of factors. Various inhibitors are listed in boxes near the corresponding members.

expression or activity of specific proteins, which are involved in cell proliferation, differentiation, metastasis and apoptosis etc.

However, the activation of ERK pathway is very complex because the sequence of ERK signaling cascade is not fixed. Satio T[16] has found that the activation of ERK is not only dependent on Ras, which can been activated by β-cytokine (BTC) combination with EGFR. After the phosphorylation of Tyr1068 (carboxy-terminal tyrosine) of EGFR, the recruitment of Grb2-MEKK1 complexes of the cell membrane will greatly increase the activity of ERK. Therefore, ERK pathway is very complex: in addition to cascade order is not fixed, there are multiple members of the kinase, transcription factor, caspase executioner families can be activated or inactivated by protein phosphorylation.

Raf, either through downstream MEK, or independently of MEK, can induce the phosphorylation of proteins. Activated ERK can also phosphorylate 'upstream' Raf and MEK which can alter their activities. Some studies have indicated that the activity of MEK1 will decrease when which has been phosphorylated by ERK.[17] The complex of this pathway, not fixed cascade, negative feedback loops and its cross-talks with other signaling pathways, seem to be of primary importance in determining the final cellular outcome. In clinic, the use of pharmacologic inhibitors targeting this pathway must be carefully evaluated when they are applied to cases in which ERKs are mainly oncogenic.

A decade ago, some experts[18,19] have confirmed that ERK1/2 pathway is involved in tumor drug resistance. Each component of the ERK1/2 pathway has been gradually understood and theoretical intervention in any kinase of ERK pathway can achieve the purpose of treatment of cancer. Inhibitors of the ERK1/2 signaling pathway and their upstream and downstream activators have been developed and many are currently used in clinical trials.

The Ras gene family has three members that encode four homologous 21 kDa proteins, respectively, H-ras, K-ras4A, K-ras4B and N-ras in mammals.[20] Among them, K-ras4A and K-ras4B are from the same gene splicing results. Mutations of Ras are oncogenic because they are capable of activating downstream effective pathways without any upstream stimulation. Ras mutations have been observed in approximately 20–30% of human cancers.[21] The mutations of K-ras are highly (approximately 80%) in advanced pancreatic cancers. Differences between the subtypes of K-ras mutations have been described by many studies. The most common mutation in codon 13 has been reported correlating with poor outcome in patients suffering from colorectal cancer.[22,23] Mutated N-ras has been found at high rates in melanomas in approximately 20% of clinical samples.[24] Moreover, leucine substitution for glutamine (Q61L) in exon 2 at codon 61 is the most frequent mutation, Q61R, Q61H mutations and other amino acid change in exon 1 at codon 12 and 13 were also observed.[25] However, mutated H-ras is rarer that is present in some bladder, breast, and throid cancers.[26]

There are several experiments in vivo and in vitro have confirmed that the activation of Ras gene may cause drug resistance of tumor cells[19,27] (Fig. 2). Pao et al.[28] firstly have reported that K-ras gene mutation may cause primary resistance of lung adenocarcinomas to gefitinib or erlotinib through clinical studies in 2005. Rizvi et al.[29] also have verified that the mutation of K-ras gene may lead to primary resistance of lung adenocarcinomas in 2011. Recently, Modest et al.[30] have investigated the impact of different K-ras mutations (isogenic SW48 K-ras G12A, G12C, G12D, G12R, G12S, G12V, and G13D) on treatment with sunitinib in SW48 colorectal cancer cells. They have found that all subtypes of K-ras mutations demonstrated a certain degree of resistance to sunitinib treatment. Among them, K-ras G13D mutant in SW48 cells represented the K-ras subspecies with the lowest grade of resistance. The experiment of Hoang et al.[31] have confirmed that N-Ras participated in enhance of myeloma cells adhesion to fibronectin and enhance chemoresistance of myeloma cells. Recently, Zhang et al.[32] have found H-Ras has an important role in epithelial ovarian cancer progression and cisplatin resistance by H-Ras/Raf-1/ERK pathway in 2014.

Mechanisms of Ras related to cancer chemotherapy have been identified by investigating several downstream targets of the Ras/ERK pathway and K-Ras/B-Raf/PIK3CA pathway, including