Mol Cell Biochem (2014) 385:311–318
DOI 10.1007/s11010-013-1841-1

Cell-penetrating fusion peptides OD1 and OD2 interact with Bcr–Abl and influence the growth and apoptosis of K562 cells

Hai-xia Wang · Heng Xiao · Liang Zhong · Kun Tao · Ya-juan Li · Shi-feng Huang · Jian-ping Wen · Wen-li Feng

Received: 28 May 2013 / Accepted: 26 September 2013 / Published online: 5 October 2013

Abstract The Bcr–Abl oncoprotein is the cause of chronic myelogenous leukemia (CML). Crystal structure analysis suggests that $Bcr_{30–63}$ is the core of the Bcr–Abl oligomerization interface for aberrant kinase activity; however, the precise role of other residues of $Bcr_{1–72}$ excluding $Bcr_{30–63}$ have not been evaluated. In this study, $Bcr_{30–63}$ was named OD2 and other residues of $Bcr_{1–72}$ were named OD1. Cytoplasmic transduction peptide (CTP) was used to carry molecules into cytoplasm. CTP-OD1 and CTP-OD2 fusion peptides were expressed from a cold-inducible expression system. Our results demonstrated that both fusion peptides could localize into the cytoplasm, specifically interact with the Bcr–Abl protein and further inhibit growth, induce apoptosis, and decrease the phosphorylation of Bcr–Abl in K562 cell lines. However, the viability of THP-1, a Bcr–Abl negative cell line, was unaffected. These results suggested that CTP-OD1 and CTP-OD2 may be an attractive therapeutic option to inhibit the activation of Bcr–Abl kinase in CML.

Keywords Bcr–Abl oncoprotein · Oligomerization interface · Protein–protein interaction · CTP

Introduction

Chronic myelogenous leukemia (CML) is characterized by the formation of the *bcr–abl* oncogene, the result of a (9; 22) chromosome translocation of *abl* from chromosome 9 into *bcr* on chromosome 22 [1]. The deregulated and constitutively activated Bcr–Abl tyrosine kinase reduces susceptibility to various pro-apoptotic stimuli, including growth factor deprivation [2]. The small-molecule kinase inhibitors, imatinib and nilotinib, are an effective therapy for many patients [3]; however, drug resistance can develop quickly, and they are only moderately effective in the later stages of the disease [4]. Therefore, alternative treatments will represent a significant advance.

Studies indicate that the tetramerization of Bcr–Abl in the Bcr oligomerization domain (OD; residues 1–72 or $Bcr_{1–72}$) is essential for the abnormal activation of Abl tyrosine kinase [5, 6]. It has been reported that $Bcr_{1–72}$ is critical for the formation of the Bcr oligomerization interface, which mainly consists of two α-helical coiled-coil motifs, called α1 and α2 [7]. The peptide corresponding to $Bcr_{1–72}$ or the α2 helix residues can interfere with Bcr–Abl tetramerization and counteract the kinase activity and transformation potential of Bcr–Abl, which is accompanied by an increased sensitivity for imatinib [8–10]. Moreover,

Electronic supplementary material The online version of this article (doi:10.1007/s11010-013-1841-1) contains supplementary material, which is available to authorized users.

H. Wang · H. Xiao · L. Zhong · Y. Li · W. Feng (✉)
Key Laboratory of Laboratory Medical Diagnostics Designated by the Ministry of Education, Department of Clinical Hematology, Chongqing Medical University, Chongqing 400016, People's Republic of China
e-mail: fengwlcqmu@sina.com

K. Tao
Department of Immunology, Molecular Medicine and Cancer Research, Chongqing Medical University, Chongqing 400016, People's Republic of China

S. Huang
Department of Hematology, The First Affiliated Hospital, Chongqing Medical University, Chongqing 400016, People's Republic of China

J. Wen
Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada