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Hydroxychavicol sensitizes imatinib-resistant chronic myelogenous leukemia cells to TRAIL-induced apoptosis by ROS-mediated IAP downregulation

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The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of cytokine superfamily, induces apoptosis in a number of tumor cells through the activation of extrinsic apoptotic pathway but shows little or no cytotoxicity toward normal cells. However some tumor cells are inherently resistant to TRAIL-mediated apoptosis, which needs to be addressed to establish TRAIL as a potential chemotherapeutic drug. In this study, our aim was to manipulate TRAIL-apoptosis pathway by hydroxychavicol (HCH), a polyphenol from Piper betel leaf, for the induction of apoptosis in TRAIL resistant chronic myeloid leukemia cell. When imatinib-resistant K562 cells were treated with HCH, it made these K562 cells sensitive to TRAIL. It was observed that HCH downregulated antiapoptotic proteins XIAP and FLIP, whereas the expression of TRAIL receptors, DR4 and DR5, remains unchanged. Moreover, we observed that reactive oxygen species or ROS played a crucial role in the downregulation of FLIP and XIAP because ROS scavenger significantly reversed the decrease of XIAP, and FLIP. Ubiquitin-proteasome pathway was observed to play a crucial role in the downregulation of XIAP and FLIP, as proteasomal inhibitor MG132 significantly reversed the downregulation of XIAP and FLIP. In conclusion, this study demonstrates the combinatorial treatment of TRAIL and HCH as promising alternative therapeutic approach to treat the imatinib-resistant leukemia, which are also resistant to TRAIL. ***Anti-Cancer Drugs*** **00:000–000 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of TNF superfamily and is a potent inducer of apoptosis. There are five receptors of TRAIL. Among them death receptor 4 (DR4 or TRAIL-R1) and death receptor 5 (DR5 or TRAIL-R2) are involved in the induction of apoptosis via their cytoplasmic death domains after binding to TRAIL [1]. TRAIL leads to oligomerization of intracellular death domains of the DR4 or DR5 and recruits the adaptor molecule Fas-associated death domain (FADD). FADD recruitment leads to activation of caspase-8 and downstream effector caspases including caspase-3 [2]. Although DcR1 and DcR2, the other two receptors of TRAIL, can bind TRAIL, the lack of the intracellular death domain fails to induce apoptosis. Thus, TRAIL mediates cytotoxicity in a variety of tumor cell types. However TRAIL has very little cytotoxic effects on normal cells and thus has the potential of a promising anticancer drugs [3] for various cancers.

Chronic myeloid leukemia (CML) is a disease of hematopoitic origin which results from reciprocal translocation of t(9;22)(q34;q11) and formation of constitutively active Philadelphia Chromosome [4]. Imatinib mesylate (Gleevec, previously known as STI571 and CGP 57148), a potent inhibitor of the tyrosine kinases ABL, has been remarkably successful in the treatment of patients with CML. It shows selective apoptosis of BCR–ABL$^+$ cells [5]. However, generation of resistance against imatinib has emerged as a major drawback in the treatment of CML. Although successive generations of tyrosine kinase inhibitors like nilotinib and dasatinib have been successful for CML therapy, an alternative approach other than TKI is in demand.

Inhibition of apoptosis is an important mean by which cancer cell and neuronal cell increase their survival. Inhibitor of apoptosis (IAP) proteins comprise a family of antiapoptotic proteins that assist in this prosurvival signaling pathways by interfering with the activation of caspases and thus inhibiting apoptosis [6]. There are eight IAP proteins in humans: neuronal apoptosis inhibitory protein (also known as BIRC1), cellular IAP1 (c-IAP1, also known as BIRC2), cellular IAP2 (c-IAP2, also known as BIRC3), X-chromosome-linked IAP (XIAP,

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Original article

H_2O_2 mediated FLIP and XIAP down-regulation involves increased ITCH expression and ERK-Akt crosstalk in imatinib resistant Chronic Myeloid Leukemia cell line K562

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ABSTRACT

Regulation of anti-apoptotic protein FLICE-like inhibitory protein (FLIP) and X-linked inhibitor of apoptosis protein (XIAP) remains a crucial step in the cell fate determination and thus targeting these anti-apoptotic proteins could be a viable strategy for the treatment of cancer. However the regulation of FLIP and XIAP is not very well established till date. Here we have shown that ROS decreased XIAP and FLIP by activation of ubiquitin-proteasomal pathway in imatinib resistant K562 cells. Activation of the components of MAPK pathway, ERK and JNK, played a crucial role in XIAP and FLIP degradation because ectopic expression or knock down of ERK and JNK changed the pattern of ROS mediated down-regulation of these two proteins. We have also found that JNK and ERK differentially regulates FLIP and XIAP, respectively. Moreover, our data suggests that activated ERK decreased Akt phosphorylation and thus its binding to and stabilization of XIAP. On the other hand, JNK activation increased E3 ubiquitin ligase ITCH expression and its binding to FLIP which leads to its degradation. Thus, we have, for the first time elucidated that ROS mediated ERK-Akt crosstalk regulates XIAP. We have also shown for the first time that ROS regulates ITCH expression which controls FLIP degradation.

1. Introduction

Apoptosis, a genetically programmed cellular mechanism(s) to commit suicide, is critically important for the survival of multicellular organisms by elimination of damaged or infected cells that may interfere with normal function [1–3]. However, when these normal processes of cell death goes uncontrolled, it leads to some of the leading causes of death and disability worldwide, including neurodegenerative, cardiovascular, autoimmune and infectious disease [4,5]. Despite the undeniable role of apoptosis in normal homeostasis, our understanding of cell death processes and their regulation is still nascent. Recent findings demonstrate the dynamic nature of cell death regulation during development, ageing and disease.

Cancer is one of the leading diseases worldwide that is characterized by uncontrolled proliferation of cells. De-regulation of apoptosis is one of the hallmarks of cancer. Regulation of apoptosis, both Intrinsic and Extrinsic, occurs at various levels. FLICE like inhibitory protein (FLIP) and X-linked Inhibitor of Apoptosis Protein (XIAP) are two of the well-established regulators of apoptosis.

XIAP belongs to the Inhibitor of Apoptosis Protein (IAP) family which is characterized by the presence of a 1–3 baculovirus IAP repeat (BIR) domains of 70–80 amino acids encoding a C2HC-type zinc-finger motif that tetrahedrally chelates one zinc atom, and forms a globular structure consisting of four or five α-helices and a variable number of antiparallel β-pleated sheets [6,7]. In addition to BIR domains, XIAPs contain a carboxyterminal RING (really interesting new gene) zinc-finger domain which has been shown to possess E3 ubiquitin ligase activity, directly regulating auto- or *trans*-ubiquitination and protein degradation [8–11]. XIAP prevents Caspase 3 and Caspase 9 cleavage and thus inhibit both extrinsic and intrinsic apoptosis.

FLICE-like inhibitory protein (FLIP), a pro-caspase 8 mimetic [12–15], contains two DEDs like the initiator caspase. However, due to the lack of the catalytic cysteine residue that is present in pro-caspase 8, FLIP is considered anti-apoptotic protein due to the absence of caspase like activity. FLIP also blocks the intrinsic apoptotic pathway by competing with caspase-8 to prevent BID activation. FLIP is upregulated in many cancers (e.g., pancreatic [16], breast [17], prostatic [18], and colorectal [19] cancer, glioblastoma [20], Burkitt and non-Hodgkin lymphoma [21,22]). c-FLIP upregulation promotes defects of DR-mediated apoptosis and resistance to several anti-cancer drugs [23].

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