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Quinacrine induces apoptosis in human leukemia K562 cells via p38 MAPK-elicited BCL2 down-regulation and suppression of ERK/c-Jun-mediated BCL2L1 expression

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ABSTRACT

Although previous studies have revealed the anti-cancer activity of quinacrine, its effect on leukemia is not clearly resolved. We sought to explore the cytotoxic effect and mechanism of quinacrine action in human leukemia K562 cells. Quinacrine induced K562 cell apoptosis accompanied with ROS generation, mitochondrial depolarization, and down-regulation of BCL2L1 and BCL2. Upon exposure to quinacrine, ROS-mediated p38 MAPK activation and ERK inactivation were observed in K562 cells. Quinacrine-induced cell death and mitochondrial depolarization were suppressed by the p38MAPK inhibitor SB202190 and constitutively active MEK1 over-expression. Activation of p38 MAPK was shown to promote BCL2 degradation. Further, ERK inactivation suppressed c-Jun-mediated transcriptional expression of BCL2L1. Over-expression of BCL2L1 and BCL2 attenuated quinacrine-evoked mitochondrial depolarization and rescued the viability of quinacrine-treated cells. Taken together, our data indicate that quinacrine-induced K562 cell apoptosis is mediated through mitochondrial alterations triggered by p38 MAPK-mediated BCL2 down-regulation and suppression of ERK/c-Jun-mediated BCL2L1 expression.

Introduction

Quinacrine (6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine) (Fig. 1A) is a 9-aminoacridine derivative clinically used as an antimalarial drug, which has also been shown to possess anti-cancer activity (Ehsanian et al., 2011; Preet et al., 2012). Several studies suggest that the anti-cancer activity of quinacrine is not closely related to its DNA-binding ability, but is mediated through the suppression of survival signaling in cancer cells (Ehsanian et al., 2011). Simultaneous activation of p53 and suppression of the PI3K/AKT/mTOR and NF-κB pathways plays a key role in the anti-cancer activity of quinacrine (Wang et al., 2005; Gurova et al., 2005; Guo et al., 2009; Ehsanian et al., 2011; Gallant et al., 2011). Moreover, quinacrine-induced NFκB inactivation promotes TRAIL, oxaliplatin and 5-fluorouracil cytotoxicity in human colon carcinoma cell lines via growth inhibition (Jani et al., 2010; Gallant et al., 2011). Consistently, quinacrine is a chemosensitizer that can enhance chemotherapeutic drug-induced apoptosis of cancer cells (Friedman et al., 2007; Wang et al., 2010, 2011; Wu et al., 2012). Noticeably, quinacrine-induced chemosensitization is primarily attributed to altered BCL2 family protein expression (Jani et al., 2010; Wang et al., 2010, 2011; Gallant et al., 2011). In addition to suppression of NFκB-mediated MCL1 expression (Jani et al., 2010; Gallant et al., 2011; Wang et al., 2011), quinacrine down-regulated BCL2/BCL2L1 (also known as Bcl-xL) expression and/or up-regulated BAX, leading to cancer cell death (Wang et al., 2010; Preet et al., 2012). However, Orzaez et al. (2009) found that quinacrine may bind to the BH3 domain of BCL2L1, thereby inhibiting the anti-apoptotic function of BCL2L1. Collectively, suppression of anti-apoptotic protein expression, including BCL2, BCL2L1 and MCL1, or up-regulation of pro-apoptotic proteins, such as BAX, facilitates the anti-cancer activity of quinacrine.

There are two types of leukemia; lymphocytic leukemia, which originates from lymphocytes in the bone marrow, and myelogenous leukemia, which primarily originates from granulocytes or monocytes (Abramson and Melton, 2000). The primary cause of treatment failure in acute and chronic myeloid leukemia is the emergence of multi-drug resistance, due to defects in the apoptotic pathway (Testa and Riccioni, 2007; Del Poeta et al., 2008; Rumjanek et al., 2013). Dysregulation of BCL2 protein expression is though to promote chronic and acute myeloid leukemia (Tzifi et al., 2012). Thus, drugs that overcome defects

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