Abstract

Hydroquinone-Derivatives Induce Cell Death in Chronic Myelogenous Leukemia †

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Abstract: Hydroquinone (HQ) is a phenolic metabolite of benzene, which is used as a skin whitener. Insects synthesize this natural compound as a deterrent and mushrooms as a toxin. Pro-apoptotic effects of HQ were previously documented on various cancer cell types. Here we investigated the cell-death inducing mechanisms of this compound in chronic myeloid leukemia cell models.

Keywords: chronic myeloid leukemia; apoptosis; necroptosis; autophagy

Introduction and Results

Chronic myeloid leukemia (CML) results from a t (9;22) (q34; q11) translocation, also called Philadelphia chromosome (Ph). This reciprocal translocation causes a constitutively-activated tyrosine kinase BCR-ABL fusion gene [1]. Imatinib (STI571, Gleevec) is targeting the oncogenic BCR-ABL protein to treat patients with CML [2]. However, this drug triggers resistance in CML patients and does not entirely eradicate BCR-ABL-expressing cells [3].

Necroptosis is known as type III programmed cell death that has been explained in many pathological contexts [4]. Necroptosis is regulated by ligand binding to receptors of the tumor necrosis factor (TNF) family [5]. The main molecular signaling pathway involves a multi-protein complex called necosome, including the receptor-interacting kinases RIP-1 and -3 and the mixed lineage kinase-like domain (MLKL) executioner protein [6]. Necrostatin -1 (Nec-1) is known as a specific inhibitor of necroptosis which targets to RIP1/3 necroosome complex activation [7]. Recently, induction of necroptosis has been described as an alternative therapeutic approach to trigger programmed cell death in apoptosis-resistant CML. For this reason, novel drugs are still required to improve CML therapies.

Here we investigated various tetrahydrobenzimidazole derivatives and determined their cytotoxic potential against hematopoietic cancer cell lines including Jurkat, Raji, K562 and U937 compared to peripheral blood mononuclear cells (PBMCs) from healthy donors. Some of them, especially TMQ0153 exhibited significant cytotoxicity against cancer cells [8]. Our studies then aimed to clarify the molecular mechanisms by which TMQ0153 concentration-dependently triggered caspase-dependent apoptosis at lower concentrations whereas autophagy-independent necroptosis was activated at higher concentrations in human K562 CML cells.
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References


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