proceedings

MDPI

Proceedings

Hydroquinone-Derivatives Induce Cell Death in Chronic Myelogenous Leukemia †

Sungmi Song [1], Claudia Cerella [2], Barbora Orlikova-Boyer [2], Ali Al-Mourabit [3] and Marc Diederich [1,*]

[1] College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 151-742, Korea; sungmisong35@gmail.com

[2] Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxemburg, Luxemburg; claudia.cerella@lbmcc.lu (C.C.); barbora.orlikova@lbmcc.lu (B.O.-B.)

[3] ICSN, CNRS UPR 2301, Université. Paris-Sud, Av. de la Terrasse, 91198 Gif-sur-Yvette, France; ali.almourabit@cnrs.fr

* Correspondence: marcdiederich@snu.ac.kr

† Presented at Natural Products and the Hallmarks of Chronic Diseases—COST Action 16112, Luxemburg, 25–27 March 2019.

Published: 19 April 2019

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 necrosome, 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 necrosome 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 TMQ153 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.

Author Contributions: Conceptualization, S.S., C.C., B.O.B., A.A.-M., M.D.; Writing—original draft preparation, S.S..; Writing—review and editing, S.S., M.D.

Funding: SS is supported by a grant from Brain Korea (BK) 21 Plus program, Korea. This research is supported by National Research Foundation (NRF) [grant number 019R1A2C1009231] and by a grant from the MEST of Korea for Tumor Microenvironment Global Core Research Center (GCRC) [grant number 2011-0030001]. Support from Brain Korea (BK21) PLUS program and Creative-Pioneering Researchers Program at Seoul National University [Funding number: 370C-20160062] are acknowledged. CC and BOB were supported by a grant from Télévie Luxembourg. This research is also supported by the "Recherche Cancer et Sang" foundation, "Recherches Scientifiques Luxembourg" association, "Een Häerz fir kriibskrank Kanner" association, Action LIONS "Vaincre le Cancer" association and Télévie Luxembourg. Financial support from Centre National de la Recherche Scientifique (CNRS) is also gratefully acknowledged.

Acknowledgments: This article/publication is based upon work from COST Action NutRedOx-CA16112 supported by COST (European Cooperation in Science and Technology).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ren, R. Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. *Nat. Rev. Cancer* **2005**, *5*, 172–183.
2. Baran, Y.; Salas, A.; Senkal, C.E.; Gunduz, U.; Bielawski, J.; Obeid, L.M.; Ogretmen, B. Alterations of ceramide/sphingosine 1-phosphate rheostat involved in the regulation of resistance to imatinib-induced apoptosis in K562 human chronic myeloid leukemia cells. *J. Biol. Chem.* **2007**, *282*, 10922–10934.
3. Shah, N.P.; Tran, C.; Lee, F.Y.; Chen, P.; Norris, D.; Sawyers, C.L. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* **2004**, *305*, 399–401.
4. Vanden Berghe, T.; Linkermann, A.; Jouan-Lanhouet, S.; Walczak, H.; Vandenabeele, P. Regulated necrosis: The expanding network of non-apoptotic cell death pathways. *Nat. Rev. Mol. Cell. Biol.* **2014**, *15*, 135–147.
5. Holler, N.; Zaru, R.; Micheau, O.; Thome, M.; Attinger, A.; Valitutti, S.; Bodmer, J.L.; Schneider, P.; Seed, B.; Tschopp, J. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. *Nat. Immunol.* **2000**, *1*, 489–495.
6. Florean, C.; Song, S.; Dicato, M.; Diederich, M. Redox biology of regulated cell death in cancer: A focus on necroptosis and ferroptosis. *Free Radic. Biol. Med.* **2019,** *134*, 177–189.
7. Degterev, A.; Hitomi, J.; Germscheid, M.; Ch'en, I.L.; Korkina, O.; Teng, X.; Abbott, D.; Cuny, G.D.; Yuan, C.; Wagner, G.; et al. Identification of RIP1 kinase as a specific cellular target of necrostatins. *Nat. Chem. Biol.* **2008**, *4*, 313–321.
8. Tran, M.Q.; Nguyen, T.B.; Sawadogo, W.R.; Ermolenko, L.; Song, S.M.; Retailleau, P.; Diederich, M.; Al-Mourabit, A. Unaromatized tetrahydrobenzimidazole synthesis from p-Benzoquinone and N-Arylamidines and their cytotoxic potential. *Eur. J. Org. Chem.* **2018**, *2018*, 5878–5884.