Gang-Min Hur, J Clin Exp Pharmacol 2024, Volume 14

Rubianol B isolated from Rubia philippinesis induces RIP1/RIPK3-dependentg necroptosis in human colorectal cancer cells

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Receptor interacting protein 1 (RIP1) has emerged as a key molecular switch in inducing necroptosis, an alternative programmed cell death mode that can overcome apoptosis resistance in cancer therapy. Therefore, discovering a substance that modulates the cytotoxic potential of RIP1 may provide an effective strategy to bypass apoptosis resistance in cancer chemotherapeutics. In this study, it was found that rubianol-B, a triterpenoids purified from Rubia phillippinesis, promoted RIP1-dependent apoptosis via caspase-8 activation in multiple types of human cancer cells. Interestingly, pharmacological or genetic inhibition of caspase-8 was sufficient to switch the cell death mode from apoptosis to necroptosis following rubianol-B treatment, through necrosome formation in RIPK3-expressing human colorectal cancer (CRC) cells, accompanied by the upregulation of cytotoxic potential of RIP1 phosphorylation. Conversely, rubianol-B-induced cell death was almost completely abrogated by RIPK deficiency. The enhanced RIP1 phosphorylation and necroptosis triggered by rubianol-B treatment occurred independently of tumor necrosis factor receptor signaling, and was mediated by the production of reactive oxygen species via NADPH oxidase 1 in CRC cells. Thus, it is proposed that rubianol-B is a novel anticancer agent that enhances the cytotoxic potential of RIP1, warranting further development of rubianol-B as a necroptosis-targeting compound in apoptosis-resistant CRC.

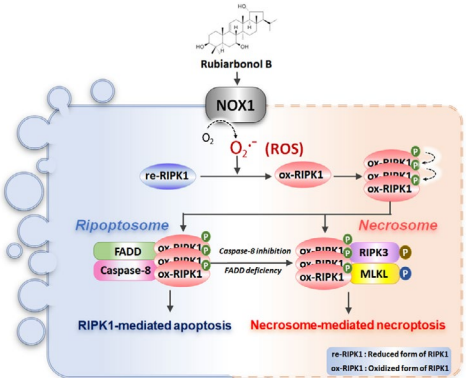

Figure 1: Schematic of the PIP1-mediated cell death induced by rubianol-B. Rubianol-B induces ROS production by targeting NOX-1, enhancing the cytotoxic potential of RIP1. This allows RIP1 to undergo auto-phosphorylation processing and activate iRIP1-mediated apoptosis via ripoptosome formation. In the absence of caspase-8 or FADD, oxidixed RIP1 can associate with RIPK3/MLKL to facilitate necroptosis

Biography

Gang-Min Hur currently holds the position of Chair Professor in the Department of Pharmacology at the College of Medicine, Chungnam National University. Additionally, he serves as a project manager at the National Research Foundation (NRF) of Korea. He completed his post-doctoral research at the National Cancer Institute, National Institute of Health, USA. He earned his PhD and Bachelor of Medicine degrees from Chungnam National University, Korea and has been recognized with several academic and scientific awards. His research focuses on cell death signaling pathways in cancer, the role of reactive oxygen species and oxidative stress in these pathways (including apoptotic and necroptotic cell death), and the investigation of natural products as potential anti-cancer agents.

Received: October 01, 2024; **Accepted**: October 04, 2024; **Published**: December 30, 2024