Indirubin-3′-Monoxime-Induced Paraptosis by Transmitting Ca2+ From Endoplasmic Reticulum to Mitochondria

Kavinda M. H. D.[1,2], Jayasooriya R. G. P. T.[3], Choi Y. H.[4], Kim G. Y.[1,2]✉

Abstract

Indirubin-3′-monoxime (I3M) induces cell death in many cancer cells; however, whether I3M regulates paraptosis is unclear. The present study aimed to investigate I3M-induced paraptosis. We found that I3M induced small vacuole formation in MDA-MB-231 breast cancer cells and transient knockdown of eIF2α and CHOP significantly downregulated vacuolation in the ER and mitochondria, as well as cell death in response to I3M, indicating that I3M-meditaed paraptosis was upregulated by ER stress. Moreover, I3M accumulated ubiquitinated proteins via proteasome dysfunction, which stimulated ER stress mediated Ca^{2+} release. A Ca^{2+} chelator significantly downregulated vacuolation in the ER and mitochondria as well as cell death, suggesting that Ca^{2+} was a key regulator in I3M-induced paraptosis. Our results also revealed that Ca^{2+} finally transited in mitochondria through mitochondrial Ca^{2+} uniporter (MCU), causing I3M-mediated paraptosis; however, the paraptosis was completely inhibited by, ruthenium red, an MCU inhibitor. I3M induced proteasomal dysfunction-mediated ER stress and subsequently promoted Ca^{2+} release, which was accumulated in the mitochondria via MCU, thus causing paraptosis in MDA-MB-231 breast cancer cells.

Keywords: *Indirubin-3-monoxime, paraptosis, proteasomal dysfunction, endoplasmic reticulum stress, reactive oxygen species*

[1] Department of Marine Life Science, Jeju National University, Jeju 63243, Republic of Korea
[2] Research Institute for Basic Sciences, jeju National University, jeju 63243, Republic of Korea
[3] Department of Bioprocessing Technology, Faculty of Technology, Rajarata University of Sri Lanka, Mihintale 50300, Sri Lanka
[4] Department of Biochemistry, College of Oriental Medicine, Dong-Eui University, Busan 47227, Republic of Korea
✉Correspondence: immunkim@jejunu.ac.kr