Ruey-Hwa Chen, Biochem Anal Biochem 2017, Volume 7
DOI: 10.4172/2161-1009-C1-016

12th World Congress on
STRUCTURAL BIOLOGY
May 14-15, 2018 Osaka, Japan

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Regulation of BIK ubiquitination determines life-death fate of cellular stress responses and anti-tumor activity

The BH3-only pro-apoptotic protein BIK is regulated by ubiquitin-proteasome system. However, the underlying mechanism of this regulation and its physiological functions remain elusive. Here, we identify a BIK ubiquitination/degradation mechanism mediated by ubiquitin ligase Cul5ASB11. Under ER stress, ASB11 is transcriptionally activated by IRE1/XBP1 axis of unfolded protein responses, which results in an enhancement of BIK ubiquitination and proteolysis. Conversely, genotoxic agents act through p53 to down-regulate IRE1 and ASB11, thereby stabilizing BIK. These opposite regulations of ASB11-medaited BIK ubiquitination participate in part to the cell adaptation to ER stress and DNA damage-induced apoptosis. Finally, IRE1 inhibitors stabilize the active form of BIK and increase its anti-tumor efficacy in triple negative breast cancers. Together, our study identifies a BIK ubiquitin ligase, uncovers the opposite regulations of this BIK ubiquitination by ER stress and DNA damage, and exploits the targeting of BIK ubiquitination pathway combined with active BIK for cancer therapy.

Biography

Ruey-Hwa Chen has received BS and MS degrees from National Taiwan University and PhD degree from Michigan State University. In 2006, she relocated to Institute of Biological Chemistry, Academia Sinica to be a Research Fellow and promoted to Distinguished Research Fellow in 2012. She was also an Associate Professor and Professor at National Taiwan University. She has served as Deputy Director of Institute of Biological Chemistry in 2011-2013. She has received several awards, including Outstanding Scholar Research Grant, National Science Council; Merit Research Award, National Science Council; Outstanding Award, TienTe Lee Biomedical Foundation; TBF Chair in Biotechnology; the 59th Academic Award, The Ministry of Education; Merit MOST Research Fellow Award and Taiwan Outstanding Women in Science, Wu Chien-Shiung Education Foundation. Her current research focuses on protein ubiquitination in tumorigenesis and tumor progression and protein ubiquitination in autophagy.

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