Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO

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"Mediators of Cell Death Regulate Cancer and Inflammation"

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11:00 a.m. - 12:00 p.m.
James Friesen | Cecil Yip Red Seminar Room
Donnelly Centre

Abstract:

Cell death regulation is vital for maintenance of homeostasis and proper development of multicellular organisms. Inhibitor of apoptosis (IAP) proteins can inhibit apoptotic and necroptotic cell death with direct implications for the regulation of cancer and inflammation. Due to their prominent ability to control cell death and elevated expression in a variety of cancer cell types, IAP proteins are attractive targets for the development of novel anti-cancer treatments. IAP proteins are also RING domain-containing ubiquitin ligases. Ubiquitination is a versatile post-translational protein modification, critical for cell survival and differentiation, as well as for innate and adaptive immunity, and its deregulation often results in development of human diseases such as cancer. Using antibodies specific for ubiquitin conjugation to the substrate proteins and for distinct ubiquitin chain linkages in combination with mass spectrometry we have investigated the spatial and temporal pattern of endogenous ubiquitination during proliferative, apoptotic and necrotic signaling. While ubiquitination of mitochondrial mediators of cell death coincides with general cellular demise, ubiquitination of RIP1 in untreated cancer cells correlates exclusively with sensitivity to IAP antagonists. Targeting ubiquitin ligases c-IAP1/2 can efficiently block TNF family stimulated activation of canonical NF-kB signaling. Similarly, antagonism of a related ubiquitin ligase XIAP effectively inhibits NOD2 mediated immune signaling and NF-kB activation. Neutralizing XIAP is especially clinically relevant in NOD2-dependent immune disorders such as Blau syndrome and Crohn's disease. Collectively, these studies define major events regulating cell death and NF-kB activation, and enhance our understanding of signaling pathways in the context of anti-tumor and anti-inflammatory treatments.

Host: Igor Stagljar