Editorial

Necroptosis: Changing Trends in Cell Biology and Cancer

Shankargouda Patil[1], Roopa S Rao[2], Barnali Majumdar[3]

Contributors:

[1]Associate Professor, Department of Oral Pathology & Microbiology, Faculty of Dental Sciences, M.S. Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India; [2]Professor and Head, Department of Oral Pathology & Microbiology, Faculty of Dental Sciences, M.S. Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India; [3]Postgraduate Student, Department of Oral Pathology & Microbiology, Faculty of Dental Sciences, M.S. Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India. Email: sbpatil1612@gmail.com

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In biology, cell death is a natural process, wherein the worn-out cells with declining function, are eventually removed from the organism. The three well-known mechanisms of cell demise are apoptosis, autophagy, and necrosis. The latest addition to this list is, still another pathway, recognized as "necroptosis."[1] In contrast to the traditional believe, that apoptosis is the only regulated or programmed cellular mechanism of cell death, established evidence suggest that necrosis can also be driven by means of a controlled succession of molecular events.[2] Such controlled necrosis is termed as "programmed necrosis" or "necroptosis."[3]

Now the query arises, how necroptosis is different from necrosis, or are all necrosis regulated? With the present evidence and data, it is essential to comprehend that regulated or controlled necrosis is a broad term that includes mitochondrial permeability transition, necroptosis, ferroptosis, pyroptosis, Poly(ADP-ribose) polymerase 1-mediated regulated necrosis, nicotinamide adenine dinucleotide phosphate-oxidase-mediated regulated necrosis, etc. However, the uniqueness of each of these pathways are yet to be validated and defined.[4]

The death receptors, which are member of tumor necrosis factor receptor superfamily, are the foremost mediators of cell death pathway. Consequently, when the death receptor is activated in a cell, the possible outcomes are described as follows. The first, if the nuclear factor – kappa B survival or mitogen-activated protein kinase pathway are initiated, the cell survives. The second, if the caspase-8 is activated in the absence of the survival pathways, apoptosis follows. Finally, under certain conditions where the caspases pathway is not triggered, the cell undergoes necroptosis.[5] This pathway involves various molecules, of which the receptor-interacting protein kinase 1 (RIP1) and RIP3 play critical role in the initiation of necrosome formation and signaling. The hypothesis is divided from here onward, i.e., whether necroptosis is mitochondria-dependent or independent. A few research suggests role of mitochondria and reactive oxygen species (ROS) dependent necroptosis while others indicate contradictory results.[1] Nevertheless, concerning the perspective of clinical application, induction of necroptosis receptors in cancer cells can be a prodigious targeted therapy.

Necroptosis is relatively a new concept and hence limited studies have been piloted investigating its role in cancer progression. One of such study showed reduced lung metastasis in a case of osteosarcoma, by induction of necroptosis via RIP1 and RIP3 receptors. The triggering of ROS bursts by means of the above pathway can potentially hamper the survival of cancer cells at distant sites, away from the primary location. Further, findings show that RIP3 activates various metabolic enzymes which regulate ROS production. In another study, it was found that the chronic lymphocytic leukemia cells exhibited failure to undergo necroptosis due to the downregulation of RIP3. Likewise, RIP3 gene variation were identified in non-Hodgkin lymphoma patients.[3] Apart from cancer cells, necroptosis has also been proposed to occur in immune and neuronal systems.[2] Though not evidenced yet, it is postulated to mediate gastrointestinal and skin disorders like atopic dermatitis and inflammatory bowel diseases.[4]

At the present time, there is dearth of information regarding necroptosis and cancer spread. This novel concept arises many queries yet to be answered, such as the mechanism of action involving the mitochondrion; triggering factors of necroptosis pathway; how does the tumor cells bypass necroptosis and escape cell death; its role in regulating cancer metastasis; to mention a few.

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