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Editorial

New insights into programmed necrosis.

When Rudolf Virchow published his mater piece "Cellular Pathology…" in 1858. He wrote that the cell is "the ultimate irreducible form of every living element, and . . . from it emanate all the activities of life both in health and in sickness". He could see far beyond his contemporaries and established cellular basis of disease.

Irreversible cell injury may take the path of either apoptosis or necrosis. Both are forms of cell death and participate in both physiological and pathological processes. Apoptosis drew lot of attention due to its orchestrated events which ultimately culminate in cell death. On the other hand necrosis was ignored for a long time as it's regarded as passive and uncontrolled mode of cell demise associated with membrane damage and leakage of contents, especially HMGB1, attracting inflammation.

Recent discoveries unraveled many types of programmed cell deaths which include, apoptosis, necroptosis, MPT mediated necrosis, pyroptosis and other forms of regulated necrosis.The main difference between apoptosis and programmed necrosis (Necroptosis) is caspase dependency of the former and the later is caspase independent. Altered cells or cells which served their purpose will be driven to death by signals (TNF, FasL or Bacterial products) activating death receptors (Fas, TNFR, TRAIL-R, TWEAKR) or TLR. Such ligation results in formation of intracytoplasmic death domain complex (TRADD or FADD) in which RIPK1 is the main partner. This in turn activated RIPK3 there by facilitating formation of a supramolecular complex (RIPK1-RIPK3 complex). RIPK1-RIPK3 complex binds to caspase-8. If caspase-8 is activated by this process, cell is driven to apoptosis. On the contrary, failure of caspase-8 activation results in necrosome formation and the cell undergoes necroptosis. Activated caspase-8 can negatively regulate RIPK1- RIPK3 mediated necroptosis.

Apoptosis and necroptosis may suppress each other. However, necroptosis may serve as an alternative when apoptosis is inhibited or absent. Unlike apoptosis, there are no biomarkers for in situ detection of necrosis. However, release of intracellular proteins like HMGB1 and CypA are possible biomarkers of necroptosis. Tissue examination by H&E sections (for intact extracellular nuclei and inflammatory cells) supplemented with electron microscopy may help to establish necroptosis. Colocalization of RIPK1 and RIPK3 may also indicate necroptosis.

Clinical implications

Basis of apoptosis in morphogenesis, neurodegenerative disorders, autoimmunity and malignancy are well characterized. However, role of necroptosis and related programmed necroses in disease are yet to be completely unravelled. The discovery of necroptosis and a druggable target that mediates it i.e. RIPK1, elicited great interest in studying the role of necroptosis in human diseases.The following are some of the examples.

Crohn's disease and Pancreatitis: In experimental animals, deletion of FADD or Caspase-8 gene in enterocytes resulted in loss of Paneth cells and goblet cells by necroptosis, making them susceptible for colitis. The patients,suffering from Crohn's disease / Pancreatitis have increased levels of RIPK3 in Paneth cells / pancreatic acinar cells suggest the possibility of necroptosis in the pathogenesis of these diseases.

Ischemic reperfusion injury: In experimental animals administration of Necrostatin-1 (Nec-1), inhibitor of RIPK1, mitigated the ischemic reperfusion injury in brain, kidney and myocardium. Nec-1 markedly reduced the size of infarction, cell damage and neutrophilic infiltration. It is also noted that Nec-1, offered protection when it is given both prior to occlusion and post occlusion of vessels.

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Neurodegenerative diseases: There is progressive loss of structure and function of neurons. The exact cause in human is not known. Excitotoxicity is implicated in these diseases. Neuronal cell death is the last step in these diseases, hence may be amenable medical intervention. Nec-1 found to be protective of cells against excitotoxicity in rat cortical and mouse hippocampal cell cultures, suggesting the possible role of RIPK1.

Active research is going on in targeting necroptosis. Discovered necrostatins are very useful in targeting and understanding RIPK1 mediated processes in vivo.

Definition of 'Necrosis' – The sum of morphological changes that are brought about by progressive degradative action of enzymes on a lethally injured cell in living tissue – which is mainly morphological may change in the future to include molecular inscriptions. Hence, necroptosis denote, not just any form of necrosis, but, RIPK3 dependent cell death.

And we may have drugs in the near future, which may help to increase the myocardial salvage in ischemic reperfusion injury, prevent photoreceptor loss in retinitis pigmetosa and lessen inflammation in pancreatitis.

CypA – Cyclophilin A
HMGB1 – High mobility group box 1 protein
RIPK – Receptor interacting protein kinase
TNFR – Tumor necrosis factor receptor
TRADD – TNF receptor associated death domain
TWEAK -TNF-related weak inducer of apoptosis
TRAIL - TNF-related apoptosis-inducing ligand.

References

1. Linkermann A and Green DR. Necroptosis. N Engl J Med 2014; 370:455-465.

2. Zhou W and Yuan J. Necroptosis in health and diseases. Seminars in Cell & Developmental Biology 2014; 35:14-23.

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