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EDITORIAL

Necrosis, Apoptosis, Necroptosis, Pyroptosis: It Matters How Acinar Cells Die During Pancreatitis

Acute pancreatitis is an unpredictable disease. Most patients develop edema of the pancreas and quickly recover whatever the therapy (or lack thereof), but a minority develop severe complications with significant morbidity and mortality. When the disease is studied in experimental animal models,[1] to distinguish between the 2 forms, it appears that all processes begin in acinar cells[2] but then develop in different directions. The way acinar cells undergo injury and cell death seems to determine the ultimate severity. A highly regulated form of cell death is apoptosis, characterized by the activation of multiple caspases, in response to which acinar cells shrink and disintegrate into neat membrane-confined packages that are taken up by neighboring cells or macrophages. No cellular content is released and no tissue infiltration with inflammatory cells is triggered. Conversely, when acinar cells undergo necrosis, a process previously regarded as completely unregulated, their membranes disintegrate, their proteolytic enzymes and organelles are spilled into the interstitial space[3] where some components act as damage-associated molecular patterns such as free adenosine triphosphate, free DNA, or released histones.[4] Although cell death is never a good thing, a shift from necrosis to apoptosis in response to a pathologic stimulus can render experimental pancreatitis significantly less severe[5] and thus confers a beneficial effect.

Recent studies have shown that necrosis is not necessarily haphazard or spontaneous and can be tightly regulated as well. The best investigated form of regulated necrosis was termed *necroptosis* and involves activation of the receptor-interacting protein kinases (RIP)1/RIP3/mixed lineage kinase domain-like (MLKL) pathway.[6] This is where Louhimo et al[7] started. They investigated 2 reductionist, isolated, acini-based models of pancreatitis, 1 using supramaximal secretagogue stimulation and the other meant to mimic gallstone-induced pancreatitis,[8] asking what form of cell death prevails and which role necroptosis plays. By using genetic deletion of RIP3 and a potent inhibitor of the RIP1/RIP3 pathway, necrostatin,[9] they found not only that necroptosis is the predominant form of acinar cell death in these models (rather than apoptosis), but that the prevention of necroptosis greatly affects the disease severity in vivo—for the better. This makes necroptosis an attractive target for the prevention of pancreatitis or at least for the reduction of its severity. In another set of experiments, Louhimo et al[7] established that a therapy directed against necroptosis can still be effective when pancreatitis is already established, making therapy, rather than prevention, an attractive goal.

A signaling mechanism reported to be involved in necrosis[10] as well as apoptosis is that involving tumor necrosis factor (TNF)α as a ligand. He et al[6] showed that TNFα is also the critical stimulator of the RIP1/RIP3/MLKL pathway and induces necroptosis. In pancreatic acinar cells, injury has previously been attributed to high cytosolic Ca^{++} concentrations[11] released in response to pathologic cholecystokinin or acetylcholine concentrations. What Louhimo et al[7] established is that necroptosis not only depends on TNFα, but also on pathologic Ca^{++} signaling. Louhimo et al[7] correctly concluded that targeting necroptosis is probably the most attractive way of reducing the severity of pancreatitis.

However, according to the data of Louhimo et al,[7] inhibiting necroptosis still leaves 40% of cells dead, with neither necroptosis nor apoptosis being involved in their demise. Could another programmed form of necrosis called pyroptosis account for the rest? Pyroptosis, a highly inflammatory variety of cell death, involves activation of nuclear factor-κB and the expression of components and effectors of the NACHT, LRR and PYD domains-containing protein 3-inflammasome, a cytosolic protein complex consisting of NACHT, LRR and PYD domains-containing protein 3, apoptosis-associated speck-like protein (Apoptosis-associated speck-like protein containing a CARD), and procaspase 1. It proteolytically activates pro-interleukin (IL)1β and pro-IL18, and induces release of active IL1β, IL18, and high-mobility group protein B1 in response to a wide range of stimuli, including extracellular adenosine triphosphate, Nicotinamide-Adenin-Dinucleotide, and saturated free fatty acids. Interestingly, when components of the inflammasome pathway are genetically deleted, the cell death rate in pancreatitis is reduced to the same extent[4,12] as found by Louhimo et al[7] when they prevented necroptosis. These observations must not be mutually exclusive because they were both obtained in highly reductionist models of pancreatitis. We believe they are linked and that preventing one type of regulated cell death induces activation of an alternative pathway of programmed cell death.

What remains to be investigated in our view is whether the defensive mechanism of the pancreas such as autophagy[13] and endosomal/lysosomal degradation[14] can counteract necroptosis effectively. It further needs to be determined whether the necrosis/inflammation/fibrosis sequence that mediates the progression from an isolated episode of acute pancreatitis to chronic pancreatitis[15] with atrophy, exocrine insufficiency, and endocrine insufficiency also lends itself to therapeutic intervention based on preventing necroptosis. Louhimo et al[7] have accomplished a significant step forward in this direction.

MATTHIAS SENDLER, PhD
JULIA MAYERLE, MD
MARKUS M. LERCH, MD, FRCP
Department of Medicine A
University Medicine Greifswald
Ferdinand-Sauerbruch-Strasse
Greifswald, Germany

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Correspondence
Address correspondence to: Markus M. Lerch, MD, FRCP, Department of Medicine A, University Medicine Greifswald, Ferdinand-Sauerbruch-Strasse, 17475 Greifswald, Germany. e-mail: lerch@uni-greifswald.de.

Conflicts of interest
The authors disclose no conflicts.

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