Spying on Cellular Suicide

Short-circuiting a recently discovered form of programmed cell death could lead to new cancer treatment strategies.

The underworld of cell death was once divided into the molecularly programmed suicide of apoptosis and the messier, undirected disruption of necrosis. Necrosis leads to rupture of the plasma membrane, releasing cellular contents into the tissue milieu. As with many morphological descriptions placed under modern molecular scrutiny, however, necrosis turns out to have more nuanced underpinnings than previously suspected. In particular, scientists have discovered a form of programmed necrosis—now called “necroptosis”—that relies on a macromolecular complex containing receptor-interacting protein 3 (RIP3) and is characterized by a rise in intracellular Ca\(^{2+}\), generation of reactive oxygen species, intracellular acidity, and depletion of ATP. Because necroptosis exposes intracellular antigens to immunological attack, it may have evolved as a mechanism to fight viral infections. However, this newly identified form of cell death has also been found to play a role in a wide variety of diseases from neurodegeneration to cancer, and, as such, represents a novel target pathway for therapeutic intervention.

In 2012, Zheng-Gang Liu, Ph.D., Senior Investigator in CCR’s Laboratory of Genitourinary Cancer Pathogenesis, and his colleagues discovered a key protein involved in necroptosis called mixed lineage kinase domain-like protein (MLKL). More recently, in an issue of Nature Cell Biology, Liu’s team tracked the movements of MLKL throughout the cell and discovered that the molecule initiates necroptosis by triggering the influx of Ca\(^{2+}\).

Liu’s team found that MLKL is recruited into the necrosome upon phosphorylation by RIP3. Using imaging to visualize fluorescently labeled MLKL and RIP3 in human embryonic kidney cells further revealed that MLKL escorts RIP3 and the rest of the necrosome to the plasma membrane, a journey found to be critical for necroptosis.

Knowing that Ca\(^{2+}\) influx is a characteristic of necroptosis, the researchers explored whether the MLKL that reaches the plasma membrane plays a role in facilitating the ion’s movement into the cell. Short hairpin RNA-silencing of the gene that encodes MLKL resulted in complete blockage of Ca\(^{2+}\) influx, which was restored when MLKL expression was induced. Next, the team discovered that blockers of non-voltage-sensitive ion channels spared cells from necroptosis. In a knockdown experiment in which a genetically encoded fluorescent Ca\(^{2+}\) indicator tracked the ion’s movement, the team found that TRPM7, a non-voltage-sensitive ion channel previously implicated in necroptosis, was the channel activated by MLKL.

Taken together, this work identifies MLKL as a key component in the initiation of necroptosis, making the molecule a potential novel drug target for inflammation-related cancers. Kick-starting necroptosis can also be an effective weapon against cancer. “It has been reported that many anticancer drugs trigger necroptosis in cancer cells,” said Liu. “Therefore, the induction of necroptosis in cancer is also a promising strategy for potential cancer therapy, particularly in apoptosis-resistant cancer cells.”

To learn more about Dr. Liu’s research, please visit his CCR website at http://ccr.cancer.gov/staff/staff.asp?name=zgliu.