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A controlled explosion – how our cells kill themselves

Every day, millions of cells die in our body. Many kill themselves. Other than generally assumed, cells do not simply burst at the end of their lives but rather a specific protein serves as a breaking point for cell membrane rupture. The team of Prof. Petr Broz at the Department of Immunobiology of the UNIL has now been able to elucidate the mechanism at the atomic level.

Cell death is crucial for all organisms. Damaged cells or cells infected with viruses or bacteria eliminate themselves by starting a built-in "suicide" program, which prevents the development of tumors or the spread of pathogens in the body.

Until recently, it was assumed that cells simply burst and die at the end of their life. However, a team of scientists in the USA recently refuted this hypothesis. Now, an international team led by researchers at the University of Lausanne and the University of Basel have provided new insights into the final step of cell death. In the scientific journal "Nature", they describe how a protein called ninjurin-1 assembles into filaments that work like a zipper and open the cell membrane, thus leading to the disintegration of the cell. The new insights are an important milestone in the understanding of cell death.

Protein acts as a breaking point in the cell membrane

The researchers studied a highly inflammatory form of cell death named pyroptosis. At the final stage of this process, cells activate a protein named gasdermin-D, which perforates the plasma membrane and allows liquids to stream into the cell. "The common understanding so far was that following gasdermin-D activation the cell slowly swells until it finally bursts due to increasing pressure," explains Petr Broz. "We are now overturning this long-held paradigm. Instead of the cell bursting like a balloon, the protein ninjurin-1 provides a breaking point in the cell membrane, causing rupture at this specific site and not just randomly."

How the ninjurin-1 protein induces membrane rupture

Using advanced techniques such as super-resolution and Cryogenic electron microscopy (Cryo-EM), the scientists have been able to elucidate the mechanism by which ninjurin-1 induces membrane rupture at the level of individual atoms. This small protein is embedded in the cell membrane and is normally completely harmless.

"Yet upon receiving the suicide command, the ninjurin-1 proteins cluster within minutes to form long filaments in the cell membrane," explains José Santos, author of the study. "These filaments have a distinct hydrophilic and hydrophobic face, which causes the formation of large lesions and holes in the cell's protective barrier. In this way, the cell membrane is broken piece by piece until the cell disintegrates completely." The cell debris is then removed by phagocytes, the body's own cleaning service.

"It is now evident that the cells do not burst without ninjurin-1. This has an important impact on how cell death is perceived by our immune system, since molecules released from bursting cells cause inflammation within the tissue," adds Prof. Broz "The textbooks chapter on cell death will now have to be expanded with this important discovery."

Therapy to prevent or promote cell death

A deeper understanding of cell death can facilitate the search for novel drug targets. Therapeutic interventions to treat cancer would be conceivable, since some tumor cells simply evade programmed cell death. Inflammation caused by bursting cells is associated with neurodegenerative diseases or in life-threatening conditions such as septic shock; here drugs that interfere with ninjurin-1 activation could be a potential treatment option.