

Under control to the very end -- how our cells kill themselves

Date: May 22, 2023

Source: University of Basel

Summary: Every day, millions of cells die in our body. 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. Researchers have now been able to elucidate the exact mechanism at the atomic level.

FULL STORY

Every day, millions of cells die in our body. 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. Researchers at the University of Basel have now been able to elucidate the exact mechanism at the atomic level. They have published their results in *Nature*.

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 and the spread of pathogens in the body.

Until recently, it was assumed that cells simply burst and die at the end of their life. Now, researchers at the Biozentrum of the University of Basel, the University of Lausanne and the Department of Biosystems Science and Engineering (D-BSSE) at ETH Zurich 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

Various signals, such as bacterial components, trigger the cell death machinery. At the final stage of this process, the cell's protective membrane is compromised by tiny pores which allow ions to stream into the cell. "The common understanding was that the cell then swells until it finally bursts due to increasing osmotic pressure," explains Professor Sebastian Hiller who heads a research group at the Biozentrum, University of Basel. "We are now resolving how the cells really rupture. Instead of bursting like a balloon, the protein ninjurin-1 provides a breaking point in the cell membrane, causing rupture at specific sites."

Using advanced techniques such as highly sensitive microscopes and NMR spectroscopy, the scientists have been able to elucidate the mechanism by which ninjurin-1 induces membrane rupture at the level of individual atoms. Ninjurin-1 is a small protein embedded in the cell membrane.

"Upon receiving the suicide command, two ninjurin-1 proteins initially cluster together and drive a wedge into the membrane," explains Morris Degen, first author of the study and PhD student at the PhD School of the Swiss Nanoscience Institute. "Large lesions and holes are formed by many further proteins attaching to the initial wedge. In this way, the cell membrane is cleaved open piece by piece until the cell disintegrates completely." The cell debris is then removed by the body's own cleaning service.

"It is now evident that the cells do not burst without ninjurin-1. They do swell to a certain extent due to the influx of ions, but membrane rupture is contingent on the function of this protein," adds Hiller. "The textbooks chapter on cell death will be expanded with these beautiful structural insights."

Therapy to prevent or promote cell death

The deeper understanding of cell death will facilitate the search for novel drug targets. Therapeutic interventions to treat cancer are conceivable, since some tumor cells evade programmed cell death. Also, in the case of premature cell death observed in neurodegenerative diseases such as Parkinson's disease or in life-threatening conditions such as septic shock, drugs that interfere in this process are a potential treatment option.

Story Source:

Materials provided by **University of Basel**. Original written by Katrin Bühler. *Note: Content may be edited for style and length.*

Journal Reference:

1. Morris Degen, José Carlos Santos, Kristyna Pluhackova, Gonzalo Cebrero, Saray Ramos, Gytis Jankevicius, Ella Hartenian, Undina Guillerm, Stefania A. Mari, Bastian Kohl, Daniel J. Müller, Paul Schanda, Timm Maier, Camilo Perez, Christian Sieben, Petr Broz, Sebastian Hiller. **Structural basis of NINJ1-mediated plasma membrane rupture in cell death.** *Nature*, 2023; DOI: 10.1038/s41586-023-05991-z

Cite This Page:

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University of Basel. "Under control to the very end -- how our cells kill themselves." ScienceDaily. ScienceDaily, 22 May 2023. <www.sciencedaily.com/releases/2023/05/230522131334.htm>.