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Press Release

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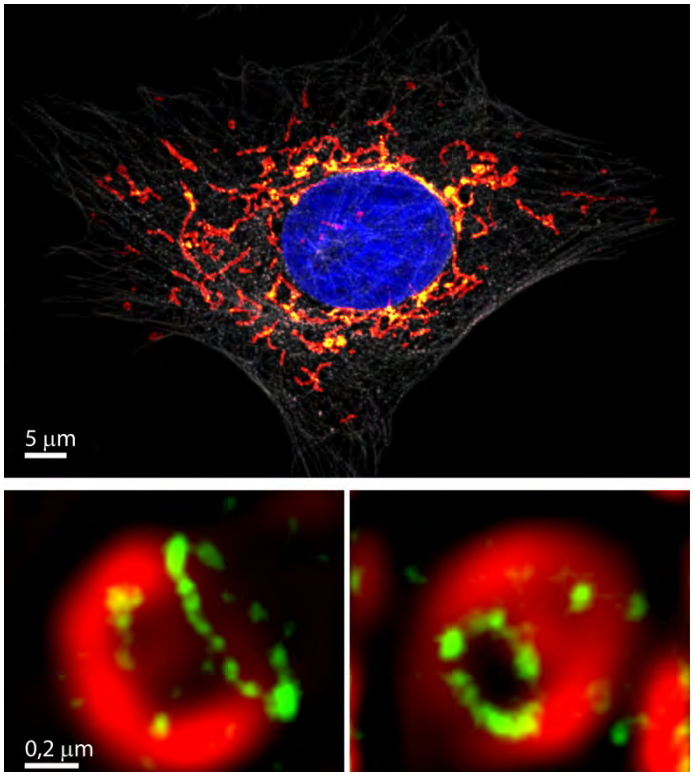
A door opener for cell suicide

Researchers show how the protein Bax makes the cell's decision to die irrevocable

Every day, billions of cells in our body kill themselves. Although this may sound dramatic: This controlled dying is vital because it protects us from cancer as well as other diseases and plays an important role in development. Responsible for this self-induced cell death, called apoptosis, are the power houses of living cells, the mitochondria. When their surfaces become permeable, it is the point of no return for the cell – it dies. Göttingen scientists around Stefan Jakobs have shown for the first time that the so-called Bax proteins form annular structures on the mitochondria. These rings could act as pores and so make the mitochondrial surface permeable. ***(The EMBO Journal, January 18, 2016)***

When body cells kill themselves, this is done for a good reason. Damaged or pathologically altered cells can pose a threat to the organism. Through their death, the organism protects itself from neurodegenerative diseases, autoimmune diseases, and cancer. Also, an embryo can only develop healthily when cells die after they have completed their task. This cellular suicide program, once trigged, follows a strict course. The mitochondria, which supply the cell with energy, play a central role here. Should a cell start this apoptotic program, holes are induced in the mitochondria's envelope. Thereby, proteins from the interior are released into the surrounding cytoplasm. As a result, a chain reaction is started, inevitably killing the cell.

Although we know many factors which are involved in making the mitochondrial membrane permeable, how this is done exactly has been unclear so far. A team of scientists led by Stefan Jakobs at the Max Planck Institute (MPI) for Biophysical Chemistry and the University Medical Center in Göttingen has now discovered that upon apoptosis the protein Bax is organized into annular rings on the mitochondria which helps to open up the membrane.



Top: A healthy human cell with the typical network of mitochondria stained red. Additionally, the nucleus in blue and the microtubule cytoskeleton in gray are shown. Bottom: Enlarged single mitochondria of an apoptotic cell. By means of ultra-high-resolution STED microscopy it can be seen that the Bax proteins (green) form rings in the outer membrane (red) of the mitochondria. *(Image: Stefan Jakobs / Max Planck Institute for Biophysical Chemistry)*

As long as the cell is healthy, the Bax proteins are located mostly in the cytoplasm. But when apoptosis begins, they change their molecular shape and concentrate in large numbers on the mitochondrial membrane. "Previous microscope images showed that Bax proteins form large aggregations which are anchored in the membrane," Stefan Jakobs explains. "But so far unanswered was the question: What is the function of these aggregations?" There was only a guess: Bax could in a sense act as "channel digger" in the mitochondrial membrane and create holes through which the apoptotic proteins could get into the cytoplasm. "However, so far, no one had found according arrangements of Bax in cells," says Jakobs.

Using ultra-high resolution STED microscopy, Jakobs' team has now managed to examine the distributions of Bax proteins with unprecedented detail. "In our high-resolution images it can be clearly seen that the Bax gatherings in reality often are rings of different sizes," says Daniel Jans, scientist in the Jakobs team. More elaborate experiments revealed another important detail: "Normally, the outer mitochondrial membrane is tightly packed with numerous proteins. But inside the Bax rings, these proteins are missing. This suggests that in the interior of the rings the membrane is displaced, implying a hole – like channels."

The scientists thus show for the first time that Bax proteins could form pores in the membrane of the mitochondria. The new findings provide an important contribution to better understand the mechanistic details of apoptosis. (Jaydev Jethwa/fk)

Original publication

Lena Große, Christian A. Wurm, Christian Brüser, Daniel Neumann, Daniel C. Jans, Stefan Jakobs: Bax assembles into large ring-like structures remodeling the mitochondrial outer membrane in apoptosis. *The EMBO Journal*, January 18, 2016. doi: 10.15252/embj.201592789.

See also:

Raquel Salvador-Gallego, Markus Mund, Katia Cosentino, Jale Schneider, Joseph Unsay, Ulrich Schraermeyer, Johann Engelhardt, Jonas Ries, Ana J García-Sáez: Bax assembly into rings and arcs in apoptotic mitochondria is linked to membrane pores. *The EMBO Journal*, January 18, 2016. doi: 10.15252/embj.201593384.

News & Views: Doughnuts, daisy chains and crescent moons: the quest for the elusive apoptotic pore. *The EMBO Journal*, January 18, 2016. doi: 10.15252/embj.201593723.

Further information

www.mpibpc.mpg.de/de/jakobs – Website of the Research Group Structure and Dynamics of Mitochondria, Max Planck Institute for Biophysical Chemistry, Göttingen

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