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Decision About Life or Death

When there is too much strain, the cell's control center gives order to commit suicide

Minute bodies in the nucleus, the nucleoli, have the function of stress sensors and give the starting signal for the cellular suicide program (apoptosis) when there is too much strain. This has been found out by molecular biologists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). As the investigators describe in the latest issue of the specialist journal *Molecular Cell*, stress leads to activation of apoptosis protein p53. It triggers a signaling cascade that ultimately leads to the cell's death.

Health and growth of a cell are dependent, to a large extent, on well-functioning ribosomes, the protein factories of cells. However, an essential component of ribosomes, namely ribosomal ribonucleic acid (rRNA), is only formed when the transcription factor TIF-IA in the nucleoli stimulates the RNA polymerase I to dock on to the genes for ribosomal RNA and produce a copy of these. If TIF-IA is absent or inactivated, serious changes in the nucleoli are the result; the cells stops dividing and the suicide program starts.

Professor Dr. Ingrid Grummt, head of the Division of Molecular Biology of the Cell II, and her co-worker, **Dr. Xuejun Yuan,** jointly with DKFZ colleagues were able to generate genetically modified mice who are unable to produce TIF-IA ("knockout mice"). They found out that these animals are not viable; the embryos died after only nine and a half days. The unborn animals were considerably smaller and less developed compared to their normal peers.

Cultures of embryonic murine cells in which TIF-IA was eliminated or blocked showed the following picture: The nucleoli were disrupted, cell division came to a halt. The level of active p53 was significantly elevated and the cells showed all signs of programmed cell death. Furthermore, the scientists found out that disintegration of ribosomes is accompanied by the release of ribosomal proteins. Several of these, including protein L11, have the ability to bind to the MDM2 protein. When this happens, p53 is simultaneously released from its "embrace" by MDM2 so that it can mediate the apoptosis signal.

This fundamental research shows that the function of the nucleoli is not restricted to the production of ribosomes. They also play an important role in the control of cell preservation and cell growth. Therefore, these findings might also contribute to a better understanding of cancer, since overproduction of rRNA appears to be a first step in tumor development.

*Xuejun Yuan, Yonggang Zhou, Emilio Casanova, Minqiang Chai, Eva Kiss, Hermann-Josef Gröne, Günter Schütz, and Ingrid Grummt: "Genetic Inactivation of the Transcription Factor TIF-IA Leads to Nucleolar Disruption, Cell Cycle Arrest, and p53-Mediated Apoptosis", Molecular Cell, Vol. 19, 77–87, July 1, 2005, doi 10.1016/j.molcel.2005.05.023

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Dr. Julia Rautenstrauch
Division of Press and Public Relations

Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968