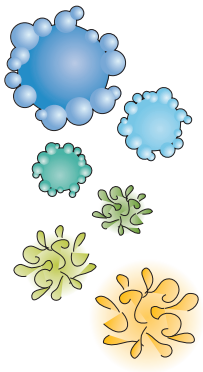
CELL DEATH

Pulling the apoptotic trigger for necrosis

Apoptosis and necrosis are considered to be distinct modes of cell death; however, apoptosis can progress to secondary necrosis if apoptotic cells are not efficiently removed by phagocytic cells. Secondary necrosis was thought to be unregulated and to occur through passive cell swelling. However, Rogers *et al.* now show that secondary necrosis is another example of programmed cell death and that it is triggered by apoptotic stimuli.

Apoptosis is executed by the activation of a cascade of proteolytic enzymes, the caspases. Pyroptosis — a form of programmed necrosis induced by microbial infection — is also activated by caspases (in this case inflammatory caspases), which are responsible for the proteolytic processing of gasdermin D (GSDMD). The amino-terminal portion of GSDMD then oligomerizes and forms pores in the plasma membrane and thereby mediates necrotic cell death. The authors found that another member of the gasdermin superfamily, DFNA5, is also a caspase target, but unlike GSDMD it is cleaved by caspase 3, the executioner caspase of the apoptotic pathway. Akin to GSDMD, this processing occurs at a single site (Asp270) and generates amino-terminal (DFNA5-N) and carboxy-terminal (DFNA5-C) portions of DFNA5.

> “secondary necrosis is a regulated process”



When DFNA5-N was ectopically expressed in human embryonic kidney 293T (HEK293T) cells, which do not express endogenous DFNA5, the cells showed morphological and biochemical features characteristic of necrotic cells. DFNA5-N was shown to associate with the plasma membrane and computer modelling approaches indicated that it can form pores, which indicates that DFNA5-N generated through caspase 3 cleavage is an inducer of necrosis.

Expression of DFNA5 (but not the non-cleavable mutant) and concomitant induction of apoptosis in HEK293T cells generated DFNA5-N and induced secondary necrosis. The DFNA5-N fragment was also detected when apoptosis was induced in macrophages, which endogenously express DFNA5. These macrophages progressed to secondary necrosis, which was impaired in DFNA5-deficient cells, indicating that DFNA5 mediates secondary necrosis and that its proteolytic processing downstream of apoptotic stimuli is essential for this activity.

This work shows that DFNA5 is a substrate of caspase 3 and drives necrosis after apoptosis induction, revealing that secondary necrosis is a regulated process downstream of apoptotic cell death. How this mode of cell death and its regulation contribute to physiological and pathological processes remains to be determined.

Paulina Strzyz

ORIGINAL ARTICLE Rogers, C. *et al.* Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms14128 (2017)

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TRANSLATION

Smoothening the coding sequence for translation

Remodelling of RNA structures by proteins such as the DEAD-box (DDX) RNA helicases regulates gene expression at various stages. The budding yeast helicase Dhh1 and its human counterpart DDX6 are known to repress translation and activate mRNA decay. Now, Jungfleisch *et al.* show that Dhh1 promotes translation initiation of a subset of mRNAs that form structures in their coding sequence.

The authors found in budding yeast that Dhh1 promotes translation initiation of the plant Brome mosaic virus (BMV) RNA2 by binding to all parts of the transcript. Because mRNA coding sequences have only rarely been associated with translation regulation, the authors focused on studying this part of the transcript and found a stem-loop structure that strongly inhibited its translation in cells lacking Dhh1.

Next, through RNA–protein crosslinking and translation analyses, the authors identified 245 yeast transcripts that are bound by Dhh1, and the translation of which is reduced in cells lacking Dhh1. Binding of Dhh1 around the translation initiation codon was much higher for these mRNAs than in other cellular mRNAs, and ribosome profiling analyses further supported a role for Dhh1 in promoting translation initiation at these transcripts.

> “Dhh1 promotes translation initiation of … mRNAs that form structures in their coding sequence”

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Compared with other mRNAs, those that depend on Dhh1 for their translation have longer and more structured coding sequences. Similarly, their human homologues also have relatively long, structured coding sequences, and translation of one such mRNA, encoding the oncogene PTCH1, was found to depend on DDX6.

This study reveals a new mechanism of translation regulation that is conserved from yeast to humans. Relying on DDX helicases and on RNA structures, including those present in coding sequences, this mechanism controls translation initiation of specific genes and can be exploited by RNA viruses.

Eytan Zlotorynski

ORIGINAL ARTICLE Jungfleisch, J. *et al.* A novel translational control mechanism involving RNA structures within coding sequences. *Genome Res.* http://dx.doi.org/10.1101/gr.209015.116 (2016)
FURTHER READING Bourgeois, C. F., Mortreux, F. & Auboeuf, D. The multiple functions of RNA helicases as drivers and regulators of gene expression. *Nat. Rev. Mol. Cell Biol.* **17**, 426–438 (2016)