# Journal club

## ESCRTS: THE FINAL CUT FOR CELLS

How a cell is cleaved into two daughter cells — a process known as cytokinesis — has fascinated biologists for more than 150 years. In 1891, Walther Flemming published beautiful drawings showing that a cleavage furrow ingresses between separated chromosomes and forms a short intercellular bridge connecting the two daughter cells. But how does abscission, the final cut of the intercellular bridge, eventually occur? It was first thought to be a trivial event, but it turned out to be a much more sophisticated and regulated process than initially anticipated.

In 2007, two seminal papers (Carlton and Martin-Serrano; Morita et al.) reported that ESCRTs (endosomal sorting complexes required for transport) were essential for the completion of cytokinesis. The activity of the ESCRT machinery culminates with the polymerization of ESCRT-III filaments, which were originally known to facilitate the scission of intraluminal vesicles from the limiting membrane of late endosomes. Also known was that retroviruses hijack this machinery at the plasma membrane to promote the budding and release of virions through the deformation of the membrane away from the cytosol. Carlton and Martin-Serrano proposed that cytokinetic abscission is a similar topological event (as if one of the daughter cells was a giant virion) that is driven by the same molecular machinery in human cells.

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These studies were influential because they proposed a straightforward mechanism for abscission. Soon afterwards, ESCRTs were implicated in cytokinesis in Archaea (Lindås et al.; Samson et al.), suggesting that abscission might be the ancestral function of this ancient molecular machinery. Live cell imaging and tomo-EM later revealed that ESCRT-III accumulates at the abscission site just before the final cut (Elia et al.) and ESCRT-dependent helices ‘pinch’ the membrane (Guizetti et al.).

The discovery of ESCRTs in cytokinesis highlights how ‘outsiders’ can make crucial contributions: the Martin-Serrano and Sundquist groups were virology specialists who had not worked on cytokinesis before.

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**ORIGINAL ARTICLES** Carlton, J. G. & Martin-Serrano, J. Parallels between cytokinesis and retroviral budding: a role for the ESCRT machinery. *Science* **316**, 1908–1912 (2007) | Morita, E. et al. Human ESCRT and ALIX proteins interact with proteins of the midbody and function in cytokinesis. *EMBO J.* **26**, 4215–4227 (2007) | Lindås, A.-C. et al. A unique cell division machinery in the Archaea. *Proc. Natl Acad. Sci. USA* **105**, 18942–18946 (2008) | Samson, R. Y. et al. A role for the ESCRT system in cell division in Archaea. *Science* **322**, 1710–1713 (2008) | Elia, N. et al. Dynamics of endosomal sorting complex required for transport (ESCRT) machinery during cytokinesis and its role in abscission. *Proc. Natl Acad. Sci. USA* **108**, 4846–4851 (2011) | Guizetti, J. et al. Cortical constriction during abscission involves helices of ESCRT-III-dependent filaments. *Science* **331**, 1616–1620 (2011)

AGEING

# mtDNA robs nuclear dNTPs

Several lines of research have led to the theory that mitochondrial DNA (mtDNA) damage directly contributes to ageing by leading to respiratory chain defects that result in increased production of reactive oxygen species, causing various types of cellular damage. Now in *Nature Metabolism*, Hämäläinen et al. challenge this view, reporting that mtDNA replication defects might cause ageing indirectly by inducing nuclear DNA replication stress.

The study was based on the previous observation that in mutator mice — a mouse model of premature ageing — which accumulate high levels of mtDNA mutations, oxidative damage is not increased; moreover, respiratory chain deficiency is not typically associated with premature ageing.

As aberrant somatic stem cell pool functions play a key part in the premature ageing of mutator mice, the authors went on to analyse the ROS-independent mechanisms underlying this defect.

> “mtDNA damage has a negative effect on nuclear genome maintenance”

Credit: V. Summersby/ Springer Nature Limited

Mutator mouse-derived induced pluripotent stem cells (iPSCs) showed signs of replication stress — cells accumulated in late G1/early S phase and nuclear DNA replication was slowed down owing to replication fork stalling, which is indicative of DNA damage. Consistently, accumulation of double-strand DNA (dsDNA) breaks and activation of the ATM and ATR–CHK1 DNA damage response pathways were observed. Nuclear DNA damage was confirmed in vivo, in mutator male gamete precursor cells. Together, these observations indicate that mtDNA damage has a negative effect on nuclear genome maintenance.

So how might mtDNA damage affect nuclear DNA replication? Normally, cellular levels of dNTP increase in preparation for S phase and remain high until DNA replication is completed. But in mutator iPSCs, whole-cell dNTP pools were depleted whereas mitochondrial dNTP pools were enriched, suggesting that following mtDNA damage, cellular dNTPs are sequestered into mitochondria to enhance mtDNA replication. The resulting dNTP depletion in the nucleus would lead to nuclear DNA damage. Indeed, slowing down mtDNA replication reduced the accumulation of dsDNA breaks and improved genome stability.

This study presents a new view of how mitochondrial dysfunction might contribute to ageing, by linking increased mtDNA replication to nuclear DNA replication stress and genome instability — another hallmark of ageing.

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**ORIGINAL ARTICLE** Hämäläinen, R. H. et al. Defects in mtDNA replication challenge nuclear genome stability through nucleotide depletion and provide a unifying mechanism for mouse progerias. *Nat. Metabolism* https://doi.org/10.1038/s42255-019-0120-1 (2019)