APOPTOSIS

How attachments aid survival

We know that close attachments between animals can help them survive difficult times, and attachments are also important for cell survival. If a cell becomes detached from the extracellular matrix, it undergoes apoptosis — a process known as anoikis. And, in *Cell*, Ruoslahti and colleagues now describe an integrin-regulated pathway that is, at least partly, responsible for the cell-survival effects of such attachments.

They first identified a pro-apoptotic protein, BIT1, which localizes to mitochondria, and they showed that cytoplasmic expression of BIT1 induces apoptosis. In addition, they showed that cytoplasmic BIT1 can form a complex with cytoplasmic AES (a protein of the Groucho transcriptional-corepressor family), and that BIT1 and AES work together to induce apoptosis in a caspase-independent manner.

Next the authors showed that cells that bound to fibronectin through the α5β1 integrin were protected against BIT1/AES-induced apoptosis: this integrin seems to produce signals that block this apoptosis. Furthermore, they found that reducing BIT1 expression in detached cells promoted cell survival, whereas increasing BIT1 expression promoted cell death.

In the final part of this study, Ruoslahti and co-workers showed that another Groucho-family protein — the anti-apoptotic protein TLE1 — can inhibit BIT1/AES-induced apoptosis by interfering with BIT1–AES-complex formation. They therefore propose a model in which cell detachment somehow induces the release of BIT1 from mitochondria, which promotes the formation of BIT1–AES complexes. They suggest that these complexes might then switch off a gene-transcription programme that promotes cell survival. Although the molecular details of this pathway need to be further clarified, this study has identified BIT1 as a potential "…guardian of anchorage dependence".

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Jan, Y. *et al.* A mitochondrial protein, Bit1, mediates apoptosis regulated by integrins and Groucho/TLE corepressors. *Cell* **116**, 751–762 (2004)

CELL–CELL COMMUNICATION

Opening communication channels

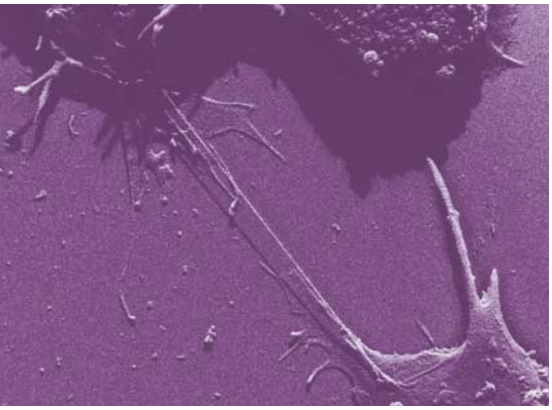

Image courtesy of Hans-Hermann Gerdes, University of Heidelberg, Germany.

Clear communication is a key requirement for successful working relationships and is essential for coordinating the growth and survival of multicellular organisms. Now, Hans-Hermann Gerdes and colleagues have discovered a new type of intercellular communication — tunnelling nanotube (TNT) networks — that could revolutionize our understanding of how cells communicate.

The authors observed TNTs in cultures of rat pheochromocytoma (PC12) cells, using three-dimensional live-cell microscopy. These ultrafine structures are 50–200 nm in diameter, can be up to several cell diameters in length and span the shortest distance between connected cells (see figure). They were also found to contain actin, but not microtubules. Scanning and transmission electron microscopy indicated that TNTs are a continuation of the cell membrane, and further investigation by video microscopy showed that they are produced *de novo* when filopodia-like projections on one cell make contact with a neighbouring cell. TNTs fail to develop in cells that are treated with a substance that depolymerizes actin, which indicated that the actin-containing projections are essential for TNT formation. But, what exactly do TNTs do?

Small vesicular objects were seen moving unidirectionally along TNTs and, using fluorescent dyes, the authors showed that membrane vesicles and organelles, but not small cytoplasmic molecules, could be exchanged between TNT-connected cells. Fluorescently labelled plasma membrane components could selectively flow between TNT-connected cells, indicating that their membranes are continuous. *In vivo* experiments confirmed that the fluorescently labelled organelles moved unidirectionally through the TNTs, as organelles were observed entering TNTs on one side of a cell–cell connection, moving through the TNT and exiting into the cell on the other side of the TNT.

From these results the authors have proposed a model in which cells form actin-driven projections towards a target cell. Once the projection contacts the target, TNT formation occurs as a result of membrane continuity between the connected cells, and this physical link allows organelles to be unidirectionally transferred to the target cell by an actin-mediated mechanism. As the authors have observed TNTs in other cell lineages, this new long-range form of cell communication probably has an important role in regulating a diverse range of cellular processes.

Emma Croager

References and links

ORIGINAL RESEARCH PAPER Rustom, A. *et al.* Nanotubular highways for intercellular organelle transport. *Science* **303**, 1007–1010 (2004)

WEB SITE

Hans-Hermann Gerdes' laboratory: http://www.nbio.uni-heidelberg.de/Gerdes.html