

Division as modified migration

A dividing cell mimics two half cells migrating away from each other, according to Chris Janetopoulos, Peter Devreotes, and colleagues (Johns Hopkins University, Baltimore, MD). A gradient of PI(3,4,5)P₃ appears to help the two ends of the cell to expand outwards, even as the middle of the cell favors contraction.

Devreotes has long studied PI(3,4,5)P₃ involvement in *Dictyostelium* migration, where signaling through chemotaxis receptors leads to PI(3,4,5)P₃ accumulation at the front of the cell. The excess PI(3,4,5)P₃ supports actin-led forward propulsion, whereas low PI(3,4,5)P₃ at the rear of the

cell results in contraction. This situation is maintained by membrane localization of PI kinases at the front of the cell and of the PIP phosphatase PTEN at the rear.

The team set out to investigate the migration function of these enzymes further by making knockouts. "That was about a year and a half ago," says Devreotes. "We still haven't got around to studying migration."

Instead they immediately came across a striking cytokinesis defect in the mutants, which couldn't regulate PI(3,4,5)P₃ levels because of a lack of both PTEN and two PI3 kinases. Cells continued to grow but cytokinesis often failed, especially for cells growing in suspension. In wild-type cells undergoing cytokinesis, by contrast, the kinases and PI(3,4,5)P₃ were concentrated at the poles of cells and PTEN was at the furrow.

This localization was blocked if spindle formation was prevented. Before cytokinesis, cells round up. This coincided in wild-type cells with the arrival of PTEN at the plasma membrane all around the cell. "That would tend to erase the polarity from migration," says Devreotes. The spindle then may reestablish two opposing polarities, setting the two ends of the cell off in opposite directions, and simultaneously instructing the middle of the cell to contract. *Dictyostelium* already has a reputation for cytokinesis that relies on daughter cells pulling themselves away from each other, so it will be important to establish whether other organisms use similar mechanisms. **JCB**

Reference: Janetopoulos, C., et al. 2005. *Dev. Cell.* 8:467–477.

Really outside signaling

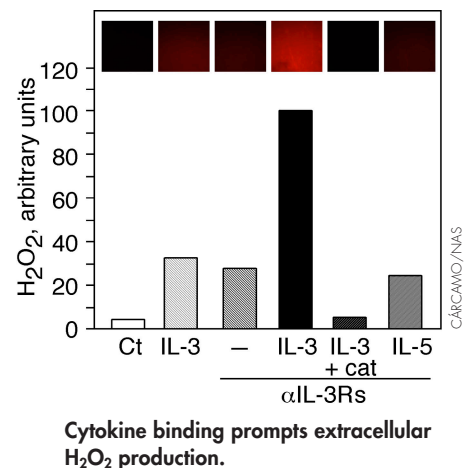
Reactive oxygen species (ROS) such as hydrogen peroxide (H₂O₂) pose a potential chemical threat in cells, so it was surprising enough when they turned up as essential signaling components downstream of receptor activation. Now Garrett DeYulia, Juan Cárcamo, David Golde (Memorial Sloan-Kettering Cancer Center, New York, NY) and colleagues have found that H₂O₂ can be generated outside cells, independent of any intracellular events, by ligand binding to cytokine receptors.

The group had earlier seen that extracellular catalase, which breaks down H₂O₂, inhibited signaling through the GM-CSF receptor. They now find that ligand binding to this receptor increases the amount of extracellular H₂O₂. This occurs even when the cells are fixed before

ligand addition or with a version of the receptor lacking intracellular signaling domains. H₂O₂ production was also evident with EGF binding to its receptor in the presence of an inhibitor of downstream signaling.

Extracellular destruction of H₂O₂ reduced signaling and cell survival downstream of GM-CSF binding. Addition of extracellular H₂O₂, by contrast, induced phosphorylation of downstream targets.

H₂O₂ makes a good second messenger—it is small, diffusible, and can be destroyed easily. It can also inactivate proteins such as phosphatases by oxidizing active site cysteine residues. How it is generated initially is a mystery. In intracellular ROS signaling the necessary electrons are supplied by NADPH oxidase, but outside the cell the only precedent is



an unusual reaction between oxygen radicals and water catalyzed by antibodies. DeYulia and colleagues plan to mutate ligand and receptor residues to track down what parts of the proteins may be responsible for ROS generation. **JCB**

Reference: DeYulia, G.J., et al. 2005. *Proc. Natl. Acad. Sci. USA.* 102:5044–5049.