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BRCA1 on the move

The tumor suppressor functions outside the nucleus to regulate cell adhesion and migration.

The E3 ubiquitin ligase BRCA1 is a tumor suppressor best known for its role in DNA damage repair. Coene et al. report a new function for the protein, revealing that it also operates at the leading edge and at focal adhesions to regulate cell spreading and motility (1).

Mutations in BRCA1 are associated with familial forms of breast and ovarian cancer. How the protein protects cells from carcinogenesis is unclear, though most of its known functions—including transcriptional regulation and DNA double-strand break repair—occur in the nucleus (2). In 2005, David Vaux and colleagues from the University of Oxford, UK, and the University of Ghent, Belgium, demonstrated that BRCA1 also localizes to mitochondria, where it presumably maintains the integrity of mitochondrial DNA (3).

Following up on this discovery, Vaux and co-workers set out to identify proteins that bind to BRCA1's C terminus—a region required for the protein's tumor-suppressive activity. "We were looking for proteins that might have a role in BRCA1's mitochondrial import," Vaux recounts. "We found a good candidate [that we're working on at the moment]. But we also found members of the ezrin, radixin, and moesin (ERM) family, which was completely unexpected."

ERM proteins link the plasma membrane to the underlying actin cytoskeleton (4). Coene et al. saw that BRCA1 colocalized with ERM proteins and F-actin in both plasma membrane ruffles and focal adhesions. To determine whether BRCA1 had any function at these locations, the researchers used a C-terminal fragment of the protein that displaced endogenous BRCA1 from the plasma membrane.

Cells overexpressing this dominant-negative construct spread more slowly after plating on adhesive surfaces and showed increased motility compared with control cells. Moreover, human breast cancer cells with mutations in BRCA1 moved faster than breast cancer lines with an intact BRCA1 gene. Re-introducing wild-type BRCA1 reversed this increase in motility, but a mutant version of the protein that lacked ubiquitin ligase activity was unable to restore migration to normal speed. "This suggests that BRCA1 not only needs to be at the cell periphery but that it also has to be active when it's there," says Vaux.

Coene et al. used an in vitro scratch-wound assay to assess whether the increased migration of cells lacking BRCA1 had any functional consequences. Cells expressing the BRCA1 C-terminal dominant-negative fragment closed the wound at the same rate as control cells, but video microscopy revealed that they behaved very differently as they did so. "Control cells close the wound almost like a curtain. Cells at the wound edge remain in contact with cells further back in the monolayer," Vaux explains. "But cells overexpressing the BRCA1 C-terminal domain fill the wound with individual cells that have no contact with the leading edge."

> "[BRCA1] might regulate the migration of cells from a variety of solid tumors."

The decrease in intercellular adhesion and increase in motility suggest that loss of BRCA1 may make tumor cells more likely to metastasize. Indeed, some studies have found that BRCA1 expression is lower in metastatic deposits than in primary tumors. "In the longer term, we want to look at murine models of metastasis with different levels of BRCA1 at the cell periphery," Vaux says. "The protein might regulate the migration of cells from a variety of solid tumors."

In the shorter term, however, Vaux's goal is to identify targets of BRCA1's ubiquitin ligase activity and to determine how they affect adhesion and migration. Vaux explains: "I think of BRCA1 as a timer for assembling and stabilizing complexes in particular places. The ability of BRCA1 to ubiquitinate and stabilize DNA repair complexes at double-strand breaks may turn out to be similar to its function at the cell periphery, where it might, for example, orchestrate a complex that modulates integrin availability."

Focal Point

Elisabeth Coene (left), David Vaux (right), and colleagues (not shown) reveal that the tumor suppressor and E3 ubiquitin ligase BRCA1 is targeted to the cell periphery by ezrin, radixin, and moesin proteins, where it regulates cell adhesion and migration. Compared with control cells (top), cells expressing a dominant-negative version of BRCA1 (bottom) migrate faster but close wounds in a more disorganized fashion, as individual cells lose contact with their neighbors. The findings suggest that BRCA1 ubiquitinates proteins involved in cell–cell and cell–matrix adhesion and that the tumor suppressor may also limit the ability of cancer cells to metastasize.

PHOTOS COURTESY OF CHRISTINA COENE (LEFT) AND RICHARD BERWICK (RIGHT)

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