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β-Catenin gets an honorable discharge

Wnt signaling component is removed from active duty by exosomes.

Beta-catenin binds E-cadherin to facilitate the formation of intercellular adhesions, but it's also a central component of the Wnt signaling pathway that controls cell proliferation and differentiation (1). Activation of the Wnt pathway stabilizes β-catenin, enabling it to translocate into the nucleus and pair up with transcription factors to induce target gene expression. In the absence of a Wnt signal, β-catenin's activity is kept in check by its sequestration at cell junctions and by the kinase GSK-3β, which phosphorylates the protein to trigger its ubiquitination and degradation by the proteasome. Chairoungdua et al. reveal a new way in which cells restrain β-catenin and potentially suppress tumor metastasis: the protein can be ejected from cells in small vesicles called exosomes (2).

Michael Caplan's group at Yale University uncovered this process after finding that E-cadherin binds to CD82, a member of the tetraspanin family of transmembrane proteins, which are involved in a variety of different cellular processes including cell adhesion and signal transduction (3). Overexpressing CD82 or a related tetraspanin called CD9 suppressed Wnt signaling and reduced β-catenin protein levels. Surprisingly, this decrease did not involve GSK-3β or the proteasome. Nor did it involve protein degradation by lysosomes. "We were sort of stumped," Caplan admits, "until we saw a talk that mentioned that tetraspanins like CD82 are associated with exosomes."

> **"CD82 may act as a metastasis suppressor by targeting β-catenin for exosomal release."**

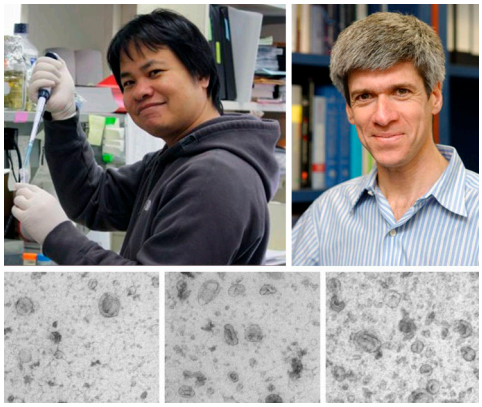
Exosomes are small vesicles that form inside endosomes by the inward budding of endosomal membranes. The vesicles are then secreted when the endosome fuses with the plasma membrane (4). Chairoungdua et al. found that CD9 and CD82 boosted the release of exosomes containing β-catenin, thereby reducing cellular levels of the protein and inhibiting the Wnt pathway. Cells lacking CD9, on the other hand, produced fewer exosomes and showed higher Wnt signaling activity.

"We think that these tetraspanins facilitate exosome biogenesis," says Caplan. Tetraspanins associate with each other to form patches within cell membranes that, in concert with specific lipids, might induce vesicle budding into the endosomal lumen. β-Catenin could be targeted to these vesicles through the interaction of E-cadherin with tetraspanins. E-cadherin was also found in exosomes and CD82 didn't affect Wnt signaling when it was overexpressed in cells lacking the adhesion molecule. Caplan and colleagues now want to investigate whether this is how tetraspanins target β-catenin to exosomes.

The exosomal release of β-catenin may be compromised in certain cancers, where Wnt signaling is often hyperactive. CD82 and CD9 are both suppressors of metastasis whose expression is lost in several types of late stage tumor. Chairoungdua et al. could block Wnt signaling in a metastatic cell line by restoring CD82 expression. "CD82 may act as a metastasis suppressor by targeting β-catenin for exosomal release and thereby reducing its availability as a Wnt signaling mediator," Caplan proposes.

But why would cells use tetraspanins and exosomes to dispose of β-catenin when they already have GSK-3β and the proteasome to get rid of the protein? Or, as Caplan puts it: "Why throw β-catenin overboard instead of simply grinding it up? One possibility is that exosomal β-catenin is like a message in a bottle that signals to neighboring cells." Exosomes have previously been shown to transmit messages between cells. They can, for example, deliver microRNAs from one cell to regulate mRNAs in a second (5). Alternatively, exosomes may be a more reversible way for cells to lower their β-catenin levels. "Incorporating β-catenin into exosomes could mark it for destruction without actually destroying it," Caplan explains. "Our paper is a proof of principle for this mechanism. Now we have to establish if and how this process is regulated."

Focal Point



Arthit Chairoungdua (left), Michael Caplan (right), and colleagues reveal a new mechanism by which cells downregulate β-catenin protein levels and activity of the Wnt signaling pathway. The tetraspanin proteins CD82 and CD9 promote the incorporation of β-catenin into exosomes—small vesicles that cells release into their environment. Electron microscopy of purified cell culture supernatants reveals that cells overexpressing CD9 (middle) or CD82 (right) produce more exosomes than control cells (left). Exosomal release of β-catenin and inhibition of Wnt signaling may explain why CD82 and CD9 suppress tumor metastasis.

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