Exosomal release of beta-catenin may explain why CD82 and CD9 suppress tumor metastasis

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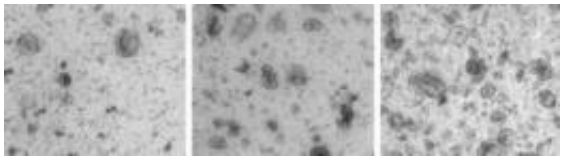

Electron microscopy of purified cell culture supernatants reveals that cells overexpressing CD9 (middle) or CD82 (right) produce more exosomes than control cells (left). Exosomal release of beta-catenin and inhibition of Wnt signaling may explain why CD82 and CD9 suppress tumor metastasis. Credit: Chairoungdua, A., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201002049.

Researchers reveal a new way in which cells restrain beta-catenin and potentially suppress tumor metastasis: the protein can be ejected from cells in small vesicles called exosomes. The study appears online on September 13 in the *Journal of Cell Biology*.

Beta-catenin is a central component of the Wnt signaling pathway that controls cell proliferation and differentiation. Activation of the Wnt pathway stabilizes beta-catenin, allowing it to move into the cell nucleus and control the expression of many different genes.

Michael Caplan's group at Yale University uncovered a new way in which cells restrain beta-catenin's activity. Overexpressing CD82 or CD9, members of the tetraspanin family of transmembrane proteins, suppressed Wnt signaling and reduced beta-catenin protein levels. Surprisingly, this decrease did not involve an established pathway of beta-catenin destruction. "We were sort of stumped," Caplan admits, "until we saw a talk that mentioned that tetraspanins like CD82 are associated with exosomes."

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. The team found that CD9 and CD82 boosted the release of exosomes containing beta-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.

The exosomal release of beta-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. Caplan and colleagues blocked Wnt signaling in a metastatic cell line after restoring CD82 expression. "CD82 may act as a metastasis suppressor by targeting beta-catenin for exosomal release and thereby reducing its availability as a Wnt signaling mediator," Caplan proposes.

More information: Chairoungdua, A., et al. 2010. *J. Cell Biol*. doi:10.1083/jcb.201002049

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