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Catenins guide cell migration

March 15, 2018–Cell migration plays important roles in morphogenetic processes, and at times in pathogenetic processes such as cancer invasion. Cells will sometimes group together and collectively migrate over long distances. Neural crest (NC) cells, which give rise to several different organs and tissues, are a typical example that undergoes collective migration. During development, a group of NC cells migrate along the developing gut to establish a mesh-like enteric nervous system. Cellular level analyses have revealed that these NC cells are adhered to one another while undergoing migration. Cell adhesion and migration are both regulated by cadherins and catenins, but it remained unclear how these factors tie the two processes together.

In a new study led by CDB research scientist Vassil Vassilev and Anna Platek of the Laboratory for Cell Adhesion and Tissue Patterning (Masatoshi Takeichi, Team Leader) and other collaborators, they demonstrated that in cells undergoing collective migration, catenins play a role not only in cell-cell adhesion, but also contribute to the stabilization of front-rear polarity within an individual cell, which is essential for their directional movement. Using mouse enteric neural crest (ENC) cells extracted from embryonic guts and cultured glioblastoma U251 cells, they further showed that β-catenin/α-catenin localized along the leading-edge of the lamellipodial membrane are internalized and activate myosin at the rear regions of the cell to stabilize its front-rear polarity. Their findings were reported in the journal *Developmental Cell*.

Movie: https://www.youtube.com/watch?v=otmnrO9WS5o
Migration of cultured cells. Normal cells (upper right) actively move unidirectionally, while catenin KOs (lower left: β-catenin, lower right: αE-catenin) move randomly.

Vassilev and Platek collaborated with former CDB Team Leader Hideki Enomoto of the Laboratory for Neuronal Differentiation and Regeneration, now at Kobe University, who has long been focusing on elucidating mechanisms underlying establishment of the enteric nervous system by closely observing the dynamic collective migration of ENC cells (See Science News: August 30, 2012). ENC cells express N-cadherin which forms a cadherin-catenin complex (CCC) to mediate cell-cell adhesion. The cytoplasmic region of cadherin binds β-catenin, which in turn binds α-catenin to stabilize cell-cell adhesion. The group first examined the role of N-cadherin and β-catenin/αE-catenin by conditionally knocking out (cKO) the genes for N-cadherin, β-catenin, and αE-catenin in mouse ENC cells and observed ENC cell dynamics in the gut. They found that β- and αE-catenin cKOs resulted in severe delay of ENC migration compared to wildtype gut and failed to complete migration. When single cell dynamics were tracked, they found N-cadherin cKO displayed chain migration with some disruption in the chain, whereas β- or αE-catenin cKOs lacked chain formation and instead formed clusters and disorganized movements.

The team next took allowed ENC cells to migrate out from gut explants onto culture dishes to observe their movements. While wildtype and N-cadherin cKO ENC cells showed relatively unidirectional migration as noted by the persistence of lamellipodia at the front-edge, the β- and αE-catenin cKO ENC cells did not undergo unidirectional migration with the lamellipodium frequently changing positions. These observations suggested that catenins did not just function in cell adhesion, but also contributes to cell migration. Using cultured cells, they examined intracellular localization of catenins and found that in addition to being distributed at cell adhesion sites, catenins were also distributed within the cytoplasm. Time-lapse imaging revealed catenins being relocalized from the lamellipodial leading edge toward the nucleus. Upon closer analyses, they discovered that cadherin, β-catenin and αE-catenin forming the CCC was internalized in vesicles, and further, that phosphorylation of β-catenin was important for signaling the intracellular uptake of the CCC. Cadherin also was seen to eventually segregate from the catenins during the relocation to the perinuclear region.

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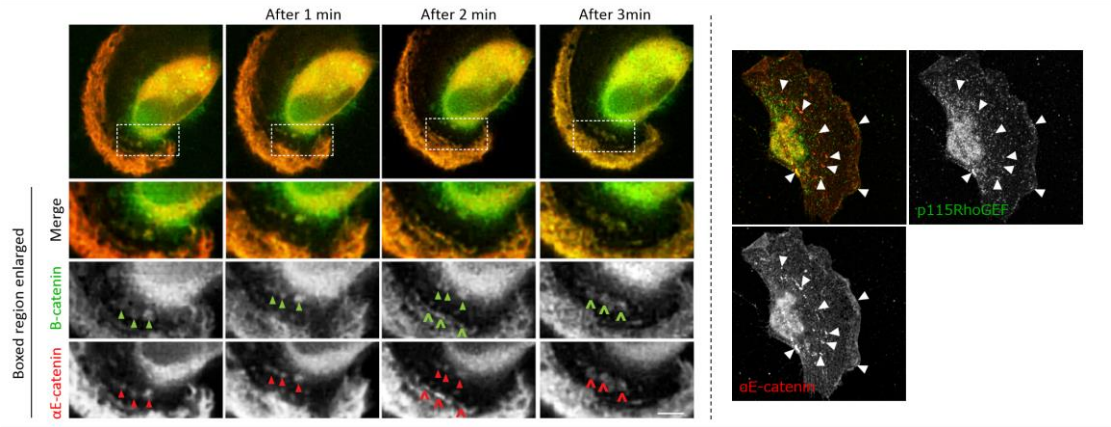

Left: αE- and β-catenins accumulated in lamellipodia are relocated toward the nucleus (U251 cell line)
Right: αE-catenin and RhoGEF distributed in arc around perinuclear area. (U251 cell line)

What role do internalized catenins play inside the cell? When cells move in a single direction, the leading-edge lamellipodia repeatedly extend focal adhesions in the direction of movement, while the rear-edge undergoes contraction via actomyosin. Activation of myosin to mediate contraction is regulated by activated RhoA. An examination of the relationship between catenin and RhoA revealed that p115RhoGEF, a RhoA activator, binds directly to αE-catenin to relocate and concentrate activate RhoA to the perinuclear region. When αE-catenin was depleted from the cells, active RhoA was seen dispersed throughout the cytoplasm. Their team also revealed that αE-catenin also bound transiently with myosin-IIB, indicating that internalized αE-catenin is needed to localize active RhoA and myosin-IIB at the perinuclear region, which results in a polarized activation of myosin that is necessary for stabilizing the front-rear polarity of the cell in migration.

“We showed for the first time that the CCC contributes not only to cell adhesion, but also stabilizes polarity in individual cells during migration. Together, these two functions drive collective cell migration,” explains Takeichi. “We think that lamellipodia continuously expresses cadherin and catenin to prepare to form new contacts with other cells. When no new contacts are formed, the CCC is internalized and recycled, but also appear to regulate cell migration. Although cadherin-catenin mediated adhesion is specific to multicellular organisms, α-catenin was discovered in unicellular *Dictyostelium*, suggesting that catenins may have a function besides cell adhesion. It will be interesting to find out whether the mechanism we reported in this study can be found in non-adhesive cells or unicellular organisms.”

Science News
A fast track to gut innervation (Aug. 30, 2012)
http://www.cdb.riken.jp/eng/04_news/articles/12/120830_trans-mesenteric.html#new_tab

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