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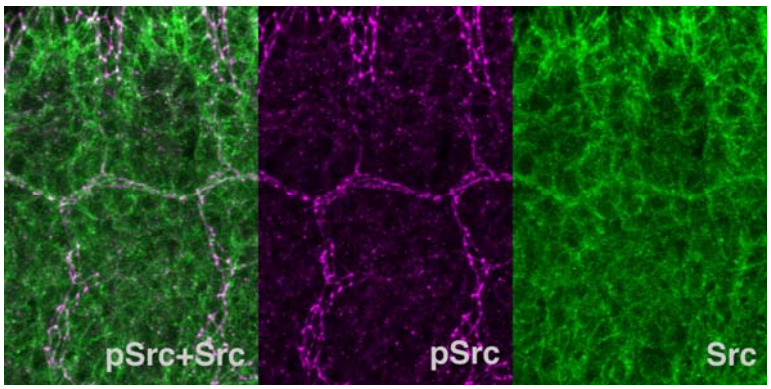
Cross purposes: Dual role for Src in control of cell-cell adhesion

March 8, 2008 – Tissues in the embryo need to be capable of both stability and plasticity, which means that the connections between their component cells must be subject to dynamic controls. This regulation of intercellular adhesion at adherens junction is achieved through the action of multiple genetic pathways working on a range of adhesion and cytoskeletal molecules. Interestingly, the same regulatory pathways can be hijacked in cancer cells, allowing them to metastasize and form tumors. The Src family of oncogenes, for example, is known to downregulate the expression of E-cadherin, a major cell-cell adhesion molecule, but the wide range of related molecules with overlapping functions has made this relationship difficult to study in mammals.



Activation of Src in adherens junctions in *Drosophila* embryos. Src42A is distributed broadly in cell membranes (right). A phosphorylated, active, Src42A (pSrc) was preferentially localized to adherens junctions of tracheal epithelium (center). Merged picture is shown at the left.

A study by Masayo Shindo and colleagues from the Laboratory for Morphogenetic Signaling (Shigeo Hayashi; Group Director) has taken a new tack by looking at the function of Src in epithelial morphogenesis in the fruit fly *Drosophila melanogaster*. Their report, published in *Development*, suggests that Src has the somewhat paradoxical dual function of suppressing cell adhesion by E-cadherin while simultaneously upregulating its expression.

The study began with a gain of function screen for mutations producing altered epithelial morphology during tracheal development in the fly, which yielded the Src family members *Src42A* and *Src64B*, both of which caused defects in tracheal integrity on overexpression. Using antibodies to monitor the activity of these genes in vivo, the authors determined that these genes were upregulated in a range of epithelial tissues undergoing cell rearrangement.

Focusing back on the embryonic tracheal system, the group next studied the effects of loss of *Src42A* function and found multiple defects involving a ramified structure known as the dorsal branch (a group of cells that gives rise to the trachea), including reductions in number of cells, and delays in branch extension and cell intercalation.

Knowing of the link between Src and E-cadherin in other contexts, Shindo et al. re-examined the function of E-cadherin in tracheal development using the cadherin gene, *shotgun* (*shg*). Loss of function *shg* mutants showed disruptions in cellular attachments in tracheal branches, while its overexpression caused delays in dorsal branch elongation and cell rearrangements. Over activation of *Src42A* caused reduced tracheal cell adhesion phenotype, which was partially suppressed by co-expression of E-cadherin, suggesting that E-cadherin is a rate-limiting component of the tracheal cell adhesion under control of Src.

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They next used a technology known as fluorescence recovery after photobleaching (FRAP), in which a fluorescent-tagged sample is zapped with high intensity light causing it to lose its fluorescence (known as “bleaching”) and then watched to determine the rate of recovery, to study the effects of Src on adherens junctions, where cadherins normally accumulate. Looking at GFP-labeled α-catenin, an E-cadherin-binding molecule, as a measure of adherens junction dynamics, they made the interesting discovery. Entry of α-catenin-GFP into adherens junction was slowed down upon loss of Src function and increased upon gain of Src function. “We suspected that Src enhances turn over of α-catenin in adherens junctions,” says Hayashi, who heads the lab in which the study was done.

One puzzling question remained. Although reduction of E-cadherin explains inhibition of cell adhesion by Src, it does not explain why activated Src permitted a larger amount of α-catenin to enter adherens junction. The hint was obtained when they investigated the expression of Armadillo (the Drosophila version of β-catenin, another binding partner of cadherin). They discovered that Src promoted Armadillo expression and its downstream target, E-cadherin. This led to the remarkable conclusion that, even as Src down-regulates the E-cadherin protein at the adherens junction, it upregulates E-cadherin transcription. This dual function explains increased turn over rate of cell adhesion molecules upon elevation of Src, making adherens junction more dynamic.

“The dual function of Src we’ve discovered provides an answer to the long-standing question of why embryonic epithelial tissues are plastic enough to be able to adopt a variety of morphologies,” says Hayashi. “The mechanism also explains why Src-transformed cells not only detach from original tissues, but also re-settle frequently in a new position, an essential feature of malignant cancer metastasis.”

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Metastatic behavior of tracheal cells expressing activated Src42A. Two cells on one of tracheal branches detached from the stalk and landed on the adjacent branch.

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