W. James Nelson: The Cadherin-Catenin Complex: Structure, Function, and Evolution

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The Cell Biology Plenary session began with W. James Nelson, professor of biology at Stanford University. Nelson studies cell junctions in multicellular structure like epitheliums, and specifically focuses on an adhesion system called the cadherin-catenin complex. Cadherins are proteins that link through their cytoplasmic domain to adaptor proteins called catenins. Cadherin binds directly to β-catenin, which then binds to α-catenin, which somehow links the complex to the actin cytoskeleton.

First, Nelson showed that the cadherin-catenin complex is under tension at cell-to-cell contacts. He then discussed how the cadherin-catenin complex is linked to the actin cytoskeleton. One model proposes that the cadherins are linked to the catenins in the cytoplasm and the α-catenin is bound to the actin cytoskeleton. The problem with this model is that in mammals, α-catenin is auto-inhibited, meaning it cannot bind actin on its own. It must be activated in some way. So Nelson looked at the cadherin-catenin complexes in a variety of animals to see if they behaved in a similar manner. After characterizing the cadherin-catenin complexes in six other animals (including zebrafish, *C. elegans*, and the sea anemone), Nelson concluded that when α-catenin is bound to β-catenin, it has a reduced affinity for binding to actin. This suggests that binding to β-catenin is somehow regulating the association of α-catenin with the actin cytoskeleton.

Next, Nelson addressed how mammalian α-catenin auto-inhibition might be overridden so that the cadherin-catenin complex is able to bind to the actin cytoskeleton. His team found that the cadherin-catenin complex has the ability to bind actin only when force is applied through the actin cytoskeleton underlying the plasma membrane. Nelson thinks this might work like a molecular clutch or ratchet, with contraction of the actin cytoskeleton allowing interaction with the cadherin-catenin complex.

Nelson›s lab is now interested in if there are any other advantages associated with the application of tension across an epithelium. He presented data that showed biaxial strain induces epithelial cells to re-enter the cell cycle, and this might be regulated through β-catenin. In addition to its role in adhesion as part of the cadherin-catenin complex, β-catenin also works as a transcription factor to switch on genes that control entry into the cell cycle. After strain is applied at cell-to-cell contacts, β-catenin travels from the cytoplasm into the nucleus, where it switches on genes involved in cell cycle progression.

Another component in this pathway is the protein Yap1. When there is no strain Yap1 is sequestered in the cytoplasm by α-catenin, but after applying strain Yap1 is translocated to the nucleus where it switches on genes involved in this transcription pathway. Nelson suggests Yap1 might enter the nucleus much earlier than β-catenin and activate downstream targets that drive the cell into the cell cycle.

Nelson ended his talk by re-emphasizing that although the cadherin-catenin complex is important for regulating cell-to-cell adhesion and the integrity of the epithelium, it is also involved in a diverse set of functions. Cell adhesion is important for the collective properties of epithelial cells, such as wound healing, gastrulation, and zipping up epithelial sheets so they organize around each other. Cadherins are involved in regulating cell sorting and the recognition between different cells. And there are many examples where mechanical tension is important for regulating gene expression and cell proliferation; the cysts in polycystic kidney disease, for instance, might form when cells respond to the pressure created by an initial expansion of the epithelium with proliferation. These examples come from a variety of animals and show the amazing breadth of properties that cell-to-cell adhesion has to bring to the organization of these structures.

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