Cell-cell interactions adapt to the stiffness of the environment

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The ability of tissue cells to stick to one another is critical for many physiological and pathological processes. But normal living cells need to do much more than just hold on tight, they must monitor their environment and respond with appropriate changes in shape, migration, and proliferation. Now, a new study published online on February 16th by Cell Press in the *Biophysical Journal* provides intriguing insight into how mechanical interaction with the external environment influences cell shape and the forces generated by a cell's internal "skeleton".

Cadherins are cell membrane proteins that regulate cell-cell connections by establishing a direct link between a cadherin molecule in an adjacent cell and the cells own internal scaffolding, called the cytoskeleton. "Cadherin-based intercellular junctions are the major means for force transmission within tissues," explains study author Dr. Benoit Ladoux from Paris Diderot University in Paris, France. "A better understanding of how mechanical forces and cellular tension influence formation of cadherin junctions might help to explain how normal tissue integrity is maintained and what promotes cancer metastasis."

Earlier studies had examined cells growing on cadherin-coated glass surfaces. However, there is no biological equivalent with the rigidity of glass in any tissue of the body. In order to gain a better insight into how cadherins function in under more physiological conditions, Dr. Ladoux, Dr. Rene Mčge and their colleagues measured the response of cells grown on cadherin-coated substrates with a range of rigidities corresponding to the different stiffnesses that cells encounter in their

natural tissue microenvironments.

The researchers found that cells cultured on softer surfaces were less spread out and had a more disorganized cytoskeleton when compared with cells growing on more rigid surfaces. "The stiffer the substrates, the larger the average traction forces and the more developed the cadherin adhesions were," reports Dr. Mčge. Inhibition of myosin II, a key cytoskeletal component, decreased traction forces and caused cadherin adhesions to disappear, suggesting that the cytoskeleton was necessary to sustain cellular traction forces.

"Taken together, our results indicate that the strength of cadherin adhesions depends on both intrinsic tension and the stiffness of the environment, and that cadherin adhesions possess some kind of force sensing mechanism to adapt their strength to the rigidity of the of the intracellular and extracellular environments," concludes Dr. Ladoux. "The remodeling of cell junctions to exert appropriate forces could be particularly significant during embryogenesis, tissue integrity, or tumor metastasis."

Provided by Cell Press