Cadherin and Catenins: A Sticky Situation

Our cells are able to come together and form tissues and organs by way of specialized proteins that act as a kind of cellular glue.

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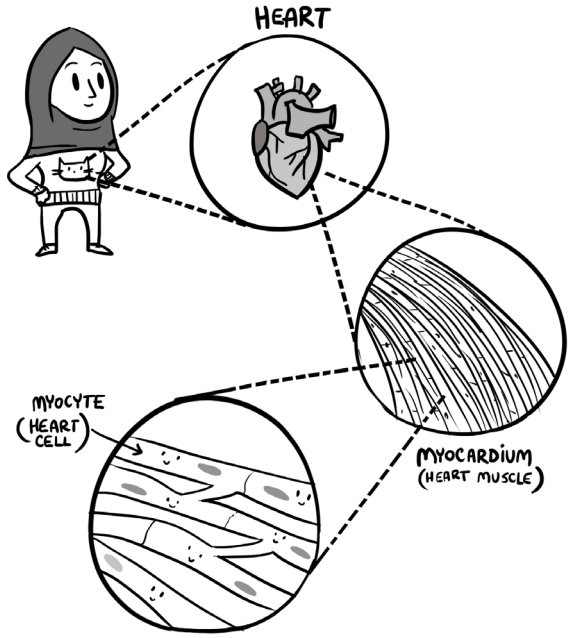
Have you ever tried to do arts and crafts without glue? Or imagine if you opened a book and all the pages fell out. Turns out that an important ingredient to building things is often a sticky substance to hold it all together, and our own human bodies have taken note of this.

While we are made up of many trillions of cells, they aren't all floating around aimlessly. Instead, many of our cells are purposefully held together to form special structures that we know as tissues which, in turn, come together to form the various organs found in our bodies. Without this level of organization, our organs simply would not work.



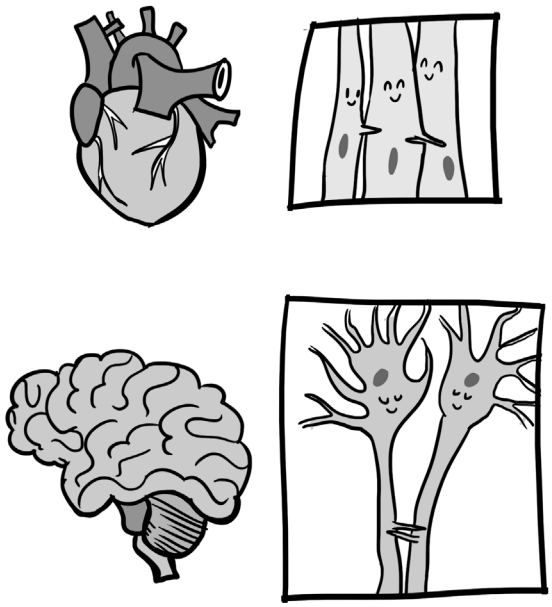
In the mid 1950's, scientists began performing experiments to figure out how similar cell types recognized each other and organized themselves into unique tissues. These early studies hinted that a certain type of protein molecule was responsible for holding cells together, although the identity of the protein remained elusive. It wasn't until the late 1970's that two scientists, Dr. Rolf Kemler and Dr. Masatoshi Takeichi, used clever experimental approaches to identify the culprit responsible for this sticky phenomenon – a calcium-binding cell surface protein that they dubbed **cadherin**.

Takeichi, whose work with cadherin recently earned him a prestigious Canada Gairdner Award, explains: "One important way to study the function of a protein is to observe what would happen in cells or tissues when that function is blocked." Here, Takeichi used **antibodies** (molecules pro-

duced by your immune system that specifically recognize and bind to target proteins) to interfere with or "block" the ability of cells to attach to each other.

In this case, imagine proteins on the surface of cells that are responsible for being sticky. The purpose of the **inhibitory antibody** strategy, is that if an antibody binds to one of these proteins, it effectively blocks the stickiness. And if you find such an antibody, you can also use it to identify the protein. Takeichi basically used this antibody-based approach to identify cadherin.

It quickly became apparent that this was a very important discovery. "The animal body consists of multiple cell types." explains Takeichi. "Individual cells are designed to exert their function only by forming tissues or organs … for example, the heart can pump blood only as a multicellular machine, and the brain can 'think' through multicellular neuronal networks. To generate and maintain these systems, cells need to adhere to each other." With cadherin acknowledged as a cellular adhesion molecule, another important question arose – how do cells of the same type, such as heart cells or neurons, specifically recognize each other to make these tissues?



Continued research efforts using similar antibody-based strategies led to the discovery that cadherin wasn't just a single protein, but was instead a large family of related proteins. It turns out that cadherins consist of multiple types, and that each type of cadherin is produced by a particular group of cells. In this way, cells can adhere to the same type of cells, because they have identical cadherins.

For example, epithelial (or skin) cells will produce the same kind of cadherin, named E-cadherin (named after "epithelium"). Those skin cells will attach very specifically to each other because of their identical cadherin molecule, and in this way form skin tissue. This observation laid the foundation for us to understand how our tissues and organs are put together at the molecular level.

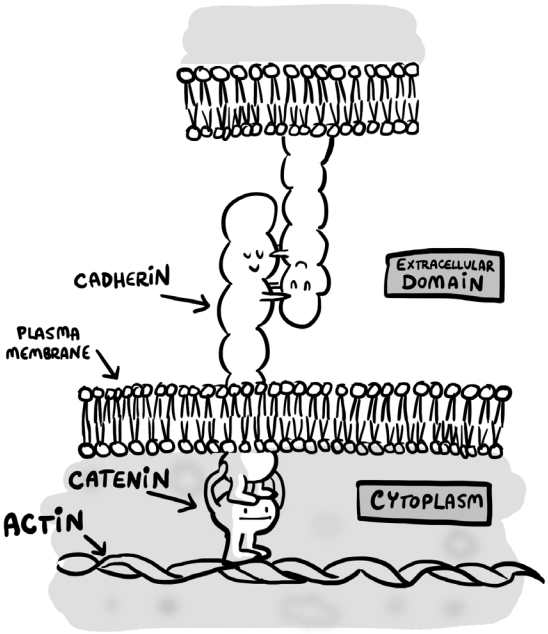
Dr. Rolf Kemler, another recipient of the Canada Gairdner Award, also played an important role in the discovery of the cadherin family. But while it was becoming increasingly clear that cadherins were crucial in the organization of tissues, it would take a few more years and the work of Kemler and his team to unravel the roles of the cadherins in **cellular communication**.

"I grew up on a farm in a little village close to the borders of the former east and west Germany," recalls Kemler. "Because domestic animals were all around, it was natural for me to study veterinary medicine." Here, Kemler developed a keen interest in biology. Eventually, Kemler's scientific interests gravitated towards tissue development and organization and after obtaining his PhD, he began studying cellular adhesion.

Like Takeichi, Kemler and his group used antibodies to seek out the cellular adhesion protein, cadherin. However, in addition to isolating a cadherin protein, Kemler and his team also identified a new protein that was often found attached to cadherins. In doing so, they had unintentionally stumbled upon another important group of proteins known as the **catenin** family. These proteins worked with cadherins to transmit signals from the surrounding environment into the cell in order to promote a biological response.

More specifically, Kemler and his team had discovered an important link between cellular adhesion and the **cytoskeleton** – the filamentous

support network found inside of cells. He explains, "We called these proteins α-catenin, β-catenin, and γ-catenin because, as we later found out, these proteins connect E-cadherin to the actin-based cytoskeletal network."



An important role of the cytoskeleton is to respond to external signals from the environment and help a cell change its shape. Essentially, Kemler's work illuminated the role of cadherins and catenins in how cells would stick together, and how this would also lead to the cells changing their shapes as needed.

These discoveries from both Takeichi, Kemler and their colleagues represented a huge advancement in our understanding of how animals develop from embryos and how organs form. When all is working as intended, groups of cadherins and catenins cooperate and guide cells to organize into multicellular organisms like human beings. However, when cadherin and catenin don't work properly, there can be devastating effects and may even lead to diseases like cancer.

One hypothesis is that the loss of cell adhesion allows a cancer cell to become free from its original tissue and therefore spread to other locations. This process is known as **metastasis**, which often results in a disease being much harder to treat. However, as Takeichi notes, the link between "cadherin or catenin mutations and metastatic behavior of cancer cells is still controversial," making it all the more important that continued study is needed to treat the disease more effectively in the future.

Still, even though we don't have all the answers right now, researchers are optimistic that we may know enough to get started. One strategy involves testing various chemicals for their ability to slow or stop the growth and spread of cancer cells, with known cadherin or catenin defects, in a laboratory setting.

The discoveries of the Canada Gairdner Award winners Masatoshi Takeichi and Rolf Kemler have fundamentally changed the way we think about how cells and tissues organize together and have also given us ideas on how to treat cancer. Their work, like many scientific breakthroughs, has generated as many new questions as it has answered. And with so many exciting questions left open, Takeichi provides a bit of advice. "Curiosity is a key motivation in conducting basic sciences. Ask yourself if you are a person who feels strong curiosity about the strange matters around you. If yes, you should consider becoming a scientist!"