Of Patterns and Cancer in Mice and Flies

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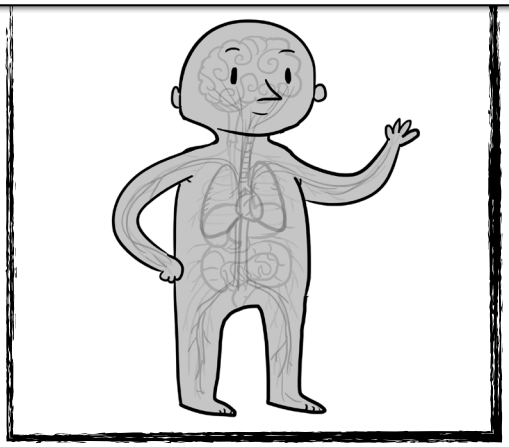
The human body has many areas of asymmetry: our spines are different than our stomachs, our feet are opposite our heads, even our thumbs demonstrate asymmetry!



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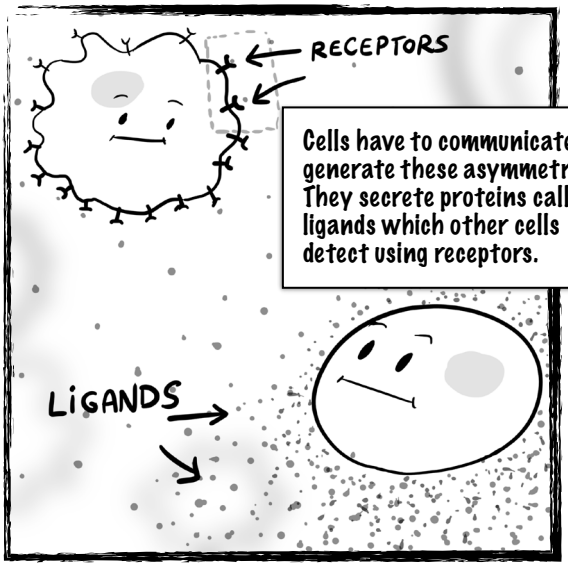

Cells have to communicate to generate these asymmetries. They secrete proteins called ligands which other cells detect using receptors.

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When specific cells send out these ligands, they create a gradient, or differing amounts of ligands in different points. These gradients begin to generate asymmetries throughout development.

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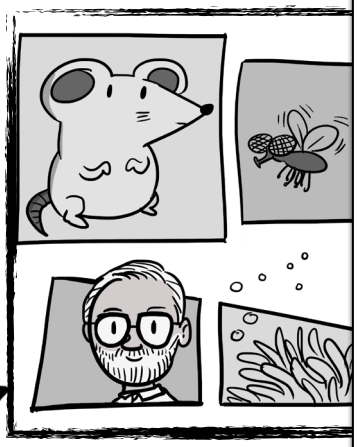

Wnt proteins are one group of ligands important for this process. Dr. Nusse first identified these in mice as contributing to cancer development. They also exist in fruit flies, where they are required for normal wing development, and as early in evolution as sea anemones!

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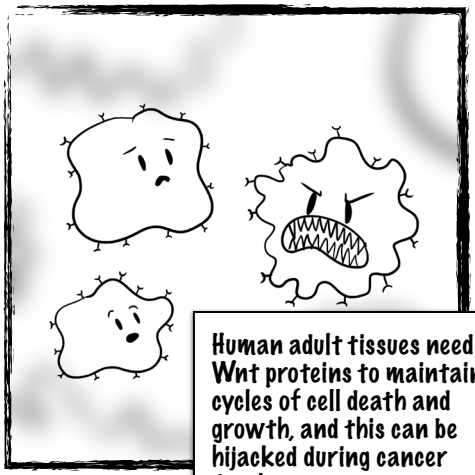

Human adult tissues need Wnt proteins to maintain cycles of cell death and growth, and this can be hijacked during cancer development.

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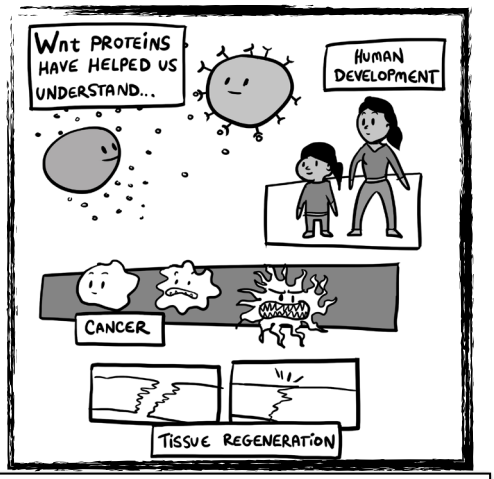

The discovery of Wnt proteins has helped scientists understand human development, cancer, and may even give us some clues about tissue regeneration!

Art by Armin Mortazavi and text by Krysta Coyle. October 2020

Of Patterns and Cancer in Mice and Flies

The connections between embryonic development and cancer - Dr. Roel Nusse's career in science

Written by Krysta Coyle
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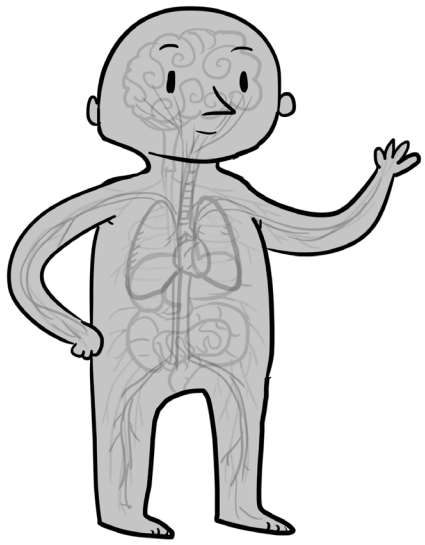
When was the last time you mistook the back of someone's head for their face? Hopefully never – because our backs are obviously very different from our fronts. The fact that we have a "front" and a "back" is because we have something called the **dorsoventral axis**. When we were just a single cell (a zygote), we developed into an embryo, and during these early steps (called **embryonic development**), there was a disruption to our symmetry. Ultimately, this change in symmetry allowed all our major organs and structures to develop in their particular places. Things in the front go in the front, and things in the back go in the back. But note that some parts of the human body remain symmetrical – for instance, your left arm and hand are likely a mirror image of your right arm and hand.

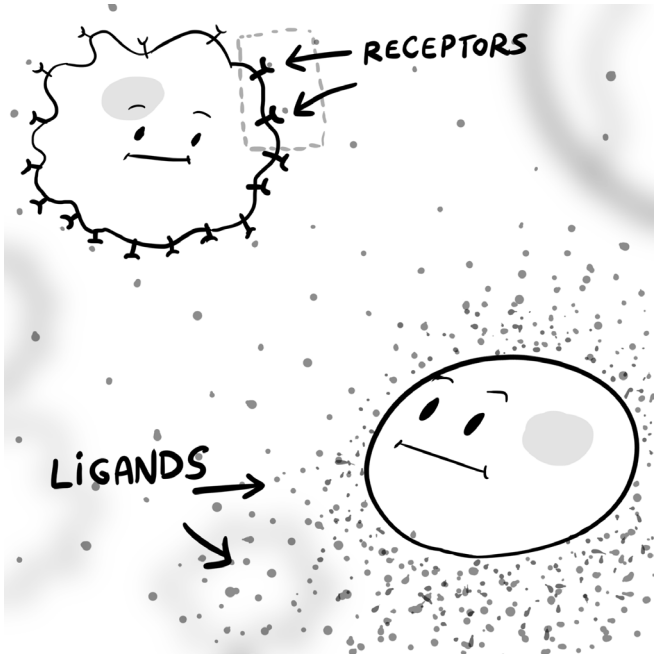


Still, there are all sorts of **asymmetries** throughout the body. The back-to-front asymmetry of the dorsoventral axis is just one example. There's also the top from the bottom, such as how our feet end up at the opposite end from our heads. And don't forget the arrangement of some of the organs inside your torso: your heart is probably on the left side of your body, and your right lung probably has one more lobe than your left lung. If you think about it – even your thumb, which only sticks out of one side of your hand, is a demonstration of asymmetry.

To generate these asymmetric axes, the cells in your body must communicate with each other. This communication is accomplished with a set of proteins, known as **ligands**, that are released from the cells into the space between them (the **extracellular space**). These ligands would then float around looking to interact with other cells who have proteins on their surface known as **receptors**. This interaction between specific ligands and specific receptors essentially allows cells to talk to each other. Think of it as a form of communication, where the cell may interpret an interaction as a signal to turn on or turn off genes. Still, how does this way of communication create asymmetry?

Imagine a cell releasing its ligand. Hopefully, you can see that the concentration of this ligand is going to be highest the closer you are to its source. Conversely, the further away you are, the less ligand there will be. This difference in the amount of ligand forms something known as a **concentration gradient**. In essence, cells can infer their relative position based on where they are located

along this gradient. This difference in the amount of ligands at one end (at one **pole**) of the axis is crucial to the process of asymmetric tissue patterning – there is a gradient that results in the back of our body being different from our front, and a different gradient in determining how our heads become different from our feet.



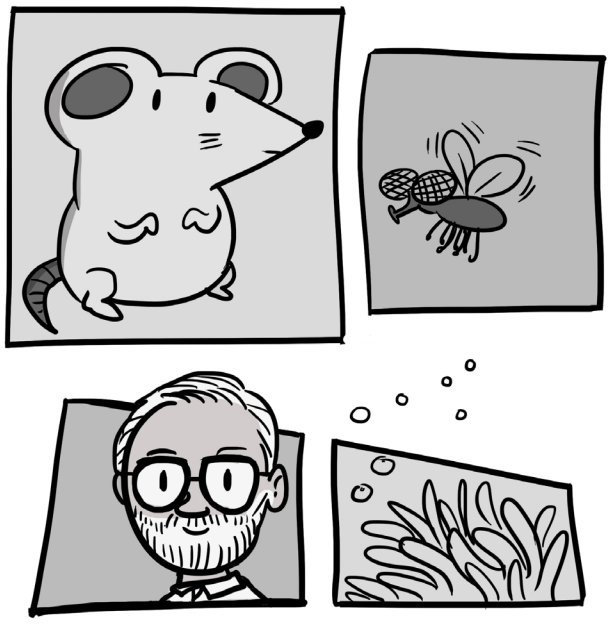
Thanks in large part to the work of Dr. Roel Nusse, we know that an important ligand-receptor in this process is involved in what is known as the **Wnt pathway** (pronounced "wint"). Furthermore, the Wnt pathway is not just crucial for asymmetry and tissue patterning, but it is also involved in the development of cancers. Dr. Nusse is a Professor at Stanford University and has been investigating Wnt signalling for many years.

Like many discoveries in science, the path from cancer to asymmetry was complicated. Initially, Dr. Nusse's PhD work in Amsterdam and postdoctoral work in California focused on understanding how a virus can cause mammary tumors in mice, with the hope of learning more about the origins of human breast cancer. Basically, Dr. Nusse asked, "How can this virus cause cancers?"

Here, he discovered that a virus could insert a copy of its DNA into the host cell. In particular, when the viral DNA is inserted near the mouse gene ***int-1***, it increased the amount of its gene product and contributed to the development of mammary tumors. This breakthrough discovery in breast cancer sparked a long scientific career linking the origins of cancer to embryonic development and to adult tissue maintenance (**homeostasis**).

Later, Dr. Nusse and his colleagues identified that the mouse *int-1* gene was **homologous**, or very closely related, to the *Drosophila* (fruit fly) gene ***wingless***. *Wingless* was aptly named because mutations in this gene could result in fruit flies not having wings. More importantly, *wingless* turned out to be involved in tissue patterning during *Drosophila* development.

With these observations, Dr. Nusse's work helped confirmed that the mechanisms of cell division and embryonic development are remarkably similar throughout the animal kingdom - not only between mice and flies, but even further back in evolutionary time, to the small freshwater hydra and the predatory sea anemones. All of these organisms have genes very similar to *int-1/wingless*, which we now refer to as Wnt. The fact that these Wnt genes are very similar (or **conserved**) between organisms, suggested that they must play important and basic roles in development, growth, and survival.



Looking more closely, humans and other vertebrates have several different Wnt genes. And Dr. Nusse has been intrigued by this gene family for decades. He reiterates, "The most interesting thing

is that the Wnt gene actually encodes a growth factor ligand that is secreted and then interacts with a receptor on another cell." These receptors (called **Frizzled**), when bound to Wnt, pass on a message to the nucleus of a cell, resulting in some genes turning off, and others turning on. Overall, this intercellular communication promotes cell division and provides guidance for tissue patterning. As Dr. Nusse states, "the Wnt pathway is instrumental in making a body plan for multicellular organisms so that we aren't just a mass of cells."

While the Wnt pathway is most important in development, there are some adult tissues that also need Wnt to maintain normal function. For example, Wnt signaling in hair follicles allows for a cycle of hair growth and hair shedding. Our bones also rely on Wnt signaling to keep the proper balance between bone formation by osteoblasts and bone resorption by osteoclasts. "This implicates a function of the Wnt gene in tissues requiring turnover of cells in a measured way."

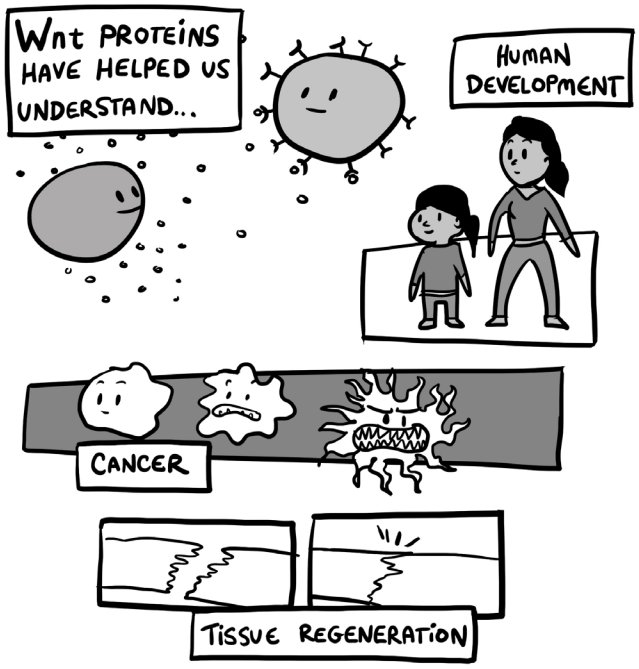
Dr. Nusse reminds us that these mechanisms in normal cells and development are often hijacked as cancer forms. Wnt ligands fundamentally signal a cell to divide, so when a mutation leads to them being inappropriately made and secreted, they can result in increased abnormal levels of cell division, which is one of the hallmark characteristics of cancer.

Dr. Nusse's research connecting a developmental pathway to cancer has laid foundations for numerous research projects around the world. Indeed, many scientists looking for human cancers with Wnt mutations, have instead found other mutations in other communication components of the Wnt pathway - in other words, mutations could exist in a myriad of other proteins that carried the message between the Wnt, Frizzled and the nucleus.

All told, many Wnt pathway genes are mutated in various forms of cancer, including colon cancer, breast cancer, leukemias, and lymphomas. These discoveries, all stemming from Dr. Nusse's work, have led to clinical trials that attempt to control Wnt signaling of tumors, with these specific mutations, to improve the survival of patients.

Sidebar: One of the quickest ways to study how a ligand like Wnt affects cell behaviour is to purify it in large amounts so it can be used in a variety of biological models and systems. Once it is purified, it can also be shared with other researchers, allowing scientific questions to be answered faster than scientists in one laboratory can do on their own. This wasn't easy for Dr. Nusse or his colleagues. Nusse recalls, "One of the most difficult things in my research was purifying the Wnt protein. It took a lot of time and effort and on many occasions, we almost gave up."

Imagine his surprise and excitement when a postdoctoral fellow in his lab succeeded! "I remember clearly, 20 years after those early attempts, when Karl Willert came up to me and showed me that he had purified the protein!" The availability of pure Wnt proteins has helped scientists investigate how they might be used to regenerate or repair damaged tissues. This triumph in the laboratory is one example of how important it is to be persistent in science.



What's next for Dr. Nusse? Currently, he's working on understanding the role Wnt signalling plays in helping repair damaged tissue. His curiosity is infectious, "As always in science, you make one discovery, and another question comes up. There are so many things we don't know that we're still working on!"