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Growing in the Right Places

The genes entrusted with organizing cells and sculpting them into the tissues that will become our fingers, hands, toes and feet can sometimes stray from their fine-tuned patterns of activity and give rise to cancer.

This insight, gleaned from the research of HHMI predoctoral fellow Lisa Goodrich and colleagues at Stanford University, began not with studies of humans with cancer but with fruit flies stricken with crippling mutations. The genes that control pattern development in flies, it turns out, bear surprising similarity to a small cache of human genes that perform the same crucial tasks, albeit on a much larger scale.

Goodrich and her colleagues tracked the interactions of the two genes in fruit flies, showing how inappropriate interactions between their human counterparts can have disastrous results. "One misstep between these two proteins and there can be catastrophic consequences, from the death of an embryo to a high risk of brain tumors," Goodrich explained.

Questions about development are a natural extension of Goodrich's abiding interest in shape, form and organization, especially in the brain. "My senior year in high school, I studied fish and was completely astonished that there could be a tiny mass of cells one morning and then a recognizable organism 24 hours later." Goodrich also knew that beneath the aesthetically pleasing cell patterns that form as organisms develop, there is an inherent fragility. "One of my sisters has Down Syndrome, and as I got older, I wanted to understand neural development and how it can go wrong."

Not surprisingly, when she arrived at Stanford in 1992 after undergraduate biology studies at Harvard, Goodrich was immediately drawn to study the underlying causes of pattern formation deficits. In humans, these kinds of developmental mistakes can result in conditions such as polydactyly (extra digits on hands or feet) or mirror-image orientation.

One way to answer how such mistakes arise is to look for genes that cause similar patterning errors in flies. Understanding the signals that create proper pattern formation in flies and other model organisms may tell researchers why polydactyly occurs in humans. Mutations in the fly *patched* gene, for example, can cause part of a body segment to be lost and replaced by a mirror-image duplicate of the part that remains. Researchers speculated that

the patched protein might have a similar role in cell signaling and the determination of cell fate in vertebrates, but its true function remained a mystery as Goodrich embarked on her studies. "No one knew what it did," said Goodrich.

For a neurosciences student new to the Stanford laboratory of HHMI investigator Matthew Scott, the search for a mammalian relative for patched was daunting. Scott encouraged her curiosity, fueled as it was by her belief that, as with many other fruit fly genes, there likely was a comparable gene in mammals.

When Goodrich began her search in 1993, only the fly *patched* gene was known, but there were hints that the patched protein might have a relationship with a signaling protein called hedgehog. A few months into her project, *hedgehog* genes were found in vertebrates, suggesting to Goodrich that the *patched* gene probably had been preserved as well.

One year after she began her search for the gene, Goodrich and her colleague Ron Johnson, a postdoctoral fellow at Stanford, found a *patched* gene in mice. With that discovery, the research possibilities suddenly blossomed. One of the first studies involved the human *patched* gene. Genetic research in fruit flies had implied that a balance between hedgehog and patched protein activities is essential for cells in a developing organism to assume their proper fates and for tissues to form correctly. Hedgehog and patched are now known to have an important role in organizing everything from the neural tube and skeleton to the limbs and skin.

Still, when Goodrich helped Johnson and University of California, San Francisco (UCSF), dermatologist Ervin Epstein to investigate how mutations in the human *patched* gene might cause disease, they were startled by the results. Patched not only played an important role in human development, as they had expected; it also prevented cancerous growth.

"Who would have thought that patched was a tumor suppressor?" Goodrich still asks with some incredulity. She and the others also showed that mutations in *patched* are responsible for an inherited disease known as basal cell nevus syndrome (BCNS), which involves rib and craniofacial deformities and extra or webbed fingers and toes.

Patched's role in polydactyly confirms the team's original hypothesis that human developmental defects can indeed be caused by the same kinds of errors that induce patterning changes in mutant flies. BCNS symptoms also include an unusually high rate of the dangerous brain tumor medulloblastoma and of skin tumors called basal cell carcinomas, the most common human cancer. Loss of *patched* function later in life, not by inheritance, also causes these tumors.

To produce an animal model of these developmental defects and tumors, Goodrich and colleagues Kay Higgins and Ljiljana Milenkovic inactivated the *patched* gene in mice. Like humans with BCNS, mice with only one working copy of *patched* are larger than normal. Sure enough, extra digits began showing up on the hind limbs of the experimental mice. But then the animals started dying suddenly. "I was surprised to find enormous brain tumors that turned out to be medulloblastomas," Goodrich said.

Moreover, mouse embryos without functional patched protein died during gestation and were found to have open and overgrown neural tubes, a clear signal that normal *patched* function is critical to the development of the brain and spinal cord.

The results of the study, with Goodrich as the lead author, were published in the August 22 *Science*, a significant achievement for the Concord, Massachusetts, native, who admits to a childhood devoid of insect collections or any great passion for science.

That is hardly the case now. Goodrich is investigating additional functions of the patched-hedgehog pathway. "It continues to amaze me that one protein is responsible for so much," she said, "and that one mistake can cause such devastating defects everywhere."

After she graduates, Goodrich will leave Scott's laboratory and her studies on patched to become a postdoctoral fellow with HHMI investigator Marc Tessier-Lavigne at UCSF. In Tessier-Lavigne's lab, Goodrich will study how neurons connect with each other to form a functional nervous system. "When I first got interested in development, I wanted to know how it all works. I still do. And I have a lot more questions to ask."