

Untangling How Body Location Promotes Cancer

Researcher Rachel Lex seeks to understand why certain regions of tissue tend to develop tumors more frequently.

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We have mutated cells throughout our bodies. But whether one of those mutated cells grows into a tumor has a lot to do with where it's located. A mutated skin cell has a different chance of turning cancerous if it's on, say, the forehead rather than the lip. But the factors that influence these location-driven probabilities have yet to be discovered.

Fred Hutchinson Cancer Center [Beronja Lab](#) postdoctoral fellow Rachel Lex, PhD, recently received a fellowship from the American Cancer Society to better understand how body location influences cancer. A better understanding of the factors that contribute to regional differences in tumor formation could point the way toward new treatments and improved prevention strategies.

"The overall question that I'm trying to answer is, why do certain regions of a tissue tend to get tumors, or cancers more frequently than other places?" Lex said.

Her three-year, \$217,500 fellowship is part of the newly created [Cancer Stem Cell Consortium](#), a [joint effort](#) between ACS and the Lisa Dean Moseley Foundation. Stem cells can renew themselves and divide more than other cells in a tissue — making them most vulnerable to cancer-causing mutations. Lex joins an interdisciplinary group of scientists working to reveal more about how cancer stem cells contribute to cancer and how they escape detection.

"I am really impressed by the clarity of Rachel's ideas, her determination and daring attitude, and look forward to the new grounds she will break during her postdoctoral training," said Fred Hutch stem cell researcher [Slobodan Beronja, PhD](#), who mentors Lex.

Chances of Cancer: Location, Location, Location

Lex will focus on skin cancer and the mutated skin stem cells that can sprout into tumors. Deep within our outer layer, skin stem cells can divide to either produce more stem cells, or the more-specialized skin cells that make up the bulk of skin tissue.

“Those stem cells are going to be responsible for replenishing our skin that’s constantly sloughed off, but they’re also the only proliferative cells in your epidermis,” Lex explained.

The ability to divide is a double-edged sword: skin stem cells are the source of skin tissue, but they are also the source of skin tumors. In healthy skin, stem cells balance divisions between self-renewal and specialization, also known as differentiation. Mutations that increase the rate at which skin stem cells divide, or tip the balance toward renewal instead of differentiation, can promote tumor formation.

But not every mutated skin stem cell will grow into a skin tumor.

“Luckily for us, the skin actually has a remarkable ability to [tolerate mutations](#) without developing cancer,” Lex explained.

When certain cancer-driving genes are expressed in skin stem cells in mouse models, the biological processes that keep tumors in check can fail at specific body sites. And in people, skin tumors are more likely to arise in certain areas of the face — despite similar levels of UV exposure and DNA damage, Lex said.

“For instance, I’m obsessive with my sunscreen, but when I occasionally get sunburnt, it’s on the bridge of my nose, my cheeks and my forehead,” Lex said. “But if you look at where skin cancers pop up, they’re actually closer to ... mucous membranes around the lips, eyelids, nose and ears.”

And the two most common kinds of skin cancers, basal cell carcinoma and squamous cell carcinoma, also favor different facial areas. Clearly it takes more than mutations to cause cancer. Beronja’s team has discovered various mechanisms that the skin — and other tissues with high cell turnover — use to keep mutated stem cells from sprouting into tumors, and Lex is exploring the regional factors that help some mutated skin stem cells overcome these hurdles.

These factors may promote cancer by tipping the balance between skin stem cell self-renewal and differentiation, she said.

“I’m focusing on those two cell fates and trying to figure out, are mutated skin stem cells increasing their proliferation, are they making more stem cells, or are they going to choose to differentiate? How is that being balanced, and how might regional factors influence these cell fate decisions to either suppress or permit tumor growth?” Lex said.

Her project will encompass factors that change across skin tissue, such as lipid composition, microbiome composition, vasculature and immune microenvironment. These factors may vary as the role that skin plays in different regions of the body also varies, Lex said. For example, skin tumors often arise in areas where one type of skin is transitioning into another, such as where cheek skin turns into mucus membrane lip skin. While the skin mostly keeps dangers out of the body, our mucus membranes must balance keeping danger out with allowing nutrients in. The immune system and microbiome, for example, could be two factors that change dramatically as the skin, and the role it plays in our health, also changes.

Lex's studies will help give scientists a much broader view of the factors that work in concert with DNA damage to cause cancer. Although her studies will focus on skin cancer, she expects that her findings may be applicable to a broader range of tumor types.

Opportunity for Collaboration

The value of her ACS fellowship goes beyond three years of research support, or the flexibility offered by independent funding, Lex said.

"What's really cool about this fellowship is that they want to create a collaborative environment for us," she said.

The Cancer Stem Cell Consortium has funded 12 senior investigators and two postdocs from around the country, including Lex, with the goal of cultivating a collaborative team that can help explore new avenues for cancer stem cell research.

"As a postdoc, this is a really unique opportunity," said Lex. "It's giving me networking opportunities and actual concrete ways that can help inspire and further drive my research."

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