New insight into the regulation of stem cells and cancer cells

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Scientists at the Gladstone Institutes have gained new insight into the delicate relationship between two proteins that, when out of balance, can prevent the normal development of stem cells in the heart and may also be important in some types of cancer.

"The news, being announced in a paper published online today in Nature Cell Biology, adds to the understanding of the role of stem cells in embryonic heart development, and how that process could be manipulated to create new heart muscle in the future. This paper also provides another example of how the same signals controlling stem cells in the embryo are those that can cause human cancers, providing new insight into treating this devastating disease."

"These findings reveal an unexpected cross-talk between two important proteins that together regulate the growth of many types of stem cells, including cardiac stem cells"," said Deepak Srivastava, MD, senior author and director of Gladstone's cardiovascular research. "More than 35,000 babies are born each year with congenital heart defects, and there are nearly 5 million adults who suffer from heart failure in the United States. We hope that our research can lead to new hope for all those impacted by these diseases."

Further, these findings underscore the value of the "basic" research—the kind in which Gladstone specializes—in which scientists focus on improving our fundamental understanding of biology. Basic research is not necessarily targeted at a specific drug target, for example, as

"applied" research often is. But basic research does often lead to breakthroughs that can significantly improve human health.

"We weren't at all focused on cancer as we created and carried out our experiments," said Chulan Kwon, PhD, who led the work at Gladstone and is now an assistant professor at Johns Hopkins University School of Medicine. "But it is gratifying that while expanding our basic knowledge of how these two proteins interact, we have increased the chances of being able to offer new solutions for those suffering from colorectal cancer."

In the paper, Dr. Srivastava and his colleagues describe how Notch and Beta-Catenin, the two proteins in question, together contribute to the regulation of cell growth and fetal development. When the protein called Notch interacted with Beta-Catenin, it results in degradation of Beta-catenin, which in turn regulates the growth of both stem cells and cancer cells. Conversely, when Notch and Beta-Catenin didn't interact, stem cells expanded out of control. Disruption of the balance of these two proteins can lead to a malformed heart during embryonic development. And in adults, over-active Beta-Catenin can promote abnormal cell growth in the intestinal wall, opening the door for colon cancer.

Dr. Srivastava, who is also a professor of pediatrics at the University of California-San Francisco (UCSF), said his group has already begun additional research meant to uncover what other proteins impact Notch and Beta-Catenin in the body. Gladstone, which is affiliated with UCSF, is a leading and independent biomedical-research organization that focuses on cardiovascular disease, neurodegenerative disease and viral infections.

"We hope that this research will lead us to new potential therapies for cancer, and towards a better understanding of heart defects in newborns," said Paul Cheng, who co-led the study and is an MD/PhD

student at the UCSF School of Medicine and who works at Gladstone.

Other scientists who participated in the research at Gladstone include Isabelle King, Peter Andersen and Vishal Nigam. Funding for the research came from a wide variety of organizations, including the American Heart Association, the National Institutes of Health, the William Younger Family Foundation, and the California Institute for Regenerative Medicine.

Dr. Srivastava is the Director of the Gladstone Institute of Cardiovascular Disease and a UCSF professor of pediatrics. His laboratory discovered the genetic basis for several types of congenital heart defects, by identifying a complex network of stem cells that work together to build the heart as it develops during gestation. He has leveraged this knowledge to reprogram adult cells directly into heart cells to re-grow damaged or nonfunctional heart tissue. Dr. Srivastava is a member of the American Academy of Arts and Sciences.

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