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GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE NEWS

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GLADSTONE SCIENTISTS IDENTIFY SINGLE microRNA THAT CONTROLS BLOOD VESSEL DEVELOPMENT *Provides potential therapeutic target for a number of diseases*

SAN FRANCISCO, CA –August 11, 2008-- Scientists from the Gladstone Institute of Cardiovascular Disease (GICD) and UCSF have identified a key regulatory factor that controls development of the human vascular system, the extensive network of arteries, veins, and capillaries that allow blood to reach all tissues and organs. The research, published in the latest issue of *Developmental Cell*, may offer clues to potential therapeutic targets for a wide variety of diseases, such as heart disease or cancer, that are impacted by or affect the vascular system.

Researchers in laboratory of GICD Director Deepak Srivastava, MD, found that microRNA (miR-126), a tiny RNA molecule, is intimately involved in the response of blood vessels to angiogenic signals. Angiogenesis, the process of vascular development, is a tightly regulated and well-studied process. A cascade of genes orchestrate a series of events leading to formation of blood vessels in an embryo.

“Some of these same gene regulatory networks are re-activated in the adult to direct the growth of new blood vessels” said Jason Fish, PhD, lead author of the study. “This can be beneficial, as in the case of a heart attack.”

Blood vessel formation can also contribute to disease in settings like cancer, where vessels feed a growing tumor.

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“Finding that a single factor regulates a large part of the angiogenic process creates a significant target for therapeutic development for any disease involving the vascular system,” said Dr. Srivastava. “The next step is to find ways to modify this microRNA in the setting of disease and test its ability to alter the disease process.”

Researchers examined cells, called endothelial cells, that line the lumen or inside of blood vessels. Once the vascular endothelial cells adopt their fate during development, they come together to form cord-like structures that are remodeled to become lumenized blood vessels. In adults, angiogenic signals, such as vascular endothelial growth factor (VEGF), activate endothelial cells and cause them to form new blood vessels. Individual microRNAs, which titrate the level of specific proteins generated by the cell, were not previously known to affect VEGF signaling or regulate angiogenesis.

The team used three model systems. First, they looked for microRNAs that were enriched in endothelial cells from mouse embryonic stem (ES) cells. They found that miR-126 was the most abundant in and most specific for endothelial cells. They next investigated the function of miR-126 in cultured human endothelial cells and found that this microRNA was involved in the structure, migration, proliferation and survival of endothelial cells. Third, they turned to the zebrafish system to investigate the in vivo function of miR-126 for three reasons. (1) It is a tractable system for perturbing microRNA levels and examining the consequences in a live organism. (2) The developing fish does not require a functioning cardiovascular system to survive through the initial stages of development. (3) The embryos are transparent and can be easily and directly visualized as they are developing. Loss of miR-126 function did not affect the initial patterning of the vascular network, but blood vessels subsequently collapsed and considerable internal bleeding occurred, illustrating the requirement of miR-126 for normal vessel formation and maintenance.

Researchers also found that miR-126 regulated endothelial responses to angiogenic signals by regulating several components of the VEGF pathway, which is important during development of blood vessels and

is required for their maintenance. miR-126 repressed the actions of the Sprouty-related protein, SPRED1, and phosphoinositol-3 kinase regulatory subunit 2 both negative regulators of VEGF signals.

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They replicated the effects of the loss of miR-126 by increasing expression of Spred1 or inhibiting VEGF signaling. Thus, miR-126 normally promotes vessel formation and stability by “repressing the repressors” of VEGF signaling. Since inhibiting VEGF signaling has been a major target of modern cancer therapies, regulating miR-126 represents an additional approach to regulate blood vessel formation in such diseases.

This work was supported in part by grants from the Lynda and Stewart Resnick Foundation, the California Institute of Regenerative Medicine, and the National Heart, Lung and Blood Institute.

About the Gladstone Institutes

The J. David Gladstone Institutes, affiliated with the University of California, San Francisco (UCSF), is dedicated to the health and welfare of humankind through research into the causes and prevention of some of the world’s most devastating diseases. Gladstone is comprised of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology and the Gladstone Institute of Neurological Disease. More information can be found at www.gladstone.ucsf.edu.

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