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Mutation causing wrong-way plumbing explains one type of blue-baby syndrome

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Total anomalous pulmonary venous connection (TAPVC), one type of "blue baby" syndrome, is a potentially deadly congenital disorder that occurs when pulmonary veins don't connect normally to the left atrium of the heart. This results in poorly oxygenated blood throughout the body, and TAPVC babies are born cyanotic - blue-colored - from lack of oxygen.

TAPVC is usually detected in newborns when babies are blue despite breathing normally. Life-threatening forms of the disorder are rare – about 1 in 15,000 live births. A closely related, but milder disorder, partial anomalous pulmonary venous connection (PAPVC), in which only some of the pulmonary veins go awry, is found in as many as 1 in 150 individuals.

Now, researchers have found that a mutation in a key molecule active during embryonic development makes the plumbing between the immature heart and lungs short-circuit, disrupting the delivery of oxygenated blood to the brain and other organs. The mutation ultimately causes blood to flow in circles from the lungs to the heart's right side and back to the lungs.

Senior author Jonathan A. Epstein, MD, chair of the Department of Cell and Developmental Biology, at the Perelman School of Medicine, University of Pennsylvania, and colleagues from The Children's Hospital of Philadelphia, describe in *Nature Medicine*, that a molecule called Semaphorin 3d (Sema3d) guides the development of endothelial cells

and is crucial for normal development of pulmonary veins. It is mutations in Sema3d that cause embryonic blood vessels to hook up in the wrong way.

Epstein is also the William Wikoff Smith professor and scientific director of the Penn Cardiovascular Institute. Karl Degenhardt, MD, PhD, assistant professor at The Children's Hospital of Philadelphia; Manvendra K. Singh, PhD, an instructor of Cell and Developmental Biology at Penn; and Haig Aghajanian, a graduate student in Cell and Molecular Biology at Penn are the co-first authors on the paper.

Physicians thought that TAPVC occurred when the precursor cells of the pulmonary vein failed to form at the proper location on the embryonic heart atrium. However, analysis of Sema3d mutant embryos showed that TAPVC occurs despite normal formation of embryonic precursor veins.

In these embryos, the maturing pulmonary venous plexus, a tangle of vessels, does not connect just with properly formed precursor veins. In the absence of the Sema3d guiding signal, endothelial tubes form in a region that is not normally full of vessels, resulting in aberrant connections. Normally, Sema3d provides a repulsive cue to endothelial cells in this area, establishing a boundary.

Sequencing of Sema3d in individuals affected with anomalous pulmonary veins identified a point mutation that adversely affects Sema3d function in humans. The mutation causes Sema3d to lose its normal ability to repel certain types of cells to be able to guide other cells to grow in the correct place. When Sema3d can't keep developing veins in their proper space, the plumbing goes haywire.

Since it's already known that semaphorins guide blood vessels and axons to grow properly, the authors surmise that Sema3d could be used for anti-angiogenesis therapies for cancer, to treat diabetic retinopathy, or to help

to grow new blood vessels to repair damaged hearts or other organs.

More information: Semaphorin 3d signaling defects are associated with anomalous pulmonary venous connections, DOI: 10.1038/nm.3185

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