

Research provides insight into development of congenital circulatory defects

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University of Pittsburgh-led researchers could provide new insight into how two common congenital circulatory problems—aortic arch deformity and arteriovenous malformations (AVMs)—develop in humans, as reported in the June 15 edition of *Developmental Biology*.

Led by Beth Roman, an assistant professor of biological sciences in Pitt's School of Arts and Sciences, the team created the first complete published description of how aortic arch vessels form and, in a separate finding also described in the paper, determined that AVMs—wherein an artery fuses with a vein and diverts blood flow—can form as a result of combined genetic and physiological factors and not solely because of genetics.

The team created the aortic arch vessel development model from zebrafish embryos, which develop similarly to humans but more rapidly. In humans, the aortic arch vessels contribute to several of the body's major arteries and often develop improperly, resulting in a wide range of vascular defects. The model could allow for a better understanding of the genetic program that governs aortic arch development, and therefore help in predicting abnormalities and determining when and how to intervene.

From the model, the team discovered that the gene *unc45a* plays a critical and previously unknown role in the formation of the aortic arch vessels—and that mutations in that gene can result in AVMs. In zebrafish harboring the mutation, two aortic arch vessels failed to

connect properly to the body's major artery, the dorsal aorta. Instead, dead-end vessels formed then swelled with blood until they touched and fused with a nearby vein.

AVMs typically form embryonically, but the particular AVMs Roman's team observed did not form in the absence of blood flow, indicating that they were not genetically hardwired, she said. Additionally, AVM formation was inconsistent in terms of location on the aortic arch vessel, Roman said. The mutants randomly developed AVMs on the side of the dead-end vessel—left, right, or both—that happened to receive blood flow first.

While AVMs in humans are generally thought to form in utero, they typically are discovered only when they cause a serious health problem later in life. AVMs can form in various organs, including the brain, lungs, spinal cord, and liver. By diverting blood, the misconnections rob parts of the body of nutrients and oxygen. The fragile fusions are prone to rupturing and hemorrhaging; a ruptured AVM in the brain can cause a stroke.

"We discover AVMs in humans when something goes wrong and we can never go back and trace the shunt's development," Roman said. "Only when we fully understand the mechanisms leading to these malformations will we be able to develop better diagnostic tests and preventative treatments to pinpoint the best time to intervene."

Source: University of Pittsburgh

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