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Scientists unlock evolutionary secret of blood vessels

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The ability to form closed systems of blood vessels is one of the hallmarks of vertebrate development. Without it, humans would be closer to invertebrates (think mollusks) in design, where blood simply washes through an open system to nourish internal organs. But vertebrates evolved closed circulation systems designed to more effectively carry blood to organs and tissues.

Precisely how that happened has remained a clouded issue. But now, a team of scientists from the California and Florida campuses of The Scripps Research Institute have shed light on the topic in a study published February 21, 2012, in the journal *Nature Communications*.

The process of building a closed circulation system is complicated biologically and, from an evolutionary perspective, time-consuming—involving billions of years. During this lengthy process, new domains (parts of a protein that can evolve and function independently of each other) have been added progressively to key molecules.

The scientists focused on one specific domain known as UNE-S. UNE-S is part of SerRS, a type of tRNA synthetase in species with closed circulatory systems; tRNA synthesases are enzymes that help charge tRNA with the right amino acid to correctly translate genetic information from DNA to proteins.

The scientists found that UNE-S is essential for proper development of an embryo, containing a specific sequence or "nuclear localization

signal" that directs SerRS to the cell nucleus. There, it affects the expression of a key regulator of new blood vessel growth.

"I think a lot happened during this evolutionary transition to a closed system and the appearance of this domain on this specific synthetase is one of them," said Xiang-Lei Yang, a Scripps Research associate professor who led the collaborative study. "Because this synthetase plays such an essential role in vascular development, it must have had a role in the transition to a closed system."

To help elucidate the role of UNE-S, the researchers turned to zebrafish as a model organism. Shuji Kishi, an assistant professor on the Scripps Florida campus who worked on the new study, noted that zebrafish have emerged over the past decade as a powerful system to study both aging and development. "Zebrafish offer a number of advantages for study because embryonic development is external to the mother and the embryos are transparent, making them an ideal model for developmental biology," he said.

To find clues to SerRS function, the team examined SerRS mutants, which are linked to abnormal blood vessel formation and defective blood circulation. In their experiments, the scientists used a variety of techniques, including crystal structure, biochemical analysis, and cell biology experiments.

Interestingly, the findings show that SerRS mutants often delete the nuclear signal or keep it hidden in an alternative conformation—like locking someone in a closet under an assumed name—rendering it ineffective. "We were astonished by what we found," said Yang. "Sequestering is a very interesting property."

The scientists were able to design a second mutation to release the sequestered nuclear signal and to restored normal blood vessel

development.

In addition to suggesting that acquisition of UNE-S has a role in the establishment of the closed circulatory systems of vertebrates, these results are the first to show an essential role for a tRNA synthetase-associated appended domain for an organism.

More information: The first authors of the study, "Unique Domain Appended to Vertebrate Trna Synthetase is Essential For Vascular Development," are Xiaoling Xu and Yi Shi of Scripps Research. Other authors include Hui-Min Zhang of Florida State University, Eric C. Swindell of The University of Texas Medical School at Houston, Alan G. Marshall of Florida State University, and Min Guo of Scripps Research.

Provided by The Scripps Research Institute