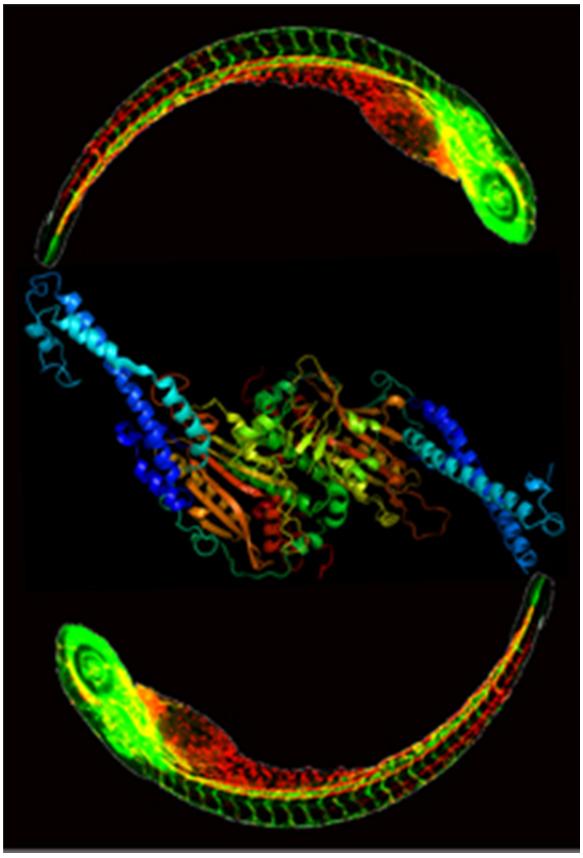
Crystal Structure and Functional Analysis Identify Evolutionary Secret of SerRS in Vascular Development

Aminoacyl-tRNA synthetases (aaRS) have been essential enzymes for protein synthesis throughout evolution. As the tree of life was ascended, tRNA synthetases added new domains, which are generally dispensable for aminoacylation, in a progressive and accretive manner. The acquisitions were timed to specific points in evolution, such as the transition from invertebrates to vertebrates. These appended domains are considered to be markers for tRNA synthetase-associated functions beyond translation (*1*). Although their appearance correlates with the increase of biological complexity in higher organisms, the functional significance of these appended domains is not understood at the organism level. This study, for the first time, establishes an essential role for an appended domain of tRNA synthetase.



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The study is focused on a unique domain appended to seryl-tRNA synthetase (SerRS) in organisms ranging from fish to humans – species that have developed closed circulatory systems not found in invertebrates. Interestingly, three independent forward-genetic studies in zebrafish showed a role for SerRS in vascular development that is independent of aminoacylation (*2-4*).

It is found that the appended domain in SerRS (UNE-S) harbors a robust nuclear localization signal (NLS) directing SerRS to the nucleus and that all of three reported vasculature-defective mutants cannot enter the nucleus. Two mutations result in the deletion of the NLS, while the third mutation, as shown by a combination of structural and biochemistry methods, masks the NLS. Based on the crystal structure of human SerRS, a second site mutation was designed to re-expose the NLS, which successfully redirected SerRS to the nucleus and removed the vascular defect *in vivo.* Thus, the essential role of SerRS in vascular development is dependent on UNE-S, whose function is to direct the synthetase to the nucleus.

The critical role for UNE-S in vascular development demonstrated in this work is the first example of an essential function for an aaRS-associated appended domain at the organism level. Given that almost all aaRS have their own distinct appended domains, this work provides motivation to discover and understand the function and significance of other tRNA synthetase domain accretions in higher organisms. This study also raised the possibility that establishment of closed circulatory systems required the coincident acquisition of UNE-S.

The crystal structure of human SerRS was determined based on data collected at Beam Line 7-1 at the Stanford Synchrotron Radiation Lightsource (SSRL).

References

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