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# Scientists reveal molecular 'yin-yang' of blood vessel growth

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Biologists at The Scripps Research Institute (TSRI) have discovered a crucial process that regulates the development of blood vessels. The finding could lead to new treatments for disorders involving abnormal blood vessel growth, including common disorders such as diabetic retinopathy and cancer.

"Essentially we've shown how the protein SerRS acts as a brake on new blood vessel growth and pairs with the growth-promoting transcription factor c-Myc to bring about proper vascular development," said TSRI Professor Xiang-Lei Yang. "They act as the yin and yang of transcriptional regulation."

Yang and her colleagues reported the new findings this week in the biology journal *eLife*.

## Multitasking Enzymes

SerRS (seryl tRNA synthetase) belongs to a family of enzymes that have fundamental, evolutionarily ancient roles in the protein-making machinery of cells. But as Yang's and other laboratories have been finding in recent years, some of these protein-maker enzymes seem to have evolved extra functions.

SerRS in particular has taken on a second basic role in animal biology. Findings from other laboratories in 2004 and 2009, mainly from genetic studies of zebrafish, first pointed to its involvement in vascular

development, also known as angiogenesis. Animals with mutations to a certain part of the SerRS gene developed abnormal blood vessel systems, accompanied by excess levels of the key blood-vessel growth factor VEGFA. The implication was that SerRS somehow is needed for the proper regulation of VEGFA.

In a report published in 2012, Yang and her laboratory analyzed the portion of the SerRS protein that appears to mediate its involvement in vascular development. They found that this part of SerRS contains a special molecular homing sequence, apparently acquired several hundred million years ago during the emergence of vertebrates. The homing sequence causes a significant fraction of SerRS proteins to be transported away from the protein-making machinery of the cytoplasm and into the cell nucleus, where SerRS performs its angiogenesis-regulating function. "In that work we were able to show that SerRS's regulation of vascular development depends on the presence of this nuclear localization sequence," Yang said.

What remained to be determined was just how SerRS proteins in the nucleus regulate VEGFA. In the new study, she and her team set out to answer that question.

## A Delicate Balance of Power

The scientists, including lead author Yi Shi, a staff scientist in the Yang Laboratory, started by confirming that a knockdown of nucleus-homing SerRS in human cells leads to a big jump in VEGFA production—consistent with nuclear SerRS's apparent role in suppressing VEGFA.

Shi, Yang and their colleagues then determined that SerRS binds to a "promoter region" of DNA near the VEGFA gene—in fact, to the same site where the transcription factor protein c-Myc, a known driver of new

vessel growth, normally binds. The scientists were able to show that SerRS essentially competes with c-Myc for binding to this promoter region.

However, they found that SerRS does more than just elbow c-Myc aside. Whereas c-Myc promotes VEGFA transcription by adding acetyl groups to the local DNA structure, opening it up and making the gene easier to reach with transcription enzymes, SerRS has the opposite effect: It gets rid of those acetyl groups so that the local DNA closes up again. In this way more than any other, SerRS suppresses the VEGFA gene transcription that c-Myc enables.

A key finding here was that SerRS achieves this deacetylation of VEGFA DNA by recruiting a partner, the deacetylase enzyme SIRT2—which had never before been linked to angiogenesis. To confirm SIRT2's role, they knocked it down in zebrafish and found virtually the same vessel overgrowth that is seen when SerRS's nuclear-homing sequence is missing.

"Clearly the balance of influences between SerRS and c-Myc on VEGFA is important for vascular development," said Shi.

## Antitumor Strategies

The new findings may end up being most relevant to antitumor strategies. SIRT2 was already considered a tumor suppressor, and c-Myc has long been known as a tumor-promoting "oncogene." A strong suggestion of this study is that SerRS, as the partner of SIRT2 in thwarting c-Myc's angiogenesis activity, may be a tumor suppressor with untapped therapeutic potential.

It may also work in that role more broadly than has been shown so far. "It has been estimated that c-Myc regulates 15 percent of human genes,

so it's important to know where else SerRS opposes its activity," said Yang. "That's a clear direction for further research."

**More information:** Paper: "tRNA synthetase counteracts c-Myc to develop functional vasculature," elifesciences.org/content/3/e02349

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