Key regulator of blood vessel formation could be a potential new target for cancer drugs

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Credit: Ryutaro Tsukata from Pexels

During formation of the vascular system, successively smaller blood vessels sprout from existing ones to form networks of capillaries in patterns uniquely adapted to the function of the organ they enter. This

process, called angiogenesis, involves complex interactions between several molecular signaling pathways, which are integrated within individual cells by various types of protein modification. Yoichi Gondo from the RIKEN BioResource Center in Tsukuba, in collaboration with a team of researchers from Canada, has now identified the molecule that regulates angiogenesis and determined its regulatory mechanism.

A research team led by Sabine Cordes of Mount Sinai Hospital in Canada discovered mutant mice exhibiting abnormal sprouting of the facial nerve and angiogenesis. Genetic analysis of the animals revealed a mutation in the 'gumby' gene (Fam105b) on chromosome 15. Gondo's team then screened RIKEN's mutant mouse library for the gene, and found nine different mutations. Cordes's group then examined two of the mouse strains in greater detail.

These gumby mice die around two thirds of the way through their three-week gestation period. The main structures of their vascular system appear normal, but the branches of blood vessels in the head and trunk are less complete than those in healthy mice.

The gumby gene encodes an enzyme that catalyzes a chemical reaction called deubiquitination. This reaction involves the removal of a small protein called ubiquitin from other protein molecules, and is one of many modifications known to alter protein function.

Further experiments revealed that the gumby protein interacts with a molecule called DVL2 to modulate the canonical Wnt signaling pathway, and with another called HOIP to remove ubiquitin molecules from the transcription factor NF-?B, thus preventing it from activating the set of genes required for angiogenesis. Using x-ray crystallography, the researchers determined the atomic structure of gumby bound to a pair of ubiquitin molecules and found that both mutations alter its three-dimensional structure, preventing it from binding to NF-?B, or from

removing ubiquitin from it.

The identification of gumby as a regulator of angiogenesis could eventually lead to new cancer drugs that prevent tumors from growing and spreading by inhibiting blood vessel formation.

Critical to the success of the study was the availability of specific mutant mouse strains at the RIKEN mutant mouse library. "Our mission is to provide mutant mouse strains for any particular target gene," says Gondo, "and we encourage researchers around the world to use our established mutant strains for screening."

More information: Rivkin, E., et al. The linear ubiquitin-specific deubiquitinase gumby regulates angiogenesis, *Nature* 498, 318–324 (2013). dx.doi.org/10.1038/nature12296

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