New discovery to aid treatment of problem infant hemangiomas: Mouse study

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Research led by the Centenary Institute and the Harvard Medical School, Boston, shows that a compound present in current beta blocker treatments could be repurposed to increase efficiency and safety of

infantile hemangioma therapies.

Infantile hemangioma, a type of birthmark that occurs when a cluster of blood vessels grows in or under a baby's skin, usually resolves on its own after a few years. However, infantile hemangiomas can cause complications such as airway or visual obstruction, cardiac failure, feeding difficulties, ulceration and disfigurement.

Propranolol and atenolol, both beta blockers, are commonly used as the mainstay treatment for infantile hemangiomas, shrinking the aberrant blood vessels but the treatment is not effective for around 20% of patients. Further, the molecular mode of action of the treatment is not fully understood by researchers.

For over 60 years propranolol has been given to humans as a beta blocker, mostly to manage blood pressure issues. Amazingly, this drug exists as a 50/50 mixture of two forms of the same molecule: the R and S enantiomers. Solely, the S-enantiomer is known to act as a beta blocker while the R-enantiomer has been considered as a by-product of chemistry synthesis with low to no biological activity.

In a new study, published in the *Journal of Clinical Investigation*, scientists discovered that R(+) enantiomers were able to inhibit infantile hemangioma blood vessels in pre-clinical models via targeting a molecular switch that is essential to gene expression of the vasculature during development. In particular, R-enantiomer blocks the activity of a protein named SOX18 which is essential to the transition from hemangioma stem cell to hemangioma endothelial cells.

The Centenary Institute's Associate Professor Mathias Francois, senior author of the study and Head of the David Richmond Laboratory for Cardiovascular Development said that they had used a combination of pre-clinical mouse models of hemangioma based on patient derived

hemangioma stem cells, together with advanced molecular imaging techniques to make their discovery. In particular the use of single molecule imaging in real time enabled the research team to firmly establish that R-enantiomer of propranolol directly engaged with the SOX18 protein.

"Approximately twenty percent of infantile hemangioma patients do not respond to current beta blocker treatments. Also, many patients suffer from beta blocker side effects including sleep disorders, bronchospasm, bradycardia, hypotension and hypoglycaemia," Associate Professor Francois said.

"We believe that R(+) enantiomers, the 'active ingredient' in beta blockers inhibiting sick blood vessels, could be further developed to increase the efficiency of infantile hemangioma treatments. Such an approach would also negate side effects resulting from current beta blocker use."

Associate Professor Francois says the finding has the potential to reposition the clinical management of this disease and will provide non-responder patients with a new therapeutic option.

The research team hope to be able to validate their findings in the clinic with hemangioma patients as a next step.

More information: Caroline T. Seebauer et al, Non-β-blocker enantiomers of propranolol and atenolol inhibit vasculogenesis in infantile hemangioma, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI151109

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