Discovery of novel mechanism for blood vessel formation suggests new vascular therapies

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An international team of researchers, including scientists at A*STAR's Institute of Medical Biology (IMB), has shed new light on how the circulatory system and blood vessels are formed in the embryo. The discovery lays the groundwork for the development of new vascular drugs and treatments. The study was reported in the life sciences journal, eLife.

Many diseases are characterised by abnormal or poor blood vessel formation. For example, chronic wounds are the result of insufficient blood vessel formation, while age-related macular degeneration is the result of abnormal expansion of blood vessels which interfere with normal processes. Blood vessel formation is also a critical step in the growth and spreading of cancerous tumours, as tumours require a dedicated blood supply to provide the nutrients for growth.

As such, discovering the underlying mechanisms of blood vessel formation is extremely critical to develop therapies targeting a wide range of illnesses, by either blocking or promoting blood vessel growth, depending on the illness.

In the embryo, blood vessels develop from cells called angioblasts, which first need to move to the correct place where the respective blood vessels will form. The aorta and cardinal vein, in particular, are the very first major vessels to be developed, so as to carry blood in and out of the

heart. Traditionally, scientists have thought that the protein Vascular Endothelial Growth Factor (VEGF) was responsible for guiding the angioblasts to the midline of the body for blood vessel formation. As such, the majority of current treatments target VEGF.

In this study, however, scientists found that VEGF is in fact dispensable for angioblast migration. Instead, angioblasts need to produce the Apelin receptor protein, which forms part of an alternate signalling pathway. The Apelin receptor protein in turn needs to be activated by two hormones, Apelin and Elabela. The team further found that Elabela alone is sufficient for the movement process. However, in cases with insufficient Elabela, the Apelin hormone may compensate for this deficiency and still allow correct development.

The role of Apelin and Elabela in establishing the circulatory system makes them potential targets in future development of therapeutic applications for illnesses ranging from the various cancers, and cardiovascular diseases, to even metabolic diseases such as diabetes. Anti-Apelin and anti-Elabela drugs could potentially inhibit the growth of new blood vessels to counter disorders such cancer and diabetic retinopathy, the leading cause of new blindness in working adults in developed countries, including Singapore.

IMB Senior Principal Investigator Dr Bruno Reversade, one of the study's authors, who also led the discovery of Elabela two years ago, stated, "I am very pleased that we have further uncovered a critical role of Elabela in the establishment of the circulatory system, following its discovery as a hormone essential for heart development in 2013. We will continue to investigate how it guides blood vessel growth, with the ultimate aim of tapping on its potential as a target to address human cardiovascular diseases."

Professor Birgit Lane, Executive Director of IMB, said, "Having

successfully identified two more hormones crucial for blood vessel formation, the team's findings have illuminated the scientific community's understanding of the formation process. Such new insight allows us to better combat the varied disorders characterised by vascular issues and paves the way for the development of more efficient and effective treatments."

More information: The hormonal peptide Elabela guides angioblasts to the midline during vasculogenesis, *eLife*, elifesciences.org/content/4/e06726

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