The unexpected role of a well-known gene in creating blood

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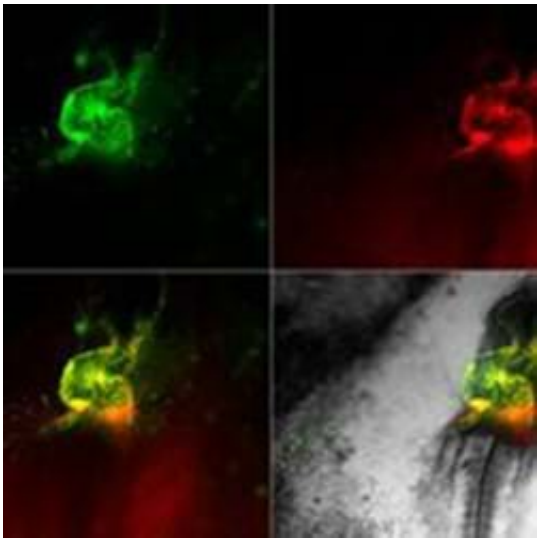

The early heart tube of a chick embryo: cardiac and endothelial cells are made visible by specifically expressing fluorescent proteins under the control of the Nkx2.5 (green) and Isl1 (red) cardiovascular genes. Credit: Weizmann Institute of Science

One of the first organ systems to form and function in the embryo is the cardiovascular system: in fact, this developmental process starts so early that scientists still have many unresolved questions on the origin of the primitive heart and blood vessels. How do the first cells – the progenitors – that are destined to become part of this system participate in shaping the developed cardiovascular system?

Dr. Lyad Zamir, a former PhD student in the lab of Prof. Eldad Tzahor in the Weizmann Institute of Science's Department of Molecular Cell Biology, developed a method to image the earliest cardiovascular progenitors and track them and their descendants through the developing embryo in real time. His movies took place in fertilized chicken eggs, in which a complex network of blood vessels forms within the yolk sac to nourish the embryo. The findings of this research were recently published in *eLife*.

Working in collaboration with the lab of Prof. Richard Harvey of the Victor Chang Cardiac Research Institute and the University of New South Wales, both in Australia, Prof. Tzahor and Dr. Zamir focused on a gene called Nkx2-5. This gene encodes a transcription factor, which is a regulatory protein that controls the expression of other genes involved in the development of the heart. "The new study revealed that Nkx2-5, independently of its role in the development of the heart, plays a central role in the genesis of the very first blood vessels and indeed the formation of blood," says Prof. Tzahor.

Looking at the onset of Nkx2-5 expression, the team revealed the existence of progenitor cells called hemangioblasts. These cells give rise to both the blood and vascular progenitor cells – those that lead to the formation of blood vessels. These unique cells are created from the mesoderm – the middle layer of cells that appears in the very early developing embryo. Researchers have been hotly debating the existence of hemangioblasts and, if they do exist, their possible function.

In the chick embryo films, the researchers could see the hemangioblasts moving to create "blood islands," which form within the primitive embryonic vessels. The researchers were surprised to observe that some of the hemangioblast cells were moving into the heart, where they formed blood stem cells. This helped make sense of other studies revealing that the early heart tube contains cells that appear to assist in

generating blood cells. The researchers also identified specialized Nkx2-5-expressing cells within the lining of the newly formed aorta, where they appeared to "bud off" to produce new blood cells. Later on in development, these specialized cells move into the liver, where they give rise to the blood-forming stem cells in the fetus.

Prof. Tzahor: "Even 20 years after one of the 'master genes' for heart development was discovered, we have managed to write a new story about its action, showing that it works briefly at a very early stage in development in the formation of vessels and blood – before the main action takes place in the heart. We have provided solid evidence for the existence of these very early cells and their contribution to heart and vascular development."

Because these findings reveal the early origins of at least some of the blood-forming stem cells in the embryo, they may be especially helpful in research into diseases affecting the cardiovascular system.

More information: Lyad Zamir et al. Nkx2.5 marks angioblasts that contribute to hemogenic endothelium of the endocardium and dorsal aorta, *eLife* (2017). DOI: 10.7554/eLife.20994

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