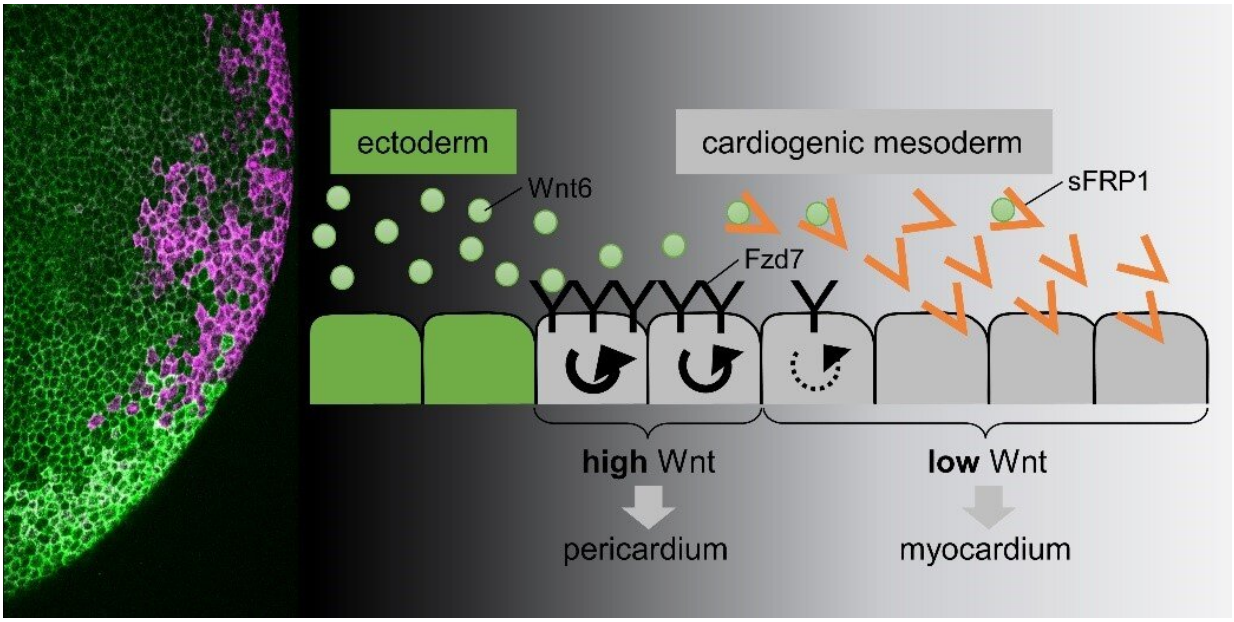
Role of morphogens in tissue patterning in heart development

August 9 2022



Wnt ligand is secreted from the epidermis (left cells). Wnt signaling is activated in a concentration-dependent manner (circular arrows), which induces Fzd7 expression and restricts Wnt ligand spreading. sFRP1 protein distribution is restricted by N-acetyl HS, which is abundant in the outer region of the cardiogenic mesoderm. Credit: *eLife* (2022). DOI: 10.7554/eLife.73818

Morphogens are molecules that travel from cell to cell in order to pattern tissues in the embryo. These molecules are important not only for the embryo during development, but also for the adult during tissue repair. However, the way these morphogens are distributed to ensure patterning

occurs is still not fully understood.

Using a combination of experiments and mathematical modeling, a research team from the University of Tokyo and their international collaborators has learned more about the role morphogens play in tissue patterning. The results are relevant to medical applications, such as drug design, and are published in the journal *eLife*.

The Wnt morphogen has emerged as a key regulator of heart development in vertebrates. These Wnt proteins are molecules that play an important role in cell development. However, it is still generally unclear to scientists exactly how Wnt regulates heart development. There are differences among the vertebrate classes, as well as redundancy in some species. However, scientists can study how Wnt regulates heart development in the Xenopus, an aquatic frog that is native to sub-Saharan Africa. The Xenopus, with its lungs and three-chamber heart, is cost-effective and useful to scientists in their study of human diseases.

In Xenopus heart development, scientists have already established that the Wnt6 morphogen is sent out by the epidermis, those outer layers of cells that make up the skin, to pattern the cardiogenic mesoderm, which is the group of cells in the embryo that will form the heart. From this patterning, a relatively thin pericardium (the membrane around the heart) and a broad myocardium (the heart's muscular tissue) develop. Scientists are still working to better understand how the Wnt6 morphogen distribution is regulated to ensure reproducible positioning of the pericardium and myocardium in the cardiogenic mesoderm.

"It is still unclear how reproducible patterning can be achieved with diffusing molecules, especially when that patterning concerns differentiation of thin tissues," said Takayoshi Yamamoto, an assistant professor at the University of Tokyo and the first author and corresponding on the paper.

Scientists do know that in early embryo development, the range of Wnt8 morphogen signaling is precisely regulated heparan sulfate and secreted Wnt binding proteins, including Frzb (which is also known as sFRP3). Heparan sulfate is a carbohydrate that is important is embryo development. Wnt signaling is one of the main processes by which tissue takes shape during the development of the embryo. The research team wondered whether mechanisms similar to those that operate in early embryos also regulate distribution of Wnt6 morphogen in the cardiogenic mesoderm.

The Wnt receptor, Frizzled7, is essential for heart development. The expression of Frizzled7 is increased by Wnt signaling in the development of the nervous system in the Xenopus and in the development of human embryonic carcinoma cells, but there are no such reports in heart development. So the research team focused their study to analyze the way Wnt signaling occurs in the development of the heart, focusing on the extracellular components—the Frizzled7 cell-surface receptor, sFRP1 (an inhibitor of Wnt6 that can also travel from cell to cell) and heparan sulfate.

"With a combination of experiments and mathematical modeling, this receptor-feedback appears essential to shape a steep gradient of Wnt signaling. In addition, computer simulation revealed that this feedback imparts robustness against variations of Wnt ligand production and allows the system to reach a steady state quickly," said Yamamoto.

Wnt6 and sFRP1 molecules not only regulate normal heart development in the embryo, but also regulate repair and regeneration after heart muscle injury, such as in the case of a myocardial infarction, or heart attack.

"Our findings will be relevant to medical applications, for example, for drug design, since cell-surface molecules such as Frizzled or a specific

modification of heparan sulfate or even the secreted molecule sFRP1, generally provide better drug targets than molecules inside cells. To reveal the precise regulation of morphogens and to consider medical applications, regulatory mechanisms of these components must be investigated further," said Yamamoto.

More information: Takayoshi Yamamoto et al, Positive feedback regulation of frizzled-7 expression robustly shapes a steep Wnt gradient in Xenopus heart development, together with sFRP1 and heparan sulfate, *eLife* (2022). DOI: 10.7554/eLife.73818

Provided by University of Tokyo