Sci-Fly study explores how lifeforms know to be the right size

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Scientists at Cincinnati Children's Hospital Medical Center report March 26 in *Nature Communications* new progress in modeling systems for studying proportional development of the *Drosophila* fruit fly. This simple life form allows researchers to build a foundation for asking the same questions in more advanced life forms, such as mammals and humans. Credit: Matt Kofron/Cincinnati Children's Hospital Medical Center

Shakespeare said "to be or not to be" is the question, and now scientists are asking how life forms grow to be the correct size with proportional body parts.

Probing deeply into genetics and biology at the earliest moments of embryonic development, researchers at Cincinnati Children's Hospital Medical Center report March 26 in *Nature Communications* they have found new clues to explain one of nature's biggest mysteries. Their data from fruit flies show the size and patterning accuracy of an embryo depend on the amount of reproductive resources mothers invest in the process before an egg leaves the ovary.

"One of the most intriguing questions in animal development is something called scaling, or the proportionality of different body parts," said Jun Ma, PhD, senior author and a scientist in the divisions of Biomedical Informatics and Developmental Biology. "Whether you have an elephant or a mouse, for some reason their organ and tissue sizes are generally proportional to the overall size of the body. We want to understand how you get this proportionality."

To tackle an age-old and very complex problem, Ma and his colleagues study fruit flies (*Drosophila*) - one of the simplest forms of animal life.

Why the fly? Ma explains this allows scientists to explore the proportional size question in a comparatively basic animal to learn fundamental principles. This produces knowledge and mathematical models that allow researchers to ask the same questions in more advanced life forms, such as mammals and humans. Ultimately, it could provide a means for helping understand the root developmental causes of certain birth defects.

The scientists start at a point when a mother fruit fly harnesses genetic and biological resources in the ovary to start forming the eggs of her future brood, and follow it through to the development of her embryos.

They combine mathematical modeling of the phenomenon with testing in the lab in search of a complete picture. The process requires a large number of experimental measurements and a well-stocked fly room.

In their current study, Ma and colleagues develop a model that allows them to measure and mathematically link core pieces of this developmental picture. They call it TEMS, which means Tissue Expansion-Modulated Maternal Morphogen Scaling. A morphogen is a protein that forms a concentration gradient along a developing axis of an embryo (for example from anterior to posterior) and instructs genes to make their products in specific parts of the embryo. These gene products will control the formation of an animal's various body parts.

In the fruit fly, a gene called bicoid produces a morphogen gradient and helps run the show. Proportional sizing in fly embryos can occur either before, during, or after all cells have started to pattern into specific tissues or organs. The *Nature Communications* paper looks at the embryo's proportional scaling front to back, which occurs before individual organs start to form.

The scientists report that the size of fruit fly embryos depends on the quantity of initial tissue expansion in the mother's ovary - specifically the growth and size of the ovarian egg chamber and the expansion of bicoid gene copy numbers. This helps decide how large the mother fly's 15 ovarian nurse cells will become, and how many duplicate copies of the fly's genome and mRNA cells will contain. This trove of developmental resources all gets transferred to the oocyte that will become the future egg.

The TEMS model lets researchers quantify the overall size of the mother fly's biological investment in this process. It also helps predict how that investment will determine the strength and robustness of the bicoid morphogen gradient that controls the proportion of body parts for her offspring. In short, a larger investment means a bigger return in the form of larger embryos that form well-proportioned body parts.

When calculating the peak numbers of bicoid gene copies in the mother fly's nurse cells, the scientists were intrigued by how these numbers resemble the peak number of cell nuclei in the offspring blastoderm (an early stage embryo). This finding leaves the researchers with new questions to unravel, such as its fundamental meaning, and how much the relationship between a mother's biological investment and the way her embryos develop is impacted by the larger principles of evolution.

In the end, Ma and his colleagues said they want to develop unified system-level views for understanding, quantifying and predicting how life forms come about the way they do. Their goal is that this new knowledge can eventually be applied to benefit people, both large and small.

Provided by Cincinnati Children's Hospital Medical Center

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