Scientists trace molecular origin of proportional development

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When it comes to embryo formation in the lowly fruit fly, a little molecular messiness actually leads to enhanced developmental precision, according to a study in the Oct. 14 *Developmental Cell* from Cincinnati Children's Hospital Medical Center.

While the fundamentals of this tiny bug's reproductive biology may seem insignificant, one day they could matter quite a bit to humans. That's because the study provides new information about how cells choose their own fates, especially in maintaining the size relationship and proportionality of body parts during embryonic development, said Jun Ma, Ph.D., a researcher in the divisions of Biomedical Informatics and Developmental Biology at Cincinnati Children's and the study's corresponding author.

"We used the fruit fly in our study to trace the molecular origin of where body proportionality comes from, directly affecting how we think about precision control mechanisms during development," Dr. Ma said. "This new information is a basic, but very important, step. Although humans are far more complex, this could one day help us understand how two different-sized babies – with different mothers providing varied environmental and genetic influences – are born alike, with properly sized heads and limbs."

Besides discovering a scientific platform that will advance studies into precise, or normal, development, Dr. Ma and colleagues hope their knowledge will facilitate research into abnormal development, like certain types of birth defects.

Although fruit flies have miniscule brains and dine on rotten fruit, genetically the species has quite a bit in common with humans – a concept known as evolutionary conservation. This relationship has long made the insect a model for studying body patterning in animals.

Dr. Ma's team probed how a gene transcription regulatory protein called Bicoid turns on another gene, known as Hunchback. Hunchback instructs the embryo's anterior to begin formation of proportional body parts in the fruit fly's head and thoracic regions. Hunchback is switched on in the anterior half of the embryo, where the level of Bicoid is high. In normal (wild-type) embryos, the process begins when Bicoid diffuses from the anterior toward the posterior end, a principal already established in existing research literature. Bicoid, which comes from the mother, then forms a gradient along this body axis.

Dr. Ma and his colleagues discovered the amount of Bicoid in early embryos depends on the size of the egg. Larger embryos in the study showed higher Bicoid levels in the anterior region, while smaller embryos showed lower levels. This relationship between embryo size and Bicoid amount helps Bicoid establish a gradient scaled precisely according to each embryo's length, which is necessary for Hunchback to respond precisely, they said.

One area of messiness in the system is that the precision levels of Bicoid and Hunchback are different. The research team reported that imaging analyses of 28 wild-type embryos showed even a precise Bicoid gradient still has positional errors that go beyond the boundaries set up by its target Hunchback. Dr. Ma's team suggests that Bicoid can self correct its positional errors through a coupling that develops between Bicoid's forming gradient and the protein's activation of target genes. The correction essentially fine tunes the mechanism to achieve further developmental precision.

Other studies have suggested Bicoid level differences among individual embryos play little or no role in the precision of fruit fly embryo development. Bicoid gradient, they say, is inherently so precise at switching on its target genes that it approaches the limits set by basic physical principles. While offering important new insights into how Bicoid establishes a precise gradient along the embryo's length, Dr. Ma said the previous research also begged the questions: What then makes the Bicoid gradient so precise, or is it really so precise?

"Instead of discounting the variability of the Bicoid gradient among different embryos, we found this noise to be an advantage of the system," said Dr. Ma, also a professor of pediatrics at the University of Cincinnati College of Medicine. "The amount of Bicoid going to small and large embryos all self corrects, so the system is built to be very robust and precise so different cells can be told to become part of the head, or part of something else, in a proportionate manner."

Besides conducting staining and imaging tests on normal wild-type embryos to test their hypothesis, Dr.Ma's team also studied Bicoid and Hunchback expression in embryos from genetically altered, mutant (staufen) female fruit flies. They found Bicoid could not form a precise and scaled gradient in embryos from these mutant females, which, they concluded, contributed to additional Hunchback variations and disproportionate development.

Source: Cincinnati Children's Hospital Medical Center