Long-held genetic theory doesn't quite make the grade, biologists find

April 26 2012

New York University biologists have discovered new mechanisms that control how proteins are expressed in different regions of embryos, while also shedding additional insight into how physical traits are arranged in body plans. Their findings, which appear in the journal *Cell*, call for reconsideration of a decades-old biological theory.

The researchers investigated a specific theory—morphogen theory, which posits that proteins controlling traits are arranged as gradients, with different amounts of proteins activating genes to create specified physical features. This theory was first put forth in the 1950s by mathematician and World War II code breaker Alan Turing and refined in the 1960s by Lewis Wolpert. It has been used to explain why a tiger has stripes, among other phenomena.

But some biologists have raised questions about the theory, which contends that physical features are necessarily tied to absolute concentrations of proteins within the morphogen gradient. If a certain critical mass of protein is present, then a given physical feature—for example, cells that make the skin on your forehead—will appear. If less than that critical mass is present, a different structure—say, the skin that makes your eyebrows—will appear, and a boundary will be formed between the two structures.

But alternative views have suggested that physical features are not necessarily the result of a specified number of proteins, but, rather, come from more complex interactions between multiple gradients that

work against one another.

The NYU biologists explored this process by studying the fruit fly Drosophila, a powerful model for studying genetic development as it is amenable to precise genetic manipulations. They focused on one protein, Bicoid (Bcd), which is expressed in a gradient with highest levels at the end of the embryo that will become the mature fly's head.

The researchers, headed by Stephen Small, chair of NYU's Department of Biology, examined a large number of target genes that are directly activated by Bcd. Each target gene is expressed in a region of the embryo with a boundary that corresponds to a specific structure.

By examining DNA sequences associated with these target genes, the NYU researchers discovered binding sites for three other proteins—Runt, Capicua, and Kruppel—which all act as repressors. All three proteins are expressed in gradients with highest levels in the middle part of the embryo, and thus are positioned in exactly the opposite orientation compared to the Bcd activation gradient.

By changing the spatial distribution of the repressors and by manipulating their binding sites, Small and his colleagues showed that these repressors antagonize Bcd-dependent activation and are absolutely critical for establishing the correct order of boundaries that are found in a normal embryo.

In other words, contrary to Turing's theory, a single gradient of proteins does not have sufficient power to form the same body plan in each member of a species; however, if there are multiple gradients that work against each other, then the system becomes robust enough for normal development.

While the results raise questions about morphogen theory, the

researchers explained that their findings did not "falsify" it, but, rather, suggested it needed some additional refinement.

Provided by New York University