Molecular Characterization of Vertebrate Neurulation

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All animal structures are created by a series of complex cellular interactions. One process critical for the formation and differentiation of tissues and organs, in virtually all organisms, is embryonic closure. In humans, for example, failure of neural groove closure leads to debilitating and often lethal birth defects. Neural tube defects affect ~40,000 neonates/year in the United States. Unfortunately, it is difficult at best to manipulate human systems for research purposes to better understand molecular mechanisms of neural tube defects. One solution to this problem is to supplement human studies with parallel studies in model organisms, such as the fruit fly and the chicken.

The process of dorsal closure in the fruit fly, Drosophila melanogaster, is similar to several vertebrate closure processes, including neurulation. Drosophila embryos undergo dorsal closure midway through the 24-hour period of embryogenesis. During closure, lateral epidermal cells elongate along the dorsoventral axis and subsequently spread dorsally to cover the embryonic dorsal surface. Closure is complete when the edges of the epidermal sheets interdigitate and suture at the dorsal midline. Thus, although dorsal closure in Drosophila does not generate the nervous system, as does neurulation in vertebrates, the two processes share highly conserved morphogenetic movements, most notable of which is the spreading of the epidermis. This epidermal spreading is the chief factor in vertebrates that drives closure of the neural groove to form the neural tube.

During the process of dorsal closure in Drosophila, mutants die during embryogenesis and exhibit a single, large hole in the dorsal cuticle. This distinctive trait has led to the identification of numerous loci required for closure. With the information acquired from closure studies in Drosophila we propose to molecularly dissect the process of neurulation in vertebrates. In particular, we are testing the idea that the genes controlling neural groove closure in chick correspond to the Drosophila genes required for dorsal closure.

Our immediate objective is to define molecular mechanisms of neurulation in the chick. In the long-term, we expect that our chick studies will lay the groundwork for defining biological pathways of neurulation in all vertebrates, including humans. From the perspective of human developmental abnormalities, our research is expected to lead to the identification of genes which when disrupted lead to the debilitating neural tube defects that affect 0.1% of all live births.