

Abstract

Vertebrate development depends on precise proliferation, migration and specification of cells to generate distinct and complex parts of an organism. Failure in any of these processes can cause defects such as organ failure, neurological syndromes or death of the embryo. Despite the importance of these processes, their pathways and regulators are not completely understood. This project will address this disparity by characterizing Toddler, a novel, highly conserved secreted peptide involved in embryogenesis and required for proper migration of the endodermal and mesodermal germ layers during gastrulation in zebrafish. Previous work in the lab demonstrated that Toddler regulates cell migration, though the change in cellular behavior and molecular mechanism stimulated by Toddler is not known. This work will test the hypothesis that Toddler is required for cell internalization during gastrulation (Aim 1) due to its regulation of E-cadherin (Aim 2) and partially overlaps in function with the known secreted peptide Apelin (Aim 3). First, genetic engineering and microscopy analysis will be used to label and track Toddler-responsive cells during development to identify the specific cellular behavior affected by Toddler signaling. Next, this work will use Western blotting, immunohistochemistry and epistatic analysis to analyze how Toddler regulates E-cadherin, an adhesion molecule known to be active during early development. Finally, this work will examine Toddler's relationship with Apelin, a conserved peptide active in development that, like Toddler, signals through the Apelin Receptors A and B. It is likely that the Toddler and Apelin pathways are partially overlapping, but the degree and requirement for this is unclear. This relationship will be assessed by generation of an *apelin* mutant followed by single and double mutant analysis including cell tracking and comparisons of morphology and reporter gene expression. As a result, this study will increase our knowledge of cell migration during development thereby enhancing our understanding of how organisms transition from single cells to complex systems. Such knowledge will aid in our ability to understand and address development related diseases. Additionally, the peptide Apelin is known to be involved in cardiovascular development and is currently being tested as a therapeutic in humans and the work carried out in this project may reveal Toddler to be a similarly promising drug target.