Abstract

The teleost fin development involves the reorganization of cell morphology and cell adhesions, cell migration and the formation of a complex extracellular matrix (ECM). Thus, the study of the mechanisms involved and of the interaction between essential components contributing to the formation of this structure will contribute to understand other similar processes, such as the development of the limb buds. In the first part of my thesis, I have analyzed the requirements for the migration of fin mesenchymal cells (FMCs) that will invade the developing subepidermal space of the fin fold and constitute the fin mesenchyme. The interaction between the FMCs and the ECM is a requirement for the migration of these cells. I found that fibronectin (FN), an ECM protein, is present at the base of the fin fold, and I speculate that FN anchors the FMCs at basal positions. I have observed that FMCs express different ECM receptors during their migration. During migration, FMCs switch the expression of Arg-Gly-Asp (RGD)-binding integrins to integrins binding to different components of the ECM. A change from Itgα5β1 to Itgαvβ3 mediated adhesion allows the cells to acquire a more motile phenotype. The interaction with the fin fold collagen fibers is known to be required for the migration of these cells. Here, by inhibiting the interaction between FMCs and collagen, I have observed that the adherence to the collagen fibers is required for proper orientation of membrane protrusions, which may contribute for the directional migration of these cells. Based on my observations I propose a model for the control of the migration of FMCs, which requires active sensing and modification of the substrate by the organization of ECM-cell adhesion complexes and the secretion of ECM components by FMCs.

In the second part of my thesis, I have studied the role of the epidermal-dermal junction in the development and maintenance of the fin fold. The epidermis is separated from the underlying dermis by a basement membrane (BM). Constitutive BM components include Laminins and Collagen IV, which form two independent networks and are cross-linked by Nidogens and Perlecan. Disruption of the epidermal-BM junction leads to a loss of epidermal integrity, while disruption of the BM-dermal junction causes blistering of the skin, a phenotype observed in *hemicentin1* (*hmcn1)* zebrafish mutants. Little is known about Hmcn1 function and interaction

partners. Recent studies in our laboratory have revealed nidogens as novel binding partners of Hmcn1 *in vitro*. I have studied the role of Nidogen2a (Nid2a) in fin development. Nid2a regulates epidermal integrity, and the knockdown of this gene results in degeneration of the fin fold, mislocalization of Laminin and E-cadherin, and reduced epidermal cell-cell adhesiveness. Moreover, I have validated a functional interaction between Nid2a and Hmcn1 *in vivo* using a morpholino-mediated knockdown approach. Moderately reduced levels of Nid2a or Hmcn1 alone do not result in a morphological phenotype. However, a moderate reduction of both genes simultaneously causes the degeneration of the caudal fin fold and detachment between epidermis and dermis. Taken together, my results prove *in vivo* that the role of the interaction between Hmcn1 and Nid2a is important in the maintenance of the homeostasis of the epidermal-dermal junction.