THE BASAL LAMINA IN EPITHELIAL-MESENCHYMAL MORPHOGENETIC INTERACTIONS.
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The generation of structural form of several embryonic epithelial organs, such as the lung, kidney, mammary and salivary glands, occurs by a common sequence. Each organ arises as a rounded bud consisting of a layer of epithelial cells, and during development, the bud undergoes a distinctive sequence of folding and branching which results in a morphology that is characteristic of the organ. The epithelia are surrounded by a highly cellular loose connective tissue, or mesenchyme, which is absolutely required for the morphogenesis. Between the epithelium and mesenchyme lie amorphous materials, fibrillar collagen and a well-defined basal lamina.

With mouse embryonic salivary glands, the mesenchyme, amorphous materials and fibrillar collagen can be removed by microdissection in collagenase, yielding epithelia which retain the basal lamina. Such epithelia maintain normal multi-lobular morphology, but require recombination with mesenchyme for continued branching morphogenesis. The lamina can be completely removed by brief treatment with nanogram amounts of testicular hyaluronidase. Such treatment causes the cells to round up and results in disruption of cellular adhesions, disorganization of cytoskeletal structures and, when the epithelium is recombined with mesenchyme, the loss of multi-lobular morphology. These observations suggest that the basal lamina is required for maintenance of normal morphology. However, delaying recombination with mesenchyme for 2 hrs, during which the epithelium replaces the lamina, reverses the alterations and prevents the loss of morphology. Thus the mesenchyme may have a property which is deleterious to epithelial recovery from hyaluronidase, but is normally involved in morphogenesis.

The lamina contains glycosaminoglycan (GAG) and labeling studies show that ca. half of the labeled GAG is hyaluronic acid, chondroitin-4- is twice chondroitin-6-sulfate and chondroitin is in trace amounts. Ultrastructural studies using tannic acid fixation and ruthenium red staining reveal the lamina to be composed of components in ordered periodic arrays intimately associated with the plasmalemma. The basal lamina may consist, in part, of supramolecular complexes of hyaluronic acid and proteoglycan which are

organized into an extracellular scaffolding that imposes structural form on the epithelium.

In intact glands, the GAG in the basal lamina is rapidly turning over. Laminar GAG is lost more rapidly at the distal ends of the lobules, the sites of greatest cell proliferation and change in cell shape, and less rapidly within the interlobular clefts. This differential rate of loss results in more GAG accumulating within the clefts and less on the lobules. The pattern of GAG metabolism is not secondary to lobular growth, nor is it altered by inhibition of cell proliferation or by inhibitors of collagen secretion or cross-linking. A similar pattern is seen during the branching morphogenesis of several embryonic epithelia, consistently reflecting the morphologic changes characteristic of each organ, but is not observed on unbranched epithelia. Thus, differential laminar GAG turnover is associated with branching morphogenesis.

The pattern of laminar GAG metabolism occurs only in the presence of mesenchyme. The mesenchyme is not involved in the synthesis, deposition or organization of the lamina, but culture in combination with mesenchyme causes a loss of GAG from the epithelium. The mesenchyme possesses activity which removes laminar GAG, producing a heterogeneous mixture of small molecular weight components. The activity requires living mesenchymal cells and is not duplicated by medium conditioned by mesenchyme. The mesenchyme, therefore, is responsible for the degradation involved in the differential turnover of laminar GAG.

Since embryonic salivary epithelia require a GAG-rich basal lamina to maintain morphology, and require mesenchyme for continued branching morphogenesis, it is likely that the effect of the mesenchyme on GAG within the lamina is involved in the changes in epithelial morphology which occur during development.