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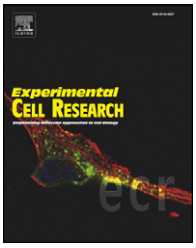

Review Article

Intestinal development and differentiation☆

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ABSTRACT

In this review, we present an overview of intestinal development and cellular differentiation of the intestinal epithelium. The review is separated into two sections: Section one summarizes organogenesis of the small and large intestines, including endoderm and gut tube formation in early embryogenesis, villus morphogenesis, and crypt formation. Section two reviews cell fate specification and differentiation of each cell type within the intestinal epithelium. Growth factor and transcriptional networks that regulate these developmental processes are summarized.

Contents

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Organogenesis of the small and large intestines

Endoderm specification, tubulogenesis and patterning

The intestinal epithelium develops from the embryonic endoderm, which is one of the three primary germ layers derived during gastrulation. The endoderm is derived from transient intermediate cells termed mesendoderm which, in mammals, are specified to the endoderm fate as they ingress through the primitive streak (reviewed by Zorn and Wells [1]). Exposure of ingressing cells to the TGF-β related growth factor Nodal is essential for determining endodermal fate. This nascent endoderm bears a molecular signature of early anterior–posterior (A–P) patterning and thus distinct organ fate. Timing and level of exposure to growth factors are important for specifying this A–P patterning. For example, high Nodal exposure promotes expression of *Hhex* and anterior endodermal fate [2]. At the end of gastrulation, the endoderm exists as a layer of cells which is patterned by expression of regional determination factors, such as Sox2 and Hhex in the anterior endoderm and Cdx2 in the posterior endoderm (Fig. 1). This posterior endoderm will give rise to the small and large intestines. The cellular movements that occur during endoderm formation and patterning are well described, however the molecular cues that specify distinct endodermal regions remain largely undefined, and are an area of active investigation.

Following induction and molecular patterning, the endoderm undergoes extensive folding to generate the embryonic gut tube. While the process of tubulogenesis remains poorly understood, it is believed to involve interaction with the mesoderm, since the completed endodermal gut tube is surrounded by a mesodermal layer which connects the gut tube to the body wall. Endodermal tubulogenesis is initiated by indentation at the anterior and posterior ends of the embryo to form pockets, termed the anterior intestinal portal (AIP) and caudal intestinal portal (CIP; Fig. 1). As the AIP and CIP grow and become deeper, the lateral midgut endoderm folds ventrally to complete tubulogenesis; this coincides with turning of the embryo at embryonic day 9 (e9.0) in mice (Reviewed by Lewis and Tam [3]).

Intestinal epithelial reorganization, villus morphogenesis and intervillus zone establishment

After the gut tube is fully formed, the simple epithelium condenses to form a pseudostratified epithelium with nuclei that appear at various levels within the apicobasal axis and all the cells attached to the basement membrane (e9.0–9.5). From e9.5 to e13.5, the gut tube lengthens and the circumference increases due to the expansion of the mesenchyme, epithelium and the lumen. As the gut tube expands in length and girth, the epithelium is thought to transition into a stratified epithelium with apical cells tightly connected by junctional complexes and loosely connected basal cells [4], although emerging evidence suggests that this transient stratification of the epithelium may not occur [5]. Around e14, the epithelium reorganizes to a columnar form coincident with the emergence of villi and initiation of cytodifferentiation. Secondary lumina (also called intraepithelial cavities) start to form within the stratified epithelium with the appearance of nascent junctional complexes connecting the cells that line secondary lumina. The junctional complexes extend to neighboring cells which expand the secondary lumina in size until they fuse with the primary lumen [6,7]. At the same time, mesenchymal cells condense under the epithelium and grow toward the central lumen to form nascent villi covered by columnar epithelium (Fig. 1). Mechanisms that initiate and control epithelial reorganization and villus morphogenesis are not well known, although crosstalk between the gut epithelium and the mesenchyme has been shown to provide both permissive and instructive cues to allow the normal development of the intestine [8]. Signaling pathways involved in this epithelial–mesenchymal crosstalk include BMP, Hedgehog, PDGF, TGF-β, and Wnt pathways which are reviewed in more detail elsewhere [8,9]. In the current model, Hedgehog and PDGF signals from the intestinal endoderm are received by the adjacent mesenchyme and regulate differentiation of the myofibroblast and smooth muscle cells [10,11]. These signals are essential for positioning and outgrowth of the nascent villi, and are interpreted in the mesenchyme by a transcription factor cascade including FoxL1, FoxF1, and FoxF2 [12,13], which regulates production of Wnt and BMP signals by the mesenchyme. Wnt and BMP signals are received by the epithelium to regulate differentiation and proliferation of the nascent intestinal progenitor and stem cells [14–17]. Crosstalk between the epithelium and mesenchyme includes several additional pathways, working in parallel and together, with multiple levels of feedback regulation.

During intestinal epithelial reorganization and villus emergence, proliferating cells are scattered throughout the endoderm. As the villi emerge (e15 in mice), proliferation is observed throughout the epithelium, but becomes progressively less prevalent on the villus epithelium such that by e17, proliferating cells are confined