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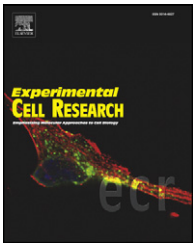

Review Article

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

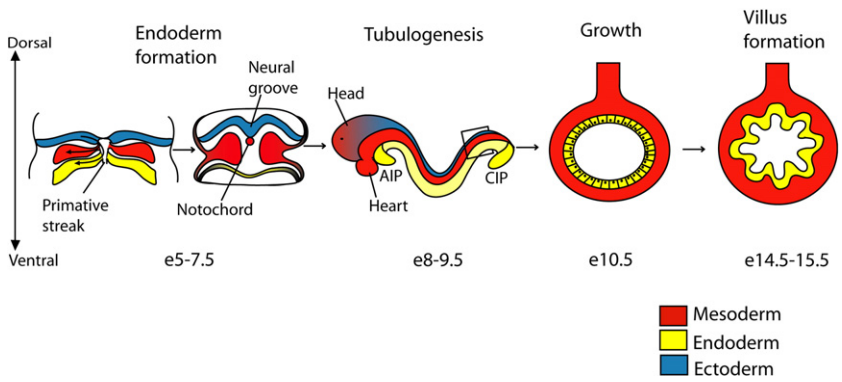

Fig. 1 – Early development of the intestine. Endoderm formation is first detected during gastrulation which, in mice, occurs from e5 to e7.5 and is shown at left in the medial to lateral plane. Cells in the transient mesendoderm state, but not ectoderm, migrate through the primitive streak and form either mesoderm or endoderm with anterior–posterior patterning depending on timing and level of exposure to Nodal. After gastrulation, the endoderm can be seen as a simple epithelial sheet underlying the mesoderm (ventral to the notochord and lateral plate mesoderm). Endodermal tubulogenesis occurs in mice from about e8 through e9.5 and is shown along the anterior–posterior axis. After formation of the endodermal sheet, the anterior and posterior ends indent and subsequently form pockets, termed the anterior intestinal portal (AIP) and caudal intestinal portal (CIP). The AIP (giving rise to foregut) and CIP (giving rise to hindgut) grow and extend deeper while the lateral midgut endoderm (not pictured, out of the plane of the image) folds ventrally to complete the tube. Splanchnic mesoderm from the lateral plate surrounds the folding endoderm during this tubulogenesis stage to enclose the gut tube and connect it to the dorsal body wall. The images at right labeled Growth and Villus formation are shown as medial to lateral cross sections of the endoderm tube. At e10.5 the intestinal endoderm is seen as a compact pseudostratified epithelium; over the next 3 days the tube lengthens and widens. Villus formation initiates in a rostral to caudal wave at approximately e14.5, as clusters of mesenchymal cells form below the epithelium and extend toward the center of the lumen, creating villi.

in the intervillus region. The Wnt/β-catenin pathway, which is well established to regulate proliferation and stem cell maintenance in the adult intestinal epithelium, is also implicated in intervillus zone establishment. In the developing intestine deletion of Tcf4, a DNA binding partner of β-catenin, had no effect on villus emergence, but instead prevented proliferation leading to fewer intervillus cells and villi [15]. Although Tcf4 is expressed in intervillus cells after villus morphogenesis (e16.5), subsequent studies have reported that canonical Wnt activity is restricted to the embryonic villus [17]. Kim et al. proposed that Tcf3, which is expressed in the embryonic villus, is the key β-catenin partner in the developing intestine and that Tcf4 regulation of proliferation is independent of canonical Wnt activity [17]. Further studies are required to delineate the role of the canonical Wnt signaling pathway in intervillus zone establishment.

Crypt development and establishment of intestinal stem cells

In mice, intestinal development continues into the postnatal period and completes by the time of weaning. Crypts of Lieberkuhn, which contain all stem and proliferating cells in the mature intestinal epithelium, emerge from the intervillus epithelium. In the current model, anchorage of precursor stem cells to the site of nascent crypts initiates crypt development, which develops by the upward movement of the crypt-villus junction (driven by mesenchymal cell movement) rather than the downward migration of the intervillus epithelium [18]. Both Wnt and BMP signaling pathways are implicated in crypt formation. Ectopic expression of the BMP inhibitor, Noggin, in the embryonic intestinal epithelium lead to the abnormal formation of crypts in the villi perpendicular to the crypt-villus axis [17,19]. Although there is insufficient direct evidence that links the Wnt signaling pathway to crypt development, its role has been suggested because its downstream targets such as EphB and c-Myc are implicated in this process [20,21]. EphrinB–EphB signaling is essential for controlling the polarized migration of cells within the crypt; loss of EphB2 and EphB3 causes migration of Paneth cells onto the villus [20]. Loss of c-Myc delays the formation of crypts during the early postnatal period [21].

Differentiation of the intestinal epithelium

Overview of cell types in the intestinal epithelium

Post mitotic differentiated cells in the intestine are classified into two groups (absorptive and secretory) based on their distinct functions and genetic differentiation programs. One type of absorptive cell (enterocyte) and four types of secretory cells (goblet, Paneth, enteroendocrine and tuft cells) comprise the small intestinal epithelium (Fig. 2). In the large intestine, Paneth cells are absent and the absorptive cells are termed colonocytes. In both small and large intestine, all post mitotic differentiated cells are derived from stem cells that reside near the base of the crypts. Two additional cell types, cup cells and M cells, have yet to be definitively assigned to the absorptive or secretory class of epithelial cells [22–24]. Intestinal stem cells continuously self-renew throughout life and give rise to progenitors (transit amplifying cells) which undergo additional cell division prior to terminal differentiation and maturation.

The initial sign of differentiation can be observed in the embryo as villi emerge. Three distinct epithelial cell types—absorptive, goblet and enteroendocrine cells—arise during this period. Unlike

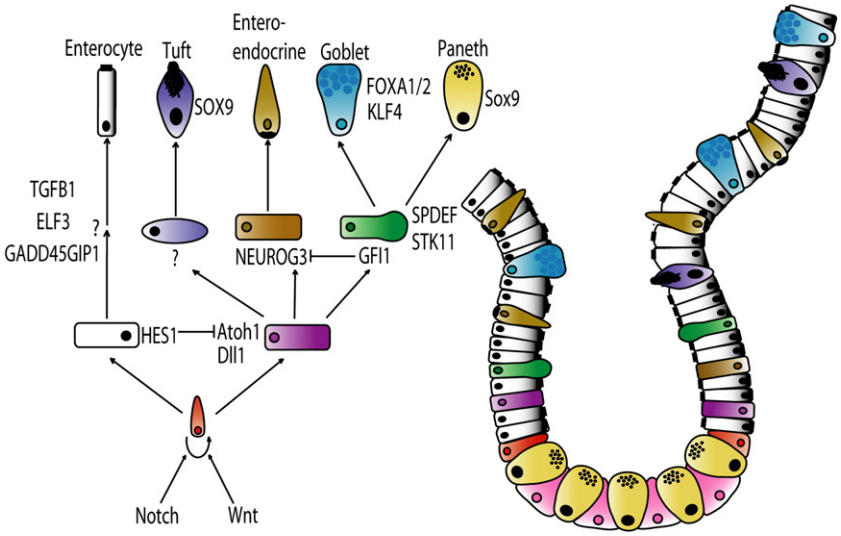

Fig. 2 – Model for intestinal differentiation. (Right) Cartoon depicting crypt structure with individual cell types shown. Cells migrate out of the crypt and onto the villus as they terminally differentiate, except Paneth cells which reside intercalated among the stem cells at the crypt base. (Left) A diagram summarizing key events in intestinal epithelial differentiation. Genes are shown next to cells in which they are expressed or have a role in their differentiation/maturation. Self-renewing stem cells (red and pink) receive signals to produce either absorptive enterocytes or secretory cells (enteroendocrine, goblet, Paneth and tuft cells). Notch induces stem cells to express Hes1 which represses Atoh1 and allows these cells to become enterocytes (white). Atoh1 expressing secretory progenitor cells (light purple) coexpress Dll1, a Notch ligand. Neurog3 specifies enteroendocrine progenitors from Atoh1-specified secretory progenitors. Gfi1 represses Neurog3 to direct progenitors to differentiate as goblet (blue) or Paneth (yellow) cells. Little is known about factors required for tuft cell (dark purple) differentiation.

the other intestinal epithelial cell lineages, Paneth cells emerge later, coincident with crypt emergence. Tuft cells, a newly identified secretory cell type, also arise after birth in mouse intestine [25].

Cell fate specification and differentiation of individual intestinal epithelial cells

Lineage allocation

All current models of intestinal epithelial differentiation support the existence of long-lived, multipotent stem cells that continuously produce new epithelial cells. One of the current models for intestinal epithelial differentiation proposes that stem cells produce multipotent progenitors that give rise to differentiated cell types by sequential binary fate decisions [26]. Another model proposes that stem cells produce several different bipotent progenitors which each commit to either absorptive or one type of secretory cell types [27]. The mechanisms by which stem cells produce the many different cell types that constitute the mature intestinal epithelium remain incompletely characterized.

The Notch pathway plays a critical role in intestinal epithelial cell fate by regulating the choice of absorptive versus secretory lineages. Ectopic overexpression of Notch Intercellular Domain (NICD) in the mouse intestinal epithelia decreased the number of secretory cells [28–30]. Conversely, inhibition of the Notch pathway leads to an increase in the number of the secretory cell lineages at the expense of absorptive enterocytes and colonocytes [31–34]. These complemetary studies strongly suggest a critical role for Notch signaling in fate determination of the intestinal epithelium. Notch1 and Notch2 were identified as the key Notch receptors regulating intestinal differentiation [33]. Among the Notch ligands, Dll1 and Dll4 were described as key intestinal epithelial ligands; compound loss of Dll1 and Dll4 promoted secretory cell differentiation in addition to a loss of proliferative progenitors in intestine, phenocopying loss of Notch activity [35]. Among the Notch transcriptional targets, Hes1 was proposed to be one of the primary mediators of intestinal Notch signals; in Hes1 deficient mice, fewer enterocytes and increased goblet and enteroendocrine cells were observed along with increased expression of secretory lineage specification factors such as Atoh1 [36]. In contrast to Hes1, Atoh1 (also called Math1) was shown to be required for secretory cell differentiation both in the embryo and the adult intestine [37,38]. In addition, Atoh1 overexpression was shown to be sufficient to direct progenitors into secretory cells [39]. Studies inhibiting Notch signaling showed an increase in Atoh1 expression, indicating that Atoh1 is negatively regulated by Notch activity [32]. Moreover, recent genetic and pharmacologic studies indicate that Atoh1 is epistatic to the Notch signaling pathway—silmultaneous loss of Atoh1 and Notch activities resulted in only the Atoh1 phenotype (loss of secretory cells and maintanence of proliferation) [31,34,40]. Together, these data indicate that the effect of Notch on lineage specification is implimented through its activity on Atoh1, and Hes1 is the Notch target that directly represses Atoh1 expression. Interestingly, a recent study proposed that Atoh1 also represses Hes1 expression [40]. Thus, reciprocal regulation between Hes1 and Atoh1, controlled by the level of Notch activity, likely plays a crucial role in balancing cell fate between absorptive and secretory cell types.

Since the identification of Atoh1 as an essential factor for secretory lineage specification, downstream factors that regulate

differentiation within the secretory lineages have been characterized. Gfi1, a transcription factor dependent upon Atoh1 for intestinal expression, was described as critical for allocating Atoh1 specified secretory progenitors among enteroendocrine and goblet/Paneth progenitors [26]. A recent study suggested that Gfi1 performs this function through repression of the pro-endocrine transcription factor Neurog3 [41]. Thus, allocation of cell fate between the secretory lineages may be achieved through the relative activity of Gfi1/Neurog3, in a manner similar to Hes1/Atoh1 selection of absorptive vs. secretory fate.

Wnt/β-catenin signaling has also been implicated in the cell fate decision between absorptive and secretory cells by interacting with Notch signaling at multiple levels during differentiation. Recent studies suggest that Atoh1 expression is regulated not only by Notch but also by the Wnt signaling pathway [42–44]. Atoh1 can be targeted for ubiquitination via GSK3-β mediated phosphorylation and subsequent protein degradation by the proteosome. GSK3-β targeting is regulated by Wnt pathway activity, such that when Wnt/β-catenin signaling is inactive, GSK3-β is directed to phosphorylate β-catenin to mark it for degradation. This basal activity of GSK3-β spares Atoh1 from phosphorylation and subsequent protein degradation; when Wnt signaling occurs, GSK3-β is redirected from β-catenin to Atoh1. Other studies indicate that Hes1 and Jag1 (a Notch ligand) are among several genes coordinately regulated by both Notch and Wnt/β-catenin pathways [42,45]. However, examination of the specific role of Wnt/β-catenin in cellular differentiation/ allocation is confounded by its critical role in regulating proliferation and stem cell activity in the intestine. Prior studies demonstrate that Wnt/β-catenin activity is required for intestinal differentiation and stem cell homeostasis, such that either increased or decreased β-catenin activity severely perturbs cellular production and differentiation of the intestinal epithelium [46–48]. Thus, further study is necessary to delineate the role of Wnt/β-catenin in lineage allocation as well as the complex crosstalk between the Notch and the Wnt/β-catenin signaling pathways in their regulation of intestinal epithelial homeostasis and differentiation.

Genes that function to regionalize the gut during embryonic development are reported to also play roles in epithelial differentiation in the adult. Ectopic expression of Cdx2 in intestinal epithelium leads to a loss of Paneth cell lineage and abnormal differentiation of goblet cells and enterocytes [49]. Gata4 and Gata6, genes important for proximal–distal specification of the intestine, are reported to influence epithelial cell differentiation [50–52]. Understanding and integrating the multiple pathways and mechanisms that regulate intestinal differentiation remains an important goal of future research.

Enterocytes and colonocytes

Enterocytes and colonocytes are the most abundant cell type in both small and large intestines. Their primary function is to absorb nutrients apically and export them basally. Their apical surfaces have characteristic microvilli that comprise a brush border. Notch activity was thought to be essential in lineage specification of the absorptive cells however recent studies showed that Notch activity is not required for absorptive cell differentiation, but instead is required to repress Atoh1 expression and thus secretory cell fate [34,40]. These results suggest (1) that in the absence of Notch pathway signals, progenitors "default" to the enterocyte lineage; (2) that other factors and pathways must direct absorptive cell differentiation. Several genes have been implicated in absorptive cell differentiation, but few influence the differentiation of only these cells: Delayed enterocyte maturation and mucosal hyperplasia was observed in Ptk6 knockout mice [53]. Concordant deletion of Hnf1α and β caused abnormal enterocyte differentiation, while also deranging secretory cell fates [54]. Hnf4α regulates a network of genes including both absorptive and secretory cell differentiation and maturation factors [55,56]. The pleiotropy of genes important for absorptive cell differentiation may reflect their role in defining basic intestinal identity.

M cells

M (*M*embranous or *M*icrofold) cells are microbial trafficking cells that are primarily found within follicle-associated epithelium (FAE) overlying Peyer's patches and lymphoid follicles [57] (Reviewed in Ref. [22]). M cells contain unusual membrane structures which facilitate presentation of microbes to underlying lymphocytes, macrophages and dendritic cells. A basic understanding of M cell differentiation is still lacking: alternate models suggest that M cells arise by a unique differentiation program from intestinal stem cells, or by transdifferentation of mature enterocytes [22]. A close relationship between developing M cells and adjacent lymphocytes (especially B cells) has been observed [22,58]. Recently, the TNF-related protein RANKLigand was shown to be necessary and sufficient for the formation of functional M cells [59]. The RANK receptor was found throughout the small intestinal villus, crypt, and FAE epithelial cells, lending support to the concept that M cells could derive from mature enterocytes.

Enteroendocrine cells

Enteroendocrine cells comprise approximately 1% of the small and large intestinal epithelium, are scattered throughout the mucosa as individual cells, and produce and secrete hormones. There are more than 16 subtypes of enteroendocrine cells identified in the mouse intestine. Lineage specification of enteroendocrine cells from Atoh1 specified secretory progenitors requires Neurogenin3 (Neurog3) [60,60]. Ectopic expression of Neurog3 in the embryo was sufficient to direct enteroendocrine differentiation at the expense of the goblet lineage, supporting the concept of an Atoh1-dependent common secretory progenitor [62]. Multiple factors expressed downstream of Neurog3 are proposed to function in terminal differentiation of enteroendocrine cells giving rise to various subsets of enteroendocrine cells, in a manner similar to pancreatic endocrine differentiation. NeuroD1/BETA2, which is expressed downstream of Neurog3, plays a role in terminal differentiation of the secretin and CCK producing subset of enteroendocrine cells [63]. Other factors described to function in terminal differentiation of enteroendocrine cells include Pdx1, IA1/Insm1, Nkx2.2, Pax4 and Pax6 [64–67], reviewed in Ref. [68]. A recent study by Ye and Kaestner showed that deletion of Foxa1 and 2 in the adult intestine lead to a decrease in several subsets of enteroendocrine cells in the small intestine [69]. That study proposed that Foxa1 and 2 act upstream of Pax6 to delineate this sublineage from Neurog3-positive, NeuroD1-negative endocrine progenitors. Mechanisms for generating the diversity and regional specificity of enteroendocrine cells will become clear as the hierarchical transcriptional network controlling enteroendocrine cell specification is elucidated. This network is likely to be highly

similar to, and informed by, the network that controls pancreatic endocrine differentiation.

Goblet cell

Goblet cells are the most abundant secretory lineage of the intestinal epithelia, comprising ~10–15% of the small intestinal epithelium and up to 50% of the colonic epithelium. They produce and secrete mucus to provide the epithelial cells a protective shield against noxious luminal contents. Our current model of the intestinal epithelial differentiation suggests that goblet cells share a common progenitor with Paneth cells. This notion has been supported by several studies reporting factors which coordinately influence both goblet and Paneth cell lineage specification and differentiation. For example, Spdef was proposed to be involved in maturation of goblet and Paneth cells [70,71]. Loss of Sox9 results in fewer goblet and Paneth cells [72]. In addition, Lkb1/STK11 deletion results in an increase in "intermediate cells" which have features of both goblet and Paneth cells [73].

Notch signaling activity plays a crucial role in goblet cell differentiation. In addition to its role in selecting secretory vs. absorptive fate, Notch may have another roles specific to differentiation of goblet cells, which express active Notch after they exit the cell cycle [74]. Ectopic expression of NICD in postmitotic precursor cells increases goblet cell number, likely through increased Hes5 expression [28]. Klf4, another differentiation factor that is regulated by the Notch pathway, was reported to be important for colonic goblet cell differentiation [75]. This result was confirmed by studies showing that intestine-specific embryonic deletion of Klf4 caused abnormal goblet cell differentiation that persisted into adulthood [76]. However, inducible postnatal deletion of Klf4 did not interfere with goblet cell differentiation nor with goblet cell metaplasia induced by Notch inhibition, suggesting that Klf4 has distinct roles in fetal versus adult cellular differentiation [35].

Simultaneous deletion of Hnf1α and β in the adult intestine increased the number of goblet cells. These factors were proposed to act upstream of the Notch pathway and regulate the expression of Atoh1 and the Notch ligand Jag1 [54]. The Wnt pathway has been suggested to regulate goblet cell differentiation in part by modulating Notch effectors such as Atoh1, Hes1, and Spdef [42,43,70].

Paneth cells

Paneth cells are secretory cells of the intestinal epithelium that produce and secrete antimicrobial peptides into the lumen. Paneth cells are unique in several respects compared to other secretory cells of the intestine. Unlike other secretory cells, Paneth cells first appear after birth during crypt emergence. Once cell fate is determined, Paneth cells migrate toward the base of the crypts where they complete their maturation. In addition, Paneth cells express nuclear β-catenin, unlike all other differentiated intestinal epithelial cells. Wnt/β-catenin signaling has been associated with Paneth cell lineage specification, differentiation and maturation. Paneth cells were displaced out of the crypts and their differentiation was disturbed by conditional deletion of APC (resulting in activation of β-catenin) in the adult mouse intestine [77]. In related studies, reduction in β-catenin activity inhibited Paneth cell differentiation [78,79]. Similarly, inhibition of Wnt/β-catenin signaling by ectopic expression of Dkk1, a secreted Wnt inhibitor, or by deletion of the Wnt receptor Frizzled-5, lead to defects in Paneth cell differentiation [46,80]. Deletion of Lgr4, a positive regulator of Wnt signaling, significantly impaired Paneth cell formation [81]. Importantly, the Wnt/β-catenin transcriptional target Sox9 was identified as an essential factor for Paneth cell lineage specification and differentiation [72,82]. Recent *in vitro* studies suggest that FGF signaling may stimulate β-catenin activity to sustain Paneth cell differentiation; the receptor FGFR-3 is essential for Paneth cell emergence and lineage allocation [83,84]. Intriguingly, Paneth cells produce ligands for Wnt, Notch, and EGF receptors [85], suggesting that they regulate the activity of adjacent intestinal stem cells and provide a niche that allows Wnt-mediated maturation of nascent Paneth cells.

Tuft cells

Tuft cells (also called brush cells) are a rare and understudied intestinal cell type with a characteristic shape including long and thick microvilli that extend actin bundles deep into their apical cytoplasm. Tuft cells are likely involved in chemical sensation of luminal contents, based on expression of proteins involved in taste sensation (alpha-gustducin, Trpm5), and secretion of opioids in response to luminal nutrients [25,86,87]. Previously, tuft cells were thought to be a rare type of enteroendocrine cell, based on their frequency in the epithelium and function in chemical sensation [87]. However, recently tuft cells were proposed to be a 4th secretory lineage based on the genetic program required for their differentiation [25]. Gerbe and colleagues reported that tuft cells were dependent on Atoh1 for their formation, thus classifying them as a secretory cell type. However, differentiation of tuft cells was not perturbed by deletion of Neurog3 (required for enteroendocrine cell differentiation), Sox9 (required for Paneth cells), Gfi1 or Spdef (goblet/Paneth factors) [25]. Differentiation factors required for unique specification of tuft cells remain to be identified. Of note, the putative intestinal stem cell marker DCLK1 was shown to be localized to tuft cells; the relationship between tuft and stem cells remains to be established [25].

Summary

We have reviewed the process of intestinal organogenesis, with a focus on the endoderm and the intestinal epithelium which it generates (Fig. 1). Much remains to be learned about factors that control regionalization of the early endoderm and formation of endodermal organs. In particular, a deeper understanding of the crosstalk between the developing endoderm/epithelium and mesoderm/mesenchyme is required to create a cohesive model of how individual morphogens and transcription factors control intestinal organogenesis. We also present a revised model of cell fate specification, now including tuft cells as a 4th Atoh1-dependent, secretory lineage (Fig. 2). We summarized the growth factor and transcriptional networks important for differentiation and maturation of the individual intestinal lineages, and include a supplementary table of genes important for intestinal epithelial differentiation (Supplementary Table 1). As the field continues to identify new genes and molecules which impact intestinal development and homeostasis, a continual challenge will be to understand how this network of factors interacts to produce and maintain the intestine.

Supplementary materials related to this article can be found online at doi:10.1016/j.yexcr.2011.09.006. A continuously updated version of this table is available at http://en.wikipedia.org/wiki/Intestinal_epithelial_differentiation_genes.

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