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Review

Gut development in *C. elegans*

Morris F. Maduro

Biology Department, University of California, Riverside, CA 92521, United States

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ABSTRACT

The midgut (intestine) of the nematode, *C. elegans*, is a tube consisting of 20 cells that arises from a single embryonic precursor. Owing to its comparatively simple anatomy and the advantages inherent to the *C. elegans* system, the gut has been used as a model for organogenesis for more than 25 years. In this review, the salient features of *C. elegans* gut development are described from the E progenitor through to the 20-cell intestine. The core gene regulatory network that drives specification of the gut, and other genes with roles in organogenesis, lumen morphogenesis and the cell cycle, are also described. Questions for future work are posed.

Contents

1. Introduction

The major functions of the *C. elegans* gut are to import dietary macromolecules, process them metabolically, and store chemical energy. The gut also serves as an entry point for pathogens and activation of immune responses. In hermaphrodites, the gut supplies chemical energy to oocytes for embryonic development after fertilization. The gut is a simple tube consisting of 20 cells that arises from a single cell called E that proceeds through a stereotyped set of cell divisions and movements. Its simple anatomy and importance in many biological functions, coupled with the many tools available in *C. elegans*, have made the gut the focus of studies for over 25 years. The least-studied aspect of the gut has been its cellular development, both in terms of the genes that drive it downstream of specification, and how the gut primordium dynamically generates the intestine. In this review, the salient features of gut morphogenesis will be described based on recent studies. As listed in Table 1, genes involved in gut development, including those important for specification, differentiation and morphogenesis, will be described. Finally, future work to fully elucidate the intestinal gene network, and address aspects of the robustness of intestinal development, will be proposed.

E-mail address: mmaduro@ucr.edu

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Table 1
Examples of genes important for *C. elegans* gut development.

Gene/Product	Mutant Phenotype	Reference(s)
Specification and Maintenance of Differentiation		
skn-1/Nrf2	loss of gut specification in ~80% of embryos	[44]
pop-1/TCF	ectopic specification of gut fate from MS; synergy for loss of gut with *skn-1*	[50,88]
med-1,2/GATA	loss of gut specification in 15–50% of embryos	[46,56,89]
end-1,3/GATA	complete loss of gut specification (double mutant)	[33]
elt-2/GATA	loss of gut integrity	[54]
elt-7/GATA	no phenotype alone; enhances *elt-2* phenotype	[55]
Morphogenesis and Cell Polarization		
vang-1/Van Gogh	misalignment of E4 primordium cells in ~40% of embryos	[13]
mab-20/Semaphorin	defects in int2 intercalation	[13]
eph-4/Ephrin	defects in int2 intercalation	[13]
lin-12/Notch	failure of pre-rotation of int2L	[13]
unc-6/Netrin	failure of int3 and int4 rotation; partial failure of int2 rotation	[13]
madd-2/E3 ubiquitin ligase	asymmetric expression of *madd-2* in left side cells of int2, int3 and int4 important for rotation of int2-4	[13]
erm-1/Ezrin	disorganization of lumen	[36]
chc-1/Clathrin	loss of apicobasal polarity, failure of lumen organization	[37]
dlg-1/Discs Large	loss of adherens junction integrity	[35]
sptl-1/lipid enzyme	loss of apical targeting of vesicles, formation of ectopic lumen	[41]
let-413/Scribble	loss of maintenance of apical localization of terminal web	[17]
ifo-1/Novel	mislocalization of intermediate filaments; synergy with *dlg-1* and *erm-1*	[34]
Cell Division		
cdc-25.1/Cdc25	supernumerary gut nuclei (gain-of-function mutation)	[75,76]
cdc-25.2/Cdc25	no nuclear or cell divisions after E16 stage	[77]

2. Nomenclature, function and anatomy

The *C. elegans* digestive tract runs most of the length of the animal (Fig. 1). The fully formed intestine serves the animal for its life span, as cells are not replaced. It is subdivided into the pharynx, intestine, and hindgut; between each pair of regions are a small number of valve cells. In the wild, animals generally consume a moist diet of microbes found primarily on rotting plants and their fruits [1]. The pharynx, analogous to the vertebrate esophagus, is a muscular organ that pumps food [2]. Within the posterior half of the pharynx is the grinder, a cuticle-lined structure that mechanically breaks down food into smaller particles that travel through the pharynx-intestine valve and into the anterior lumen of the intestine. Within the intestinal lumen, the contents slosh around along its length, while macromolecules are broken down by enzymes and the products are absorbed. Defecation through the hindgut occurs by a set of body contractions approximately every 45 s [3]. Bacteria transit the intestine rapidly: With each defecation cycle, 43 +/− 10% of the intestinal volume is expelled, corresponding to a residence time of 1–2 min [4].

The *C. elegans* intestine has additional roles. Animals can store dietary fat in lipid droplets throughout lysosomal compartments in the gut cytoplasm [5]. In hermaphrodites, the intestine is the location of synthesis of vitellogenins, yolk protein precursors that will be delivered to oocytes [6]. It is also a primary site of innate immune responses [7]. Larger macromolecules and some microorganisms can also enter gut cells intact. Consumption of bacteria expressing double-stranded RNA (dsRNA) can stimulate RNA-mediated interference (RNAi) [8]. Particles of the Orsay virus can enter intestinal cells and replicate if the host strain is deficient in RNAi [9,10] and the eukaryotic intracellular pathogen, microsporidia, infects animals through the gut lumen [11].

The entire gut is descended from a single embryonic precursor called E (Fig. 1A). A single-cell origin for gut occurs among distantly related nematodes, suggesting that this trait is ancestral [12]. The E cell undergoes a stereotyped pattern of cell divisions to produce 20 cells (and on occasion, one or two more) that will form the intestine [13–15]. Cells in the gut primordium are identified by their pattern of descent from E and the pattern of division axes, i.e. anterior-posterior, left-right or dorsal-ventral. For example, the four grand-daughters of E are Eal, Ear, Epl and Epr, where 'Eal' indicates the cell that is the left daughter of the anterior daughter of E. A particular stage is referred to by the total number of E descendants present, hence the aforementioned stage is called E4. It becomes more convenient to identify later cells according to their positions at the E16 stage [13].

The gut lumen is found on the apical surface of intestinal cells, lining the digestive tract. A transverse transmission electron microscope image through a larval intestine is shown in Fig. 2. The lumen appears as a flattened oval, lined with a brush border containing microvilli. A flattened shape may better support the body bends that occur during locomotion [13]. The microvillar membrane projections into the lumen are supported by an actin-rich network that emerges from the terminal web, a cytoplasmic layer of intermediate filament proteins (sometimes called the "endotube") that surrounds the lumen [16–18]. Along two sides of the lumen are adherens junction complexes that connect the intestinal cells [17]. The exterior surface of the microvilli, i.e. the apical surface within the lumen, is associated with a glycocalyx. This region likely consists of glycoproteins and enzymes that function in breakdown of macromolecules and protection of the microvilli [19]. The lumen can be modulated dynamically over time to suit developmental stage and food availability [20].

The gut is classically described as consisting of nine "rings" numbered int1 through int9 from anterior to posterior (Fig. 3) [14]. Rings 2 through 9 consist of a pair of cells each, while the first ring consists of four cells. The rings are conveniently referred to by their relative locations in the E16 primordium, using the naming system of Asan et al. (2016). In this notation, int2 through int9 have a left (L) and right (R) cell (e.g. int2L and int2R form int2), while the four cells in int1 are also marked dorsal (D) and ventral (V) (i.e. int1RD, int1LD, int1LV, int1RV). In the later stages of gut morphogenesis, a rotation of several rings occurs to cause most of the left-right pairs to adopt a nearly dorsal/ventral orientation [13,21]. The pairs of cells that form rings 3–9 are often diagrammed as being in anterior-posterior register with respect to one another as shown in Fig. 3. However, the right-side cells are displaced anteriorly from the left side by some 10–30% of their lengths [13]. The outside of the gut is surrounded by a basement membrane [21], and aside from attachment to the foregut and hindgut, is not rigidly attached to the body. The gut is not associated with neurons and is connected to a single muscle at its posterior [18].