Review

Nematode midgut – the unique multifunctional body unit

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Summary. The nervous system coordinates whole body behaviour and transmits signals between its different parts, while the intestine is the main digestive system for most multicellular organisms. However, due to evolution routes, nematodes acquired unusual 'neuronal' functions for intestinal enterocytes. Along with food processing, nutrient extracting, and transferring them to other tissues, endodermal nematode cells can regulate the activity of different body systems, respond to changes in the internal and external environment, and even control the complex programmed entire organism death mechanism. The defaecation motor programme of nematodes is a rhythmical behaviour that is perfectly timed, and intestinal cells transmit timing information among themselves and target tissues that execute rhythmic outputs. In this work, we analyse open data of *Caenorhabditis elegans* single-cell RNA-seq to check genes commonly involved in neuronal signal transmission activity. Our results show that the nematode intestine possesses some parts of neuronal presynaptic machinery, and we propose extra evidence of nematode intestine to neuron similarity.

Key words: defaecation motor programme, nematode intestine, scRNA-seq data, synaptic transmission.

Commonly, rhythmic behaviours (such as breathing, locomotion, *etc.*) that affect the whole animal are controlled by the nervous system. The nematode rhythmic defaecation, one of the main body functions that involve different types of cells and tissues, is a surprising exception. Molecular mechanisms of the defaecation motor programme (DMP) in nematode intestinal endoderm cells are well-coordinated. The defaecation cycle is driven by the central pattern generator and is associated with unusual all-or-none hyperpolarisation action potential (HAP) and various molecular mechanisms (*e.g.*, mechanisms that control calcium oscillations). Interestingly the initiation, propagation through the intestinal cell chain, and the coordination of the significant part of the process do not involve the nervous system (Dal Santo *et al.*, 1999). Intestinal synchronised signals engage accompanied muscle contractions directly and *via* downstream GABAergic neurons. This remarkable phenomenon is studied in detail *via* genetic and molecular biology tools for *Caenorhabditis elegans* (Thomas, 1990; Teramoto *et al.*, 2005; Branicky & Hekimi, 2006; Mahoney *et al.*, 2008) and electrophysiologically for *Heterorhabditis megidis* – that belong to the same Rhabditida order of nematodes (Kuznetsov *et al.*, 2017). Those studies show that intestinal cells can act similarly to different neuron types by implementing sensory, internuncial, and motor function. Nematode intestinal enterocyte electrical and synaptic activity combined with expression data underlines the similarity with neuronal cells and call for a re-evaluation of the excitable cell definition.

DMP mechanism

Nematode studies try to solve the puzzle of the DMP complex machinery (Liu & Thomas, 1994; Teramoto & Iwasaki, 2006). Some aspects of this mechanism are still unknown, but the core has been well studied. Inositol 1,4,5-trisphosphate (IP_3) and

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Ca^{2+} ions play a crucial role in initiating, regulating, and propagating the oscillatory process (Teramoto & Iwasaki, 2006; Nehrke *et al.*, 2008; Baylis & Vázquez-Manrique, 2012). The inositol trisphosphate receptor (IP_3R) regulates a 50-second behavioural rhythm in *C. elegans* (Dal Santo *et al.*, 1999). The process can start from GPCR and G-proteins (Xing & Strange, 2010). Gqα typically stimulates phospholipase beta (PLCβ). Hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2), a phospholipid located in the plasma membrane, by phospholipase results in IP_3 and diacylglycerol (DAG) signalling molecules production. IP_3 is a soluble molecule that can diffuse through the cytoplasm and make it to the endoplasmic reticulum (ER) (Espelt *et al.*, 2005). Once at the ER, IP_3 can bind to the $Ins(1,4,5)P_3$ receptor/ligand-gated Ca^{2+} channel found on the ER's surface. The binding of IP_3 (the ligand in this case) to IP_3R triggers the opening of the Ca^{2+} channel and thus the release of Ca^{2+} from internal stores into the cytoplasm (Dal Santo *et al.*, 1999). The IP_3R channel activity is also controlled by Ca^{2+} sensors contributing to Ca^{2+} waves and oscillations by the feedback loop mechanism (Foskett *et al.*, 2007). In nematodes, cytoplasmic Ca^{2+} concentration increases, and calcium oscillations detected in the intestinal epithelium's apical pole occurs as an intercellular Ca^{2+} wave that moves in the posterior to the anterior direction. To keep the process cycled, ER reticulum Ca^{2+}-ATPase (SERCA) restores Ca^{2+} to the baseline levels (Espelt *et al.*, 2005; Wang & Sieburth, 2013).

In addition to the system regulating ER/cytoplasm Ca^{2+} turnover, based on IP_3R channel and SERCA machinery, plasma membrane voltage-gated mechanisms are also involved in Ca^{2+} wave forming. Nematode intestinal endodermal cells produce unusual all-or-none HAP (Kuznetsov *et al.*, 2017; Slivko-Koltchik *et al.*, 2018). The shape and electrical properties of these membrane potential oscillations in the gut cells resemble transient spikes in neurons and myocytes; although it has an opposite sign and shifts membrane potential from a basic depolarised state to rapid hyperpolarisation. The frequency of these oscillations depends on the membrane potential and they could be triggered by application of external electrical pulses similar to usual spikes. In this case, transient hyperpolarisation can be caused by voltage-gated K^+ channels opening, and Ca^{2+} can be pulled into the cell by resulting voltage gradient *via* Ca^{2+} leak channels (Kuznetsov *et al.*, 2017).

The wave propagates through the whole intestine *via* gap junctions (GJ) (INX-16) (Peters *et al.*, 2007; Altun *et al.*, 2009; Liu *et al.*, 2013). It remains unclear whether Ca^{2+} signalling is required for PBO-4/NHX-7 activity during defaecation or whether acidification of the intestinal cells is sufficient to cause H^+ efflux *via* an allosteric effect of H^+ binding to PBO-4/NHX-7 (Beg *et al.*, 2008; Pfeiffer *et al.*, 2008). However, PBO-1, a calcium-binding protein, coordinates the sodium-proton activity of PBO-4/NHX-7. PBO-4/NHX-7 exchanger transfers protons to the pseudocoelome and sodium into the cell through the basolateral membrane. PBO-4/NHX-7 proton efflux from the gut cells activates PBO-5/PBO-6 proton-gated ion channel, depolarising the posterior body wall muscles and causes their contraction (pBoc). Anterior body wall muscle contraction (aBoc) is the most incompletely studied event in this process. It is known that killing AVL neurons causes substantial defects of the aBoc step. Although AVL is a GABAergic neuron, GABA dysfunction mutants have a normal aBoc step. Thus, anterior body muscles are controlled by AVL motoneurons but do not require GABA in the pathway from Ca^{2+} wave initiation to muscle depolarisation. Synaptotagmin (SNT-2) localised on the dense core vesicles (DCV) being bound to calcium promote the release of neuropeptide-like protein NLP 40 from the basolateral surface of intestinal cells. Thus, NLP-40 carries timing information from the intestine *via* the calcium-dependent rhythmic release. Secreted NLP 40 activates the AEX-2/GPCR receptor on AVL and DVB neurons, and the cAMP signalling pathway inside the neurons leads to a calcium influx, neuron excitation, and GABA release. Excitatory GABA receptor EXP-1, located on enteric muscles (anal sphincter, anal depressor, and stomato-intestinal muscles electrically coupled *via* GJ), binds GABA and causes contraction (Kuznetsov *et al.*, 2016). It results in the final expulsion DMP step (Beg & Jorgensen, 2003; Wang *et al.*, 2013).

Nematode intestine controls the programmed organismal death

Ideas of the existence of a programmed entire organism death cannot find confirmation for most model systems. Death stops the reproduction of the organism, and it is difficult to imagine the evolutionary mechanism that leads to the consolidation of this programme. Some programmed cell death mechanisms are well known, while others, especially in invertebrates, are poorly investigated. One interesting phenomenon is found in the nematode *C. elegans*. The intestine, the largest somatic organ, undergoes a stereotyped self-destruction process involving an intra- and

intercellular cascade of cellular necrosis. The blue auto-fluorescence emitted from this animal's intestinal cells changes throughout life, provides visible evidence of the spatial-temporal dynamics of its death. The death of an entire organism is accompanied by rapid burst peak intensity (400% fluorescent level increase) of blue fluorescence generated in intestinal cells during the development of the calpain-cathepsin necrotic process (Coburn *et al.*, 2013). The blue fluorescent wave source was shown to be not the oxidative damage product lipofuscin (Hosokawa *et al.*, 1994), but the anthranilic acid glucosyl esters, stored in intestinal lysosome-related organelles (Coburn *et al.*, 2013; Gagarinskiy *et al.*, 2017).

The processes initiated by the endodermal cells of the nematode gut can start the mechanism of the whole animal death. The inhibition of systemic necrosis in the endoderm allows delaying the death caused by external stimuli, showing the major contribution to the death process. The wave starts from the most anterior intestine cell and propagates from anterior to posterior through the chain of cells by calcium influx *via* INX-16 based GJ and is accompanied by cytosolic acidosis. The Ca^{2+} propagation *via* innexins GJ during the blue fluorescent death wave resembles the Ca^{2+} propagation in DMP, but with the opposite direction (Peters *et al.*, 2007; Altun *et al.*, 2009). The process triggers from the most anterior cell in any conditions, and even after artificial heating of the most posterior part of the nematode, the wave starting point remains unchanged. Fluorescent peaks arise from the dequenching of anthranilic acid in a less acidic environment caused by the release from gut granules. Necrosis in the nematode endodermal intestine cells is in some respects similar to neuronal necrosis. Neuronal necrosis is based on Ca^{2+} release from ER stores and mutations in the ryanodine and IP_3Rs, and the ER Ca^{2+} binding protein calreticulin in *C. elegans* suppress both neuronal necrotic and endoderm cell death (Xu *et al.*, 2001; Luke *et al.*, 2007; Coburn *et al.*, 2013). The simple evolutionary explanation for the emergence of this programmed entire organism death mechanism suggests that an old, incapable of subsequent reproduction, individual sacrifices itself by triggering necrotic death, that starts from the intestine and supply nutrients for the last larvae generation inside the body (McCulloch & Gems, 2003).

The intestinal cel operates as multi-task neuron

The nematode defaecation cycle is quite a remarkable biological clock (Teramoto & Iwasaki, 2006; Kobayashi *et al.*, 2011). This process is constant over the wide range of environmental clues (Liu & Thomas, 1994), such as temperature changes and food availability (Mclntire *et al.*, 1993); however, the DMP can be paused during the absence of a bacterial lawn (food) (Mori & Ohshima, 1995). The defaecation clock is self-maintained and always tends to save the periodicity, so it can resume if the animal returns to the bacterial lawn (Liu & Thomas, 1994). Two known events can reset the periodic motor programme in *C. elegans*: mechanical impact and direct electrical stimulation of intestinal cells (Croll & Smith, 1978; Kuznetsov *et al.*, 2017; Slivko-Koltchik *et al.*, 2018). The sensory input detection in nematode gut (for instance through, PIEZO1 mechanosensitive ion channel) makes enterocytes similar to afferent sensory cells in the nervous system.

It is well-known that neurons communicate with each other and with other cells by synapses. There are two types of synapses: chemical and electrical. The electrical synapse is quite simple and is based on GJ. In the nematode intestine, electrical synapses coordinate cell coupling and signal propagation along the gut. By contrast, the chemical synapse can be a complex structure with distinct presynaptic and postsynaptic apparatus. No functional or anatomical synapses from the nervous system to the intestine in *C. elegans* were found, and we do not expect to find a postsynaptic apparatus in the intestinal cells. However, a crucial part of the postsynapse – different neurotransmitter receptors – is expressed in the intestine. Neurotransmission *via* the extrasynaptic receptors with no synaptic structure is possible for neurons, and it is based on neurotransmitter distant release and diffusion in the extracellular fluid. In such a way, the nematode gut has the potential possibility to be a neurotransmission receiver. The mechanisms of signal transmission from the intestinal to other cells in nematodes could be compared to synaptic functions. On the one hand, by body muscle cell exciting, gut enterocytes act functionally as motor neurons, although the use of proton efflux as a signal molecule has no match in neuronal synapses. On the other hand, muscle cell proton receptors PBO-5/PBO-6 most likely evolved from regular postsynaptic N-acetylcholine receptors (Fig. 1).

Nematode intestinal presynaptic apparatus

An electrical impulse (action potential) in the presynaptic neuron depolarises the membrane and activates calcium intake from the extracellular space. The increase of Ca^{2+} concentration triggers the

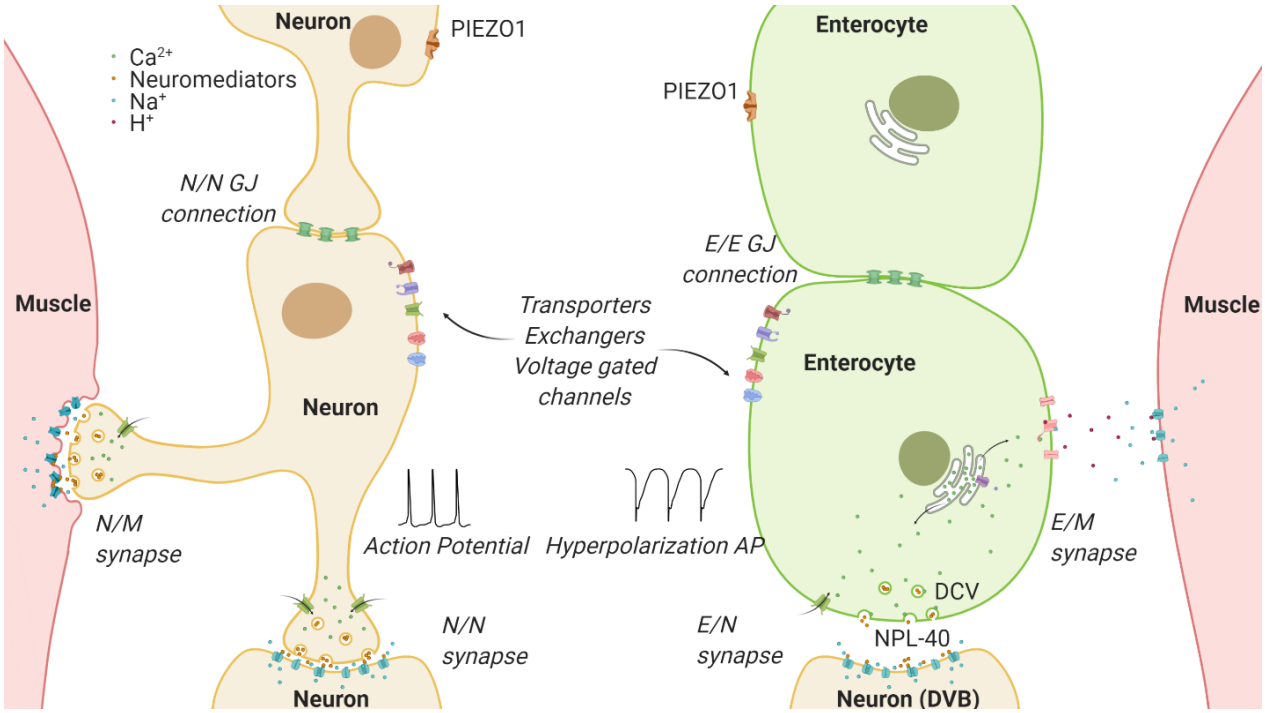

Fig. 1. Typical neuron (beige, left) and nematode intestinal enterocyte (green, right) share similar signal transmission mechanisms. After receiving the signal from external stimuli (*e.g.*, PIEZO1 mechanosensitive ion channel), the sensory neuron transfers it further to another neuron by electrical synapse *via* gap junctions (green barrels; N/N GJ connection) or by chemical synapse (N/N synapse). The signal transition from neurons to muscles also involves chemical synapse (N/M synapse). Voltage-gated ion channels participate in the generation of rapid all-or-none depolarised membrane potential spike (Action Potential).

A similar pattern of signal propagation is evident for intestinal endodermal cells. After receiving the signal from external stimuli (*e.g.*, PIEZO1 mechanosensitive ion channel), the intestinal endodermal cell transfers it further to another intestinal endodermal cell only by electrical synapse *via* gap junctions (green barrels; E/E GJ connection). Nevertheless, the signal transition to other excitable tissues, including neurons, implies synapse formation with complex Ca^{2+} dependent postsynaptic apparatus. E/N for intestinal cell – neuron synapse, where the mediator is NLP-40 and E/M for intestinal cell – muscle cell synapse with direct acidification of pseudocoelome space and PBO-5/PBO-6 proton receptors.

The common intestinal endodermal cell signal is called Hyperpolarisation AP – rapid all-or-none hyperpolarised membrane potential spike, similar to common neuronal AP. Both cells are electrically active and have many different ion channels on their membranes (Iwasaki *et al.*, 1995; Take-Uchi *et al.*, 1998; Kwan *et al.*, 2008; Kuznetsov *et al.*, 2019). Ca^{2+} ions and Ca^{2+} ion channels are coloured in green. Neuromediators are coloured in orange. Na^{+} ions and Na^{+} ion channels (mostly neuromediator receptors) are coloured in blue. H^{+} and H^{+} ion transporters are coloured in magenta. In intestinal endodermal cells, the endoplasmic reticulum is coloured green-white as the primary Ca^{2+} storage, and IP3R is coloured purple.

mediator's release from synaptic vesicles into the synaptic cleft. For nematodes, the DMP action potential inside the intestinal cells has an opposite sign and causes membrane potential hyperpolarisation instead of depolarisation. Although the polarity is the opposite of a typical neural or muscle spike, DMP action potential also increases calcium concentration. In this case, transient hyperpolarisation can be caused by K^{+} channel opening, while Ca^{2+} is pulled in the cell by resulting voltage gradient *via* Ca^{2+} leak channels (Kuznetsov *et al.*, 2017). Intestinal presynapse may act in the same way as the usual presynapse, and Ca^{2+} concentration increase may cause the mediator release. The mediator release process in the common presynapse is a variant of exocytosis or fusion of vesicles with membrane compartments inside the cell. Exocytosis or vesicle fusion are

universal and inherent in all types of cells. However, current data indicate that the set and relative concentrations of RNA expressed by genes associated with this process differ in neurons compared to other types of cells. SNARE molecular machinery plays a crucial role in neuronal presynaptic function. The primary role of SNARE proteins is to mediate the fusion of vesicles with the target membrane. The core mammalian SNARE complex is a four alpha-helix bundle formed by synaptobrevin, syntaxin, and two SNAP alpha-helixes (Sutton *et al.*, 2013). Synaptotagmin is a calcium-dependent exocytosis launcher and the final trigger for a neurotransmitter release at the synapse (Fig. 2).

All mentioned participants of the mammalian SNARE complex have orthologues in nematode proteins (Kim *et al.*, 2018; Li *et al.*, 2018). Snt-1, Snt-2, Snt-3, Snt-4, Snt-5, Snt-6, Snt-7 are orthologues of different human synaptotagmins. Nematode synaptotagmins are predicted to have several functions, including Ca^{2+} binding activity, phospholipid-binding activity, SNARE binding activity, and syntaxin binding activity. They are involved in various processes, including defaecation, positive regulation of necrotic cell death, and regulation of pharyngeal pumping. Different nematode synaptotagmins have different localization and have the highest expression rate in gonads, neurons, pharynx, and intestine.

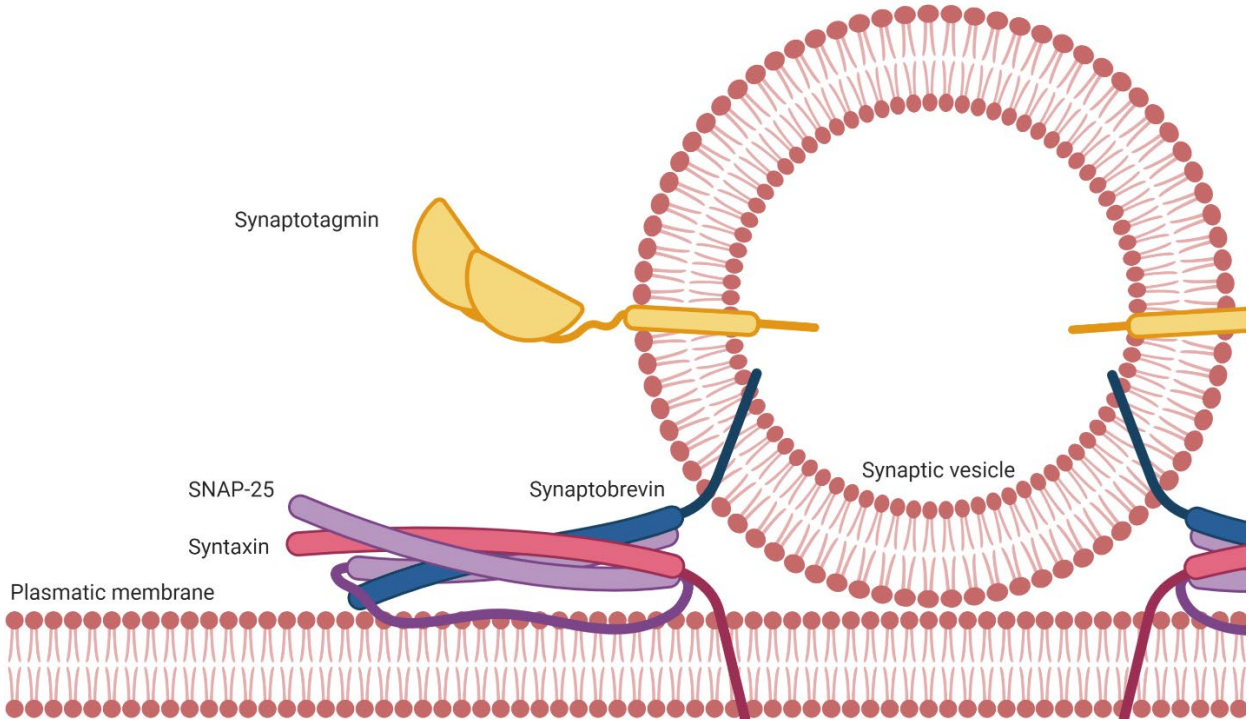

Fig. 2. SNARE molecular machinery. The complex of four alpha-helixes: synaptobrevin (blue), syntaxin (pink), and two SNAP alpha-helixes (purple) bound the plasmatic membrane and synaptic vesicle. Synaptotagmin (yellow) works as a calcium sensor in the regulation of Ca^{2+}-evoked synaptic vesicle fusion.

Syx-2, Syx-3, Syx-4, Syx-5, Syx-6, Syx-16, Syx-17, Syx-18, and Unc-64 are orthologues of different human syntaxins. They are predicted to have SNAP receptor and SNARE binding activity. Nematode syntaxins are involved in several processes, including cortical granule exocytosis, positive regulation of cytokinesis, and regulation of exocytosis in chemical synaptic transmission, insulin receptor signalling pathway, and nervous system development.

Snb-1, Snb-2, and Snb-5, Snb-6, Snb-7 are orthologues of different human synaptobrevins and are predicted to have SNAP receptor and syntaxin binding activity. They localise to several cellular components, including a neuronal axon, cytoplasmic vesicle, and a presynaptic active zone. The predominant expression of *snb-2* in the intestine cells can show the high importance of vesicle binging for this tissue.

Ric-4, Aex-4, SNAP-29 are orthologues of human SNAP-23 and SNAP-25. Along with syntaxins, they are predicted to have SNAP receptor and syntaxin binding activity.

Sng-1 and Sph-1 are orthologues of synaptogyrin and synaptophysin, respectively. Sng-1 is an integral membrane protein associated with presynaptic vesicles in neuronal cells. It is predicted to have a function in synaptic plasticity. Sph-1 is predicted to have syntaxin binding activity and localises to the cytoplasmic vesicle.

It is necessary to remark on some other proteins that participate in the process of vesicles fusion with the plasmatic membrane: Unc-18, Tom-1, T07A9.10, Unc-13, Cpx-1. Unc-18 has a syntaxin binding function. It is a human STXBP1 orthologue, mammalian munc-18 homologue, and member of the Sec1/Munc-18 family. In addition to vesicles fusion activity, Unc-18 is also involved in the axonal transport system and affects the synthesis, accumulation, and maintenance of normal acetylcholine levels. All functions mentioned above can explain the high relative expression level for this gene in the nervous tissue. The next highest relative expression level of *unc-18* gene is observed in the intestine. These data show that the process of exocytosis plays an essential role in both types of cells.

Tom-1 and T07A9.10 also have syntaxin binding function. Tom-1 is predicted to have several functions, such as syntaxin binding activity, Rab GTPase binding activity, exocytosis regulation function, and synaptic vesicles priming. Unc-13 is an orthologue of human UNC13A (homologue A Unc-13) and UNC13B (homologue B Unc-13). It is predicted to have calmodulin-binding activity and syntaxin binding activity. Unc-13 participates in the exocytosis of synaptic vesicles, forms a complex with RIM, and probably forms a part of the cellular structure that anchors synaptic vesicles, affects the positive regulation of oocyte development and regulation of the pharyngeal pump. The DAG activation of Unc-13 appears to be essential for maintaining a high synaptic release rate during prolonged repetitive stimulation.

Cpx-1 is an orthologue of human complexin, which positively regulates a late step in synaptic vesicle exocytosis. In the presence of Ca^{2+}, Cpx-1 gets replaced by synaptotagmin. Cpx-1 allows the SNARE protein complex to bind the synaptic vesicle with the presynaptic membrane. Complexin can act as an inhibitor or accelerator of the synaptic vesicle fusion and the release of neurotransmitters. In one conformation, it intercepts SNARE pin complexes, preventing vesicle fusion, while in the other conformation; it releases SNARE pins, allowing synaptotagmin to trigger the fusion.

scRNA-seq expression data of vesicle fusion genes in *Caenorhabditis elegans*

Based on previously mentioned genes with their predicted functions, the set of potential nematode SNARE complex was analysed by the relative expression rate in different excitable and non-excitable nematode tissues from open access scRNA-seq expression data (Fig. 3).

Neurons, being the normal synapse manifesting cells, have the most prominent expression of the vast group of SNARE-set and vesicle fusion related proteins. The highest level of vesicle fusion related genes expression was found in neurons. However, the intestine cells possess three strongly differentially expressed vesicle fusion related genes: *snb-2*, *aex-4*, and *aex-1*. *snb-2* and *aex-4* are predicted to have SNAP receptor activity and syntaxin binding activity. Aex-4 is involved in positive regulation of gut-specific processes – defaecation and positive regulation of Aex-5 protein secretion and is shown to be acting upstream of GABAergic GPCR signalling (Mahoney *et al.*, 2008). Aex-1 is involved in the process of defaecation and anterior body wall muscle contraction. It can also perform other functions, such as regulation of the Unc-13 localization. Unc-13 localization is necessary for synaptic vesicles fusion with the membrane, thus impacting exocytosis. The most expressed syntaxins in the intestine are *syx-3* and *syx-2*, while others are not expressed or have extremely low expression levels. Already mentioned Snb-2 seems to be the only synaptobrevin with the high intestinal expression and expressed almost entirely to this tissue. According to the scRNA-seq expression data Snt-2 and Snt-5 are possibly functional synaptotagmins in the intestinal “synapse”, especially given that Snt-2 and Snt-5 were shown to promote the release of neuropeptide-like protein NLP-40 in enterocytes (Wang *et al.*, 2013; Zhao & Schafer, 2013).

Several other genes coding for vesicle fusion related proteins have significant expression level in the gut: *unc-18*, *unc-64*, *tom-1*, *t07a9.10*, and *sph-1*. They also can be a part of the nematode synaptic apparatus in the intestine cells.

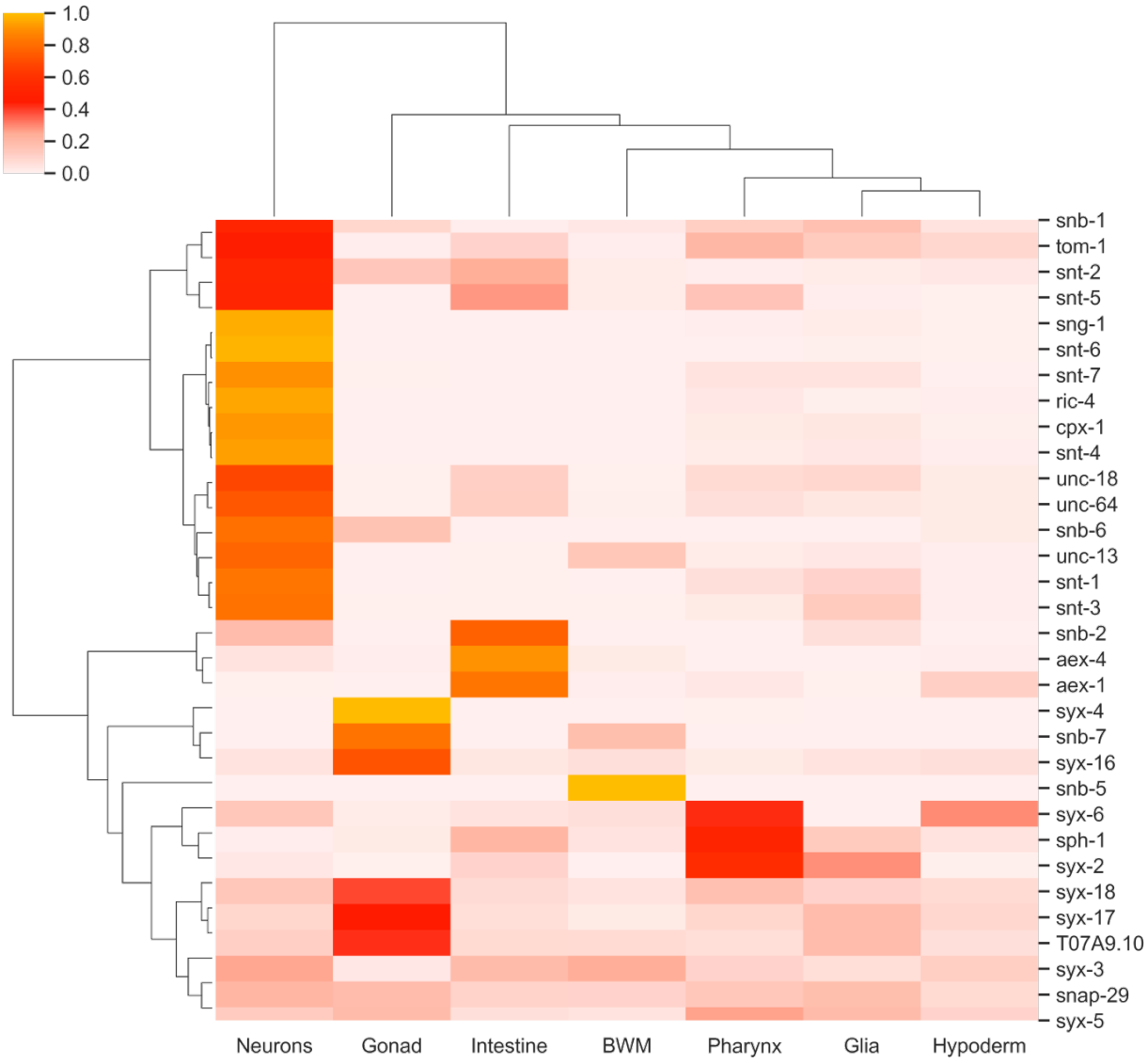

Fig. 3. Differential expression of presynaptic complex genes. Expression clustermap dendrogram for scRNA-seq expression data related to vesicle fusion (right legend) genes in *C. elegans*. For each gene in the set, the tissue/total expression ratio was calculated (relative expression) to compare gene expression levels between different tissue types (neurons, gonad, hypodermis, pharynx, body wall muscles, glia, and intestine (Cao *et al.*, 2017). The expression value for each gene, and each tissue was divided by the sum of each tissue's gene expression values. These values vary between 0 and 1, and the sum for each gene is equal to 1. Higher colour intensity represents higher expression. BWM – body wall muscles. Data were clustered and mapped with Ward's method (Müllner, 2011).

CONSLUSIONS

During the evolution process, the nematode intestine, one of the body's major organs, developed several unusual functions, such as body muscle contraction control or the whole organism systemic necrosis. Those functions require a fast and stable signal transition. Intestinal cells can act as sensory neurons by collecting environmental stimuli or as interneurons by propagating internal or external signals to other enterocytes or neurons and mimic motoneurons by carrying out the signal transmission to muscles.

Even a complex synaptic mechanism, to some extent, is presented in the intestine endodermal cells. Considering the data obtained from scRNA-seq expression analysis, it is possible to conclude that all genes necessary for postsynaptic apparatus and exocytosis are presented in the nematode intestine cells, although not in such assortment and

not in such high level of expression as in the nervous tissue. All these findings draw a fascinating and strong parallel between intestinal nematode cells that can regulate the activity of different body systems and the whole body itself and excitable cells, such as neurons or muscle cells. They give a new possible way of looking at the neuronal evolution and call for a revaluation of the definition of excitable cells.

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В.П. Кузнецов, Г.А. Сливко-Кольчик, Я.Г. Дрозд и Ю.В. Панчин. Средняя кишка нематод – уникальная многофункциональная часть тела.

Резюме. Нервная система – это совокупность взаимосвязанных структур, контролирующая как поведение всего организма в целом, так и передачу сигналов между его различными частями; кишка же является основным органом пищеварения для большинства многоклеточных организмов. Однако, в процессе эволюции, энтероциты нематоды приобрели несвойственные им функции нервных клеток. Наряду с обработкой пищи, всасыванием полезных веществ и передачей их в другие ткани, энтодермальные клетки кишки стали способны управлять активностью некоторых систем организма, отвечать на внешние и внутренние стимулы и даже контролировать сложный механизм запрограммированной смерти всего организма. Дефекационная моторная программа нематод – это высокоточное ритмическое поведение, временные параметры которого передаются клетками кишки нематоды как между собой, так и в другие системы организма для синхронизации ритмической активности. В представленной работе нами были проанализированы данные single-cell RNA-seq нематоды *Caenorhabditis elegans*, и произведен поиск потенциально вовлеченных в передачу нервного сигнала генов. На основании полученных результатов можно сказать, что в некоторой мере клетки кишки нематоды обладают генами, белки которых необходимы для формирования пресинаптического механизма, сходного с нейронным; тем самым приводится еще одно доказательство схожести энтероцитов нематоды и нейронов.