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### REVIEW

- 2704** Key elements determining the intestinal region-specific environment of enteric neurons in type 1 diabetes  
*Bagyánszki M, Bódi N*
- 2717** Paediatric gastrointestinal endoscopy in the Asian-Pacific region: Recent advances in diagnostic and therapeutic techniques  
*Huang JG, Tanpowpong P*
- 2733** Study of tumor necrosis factor receptor in the inflammatory bowel disease  
*Souza RF, Caetano MAF, Magalhães HIR, Castelucci P*
- 2747** Current trends in acute pancreatitis: Diagnostic and therapeutic challenges  
*Zerem E, Kurtcehajic A, Kunosić S, Zerem Malkočević D, Zerem O*
- 2764** Wingless/It/β-catenin signaling in liver metastasis from colorectal cancer: A focus on biological mechanisms and therapeutic opportunities  
*Selvaggi F, Catalano T, Lattanzio R, Cotellese R, Aceto GM*

### MINIREVIEWS

- 2784** Infliximab vs adalimumab: Points to consider when selecting anti-tumor necrosis factor agents in pediatric patients with Crohn's disease  
*Kim ES, Kang B*

### ORIGINAL ARTICLE

#### Basic Study

- 2798** Calcitriol attenuates liver fibrosis through hepatitis C virus nonstructural protein 3-transactivated protein 1-mediated TGF β1/Smad3 and NF-κB signaling pathways  
*Shi L, Zhou L, Han M, Zhang Y, Zhang Y, Yuan XX, Lu HP, Wang Y, Yang XL, Liu C, Wang J, Liang P, Liu SA, Liu XJ, Cheng J, Lin SM*
- 2818** BanXiaXieXin decoction treating gastritis mice with drug-resistant *Helicobacter pylori* and its mechanism  
*Li XH, Xu JY, Wang X, Liao LJ, Huang L, Huang YQ, Zhang ZF*

#### Retrospective Cohort Study

- 2836** Endoscopic and pathological characteristics of *de novo* colorectal cancer: Retrospective cohort study  
*Li SY, Yang MQ, Liu YM, Sun MJ, Zhang HJ*

#### Retrospective Study

- 2850** Prolonged hyperthermic intraperitoneal chemotherapy duration with 90 minutes cisplatin might increase overall survival in gastric cancer patients with peritoneal metastases  
*Steinhoff H, Acs M, Blaj S, Dank M, Herold M, Herold Z, Herzberg J, Sanchez-Velazquez P, Strate T, Szasz AM, Piso P*

## Observational Study

- 2864** Endoscopic ultrasound-guided fine-needle aspiration pancreatic adenocarcinoma samples yield adequate DNA for next-generation sequencing: A cohort analysis  
*Bunduc S, Varzaru B, Iacob RA, Sorop A, Manea I, Spiridon A, Chelaru R, Croitoru AE, Becheanu G, Dumbrava M, Dima S, Popescu I, Gheorghe C*
- 2875** Contributory roles of sarcopenia and myosteatosis in development of overt hepatic encephalopathy and mortality after transjugular intrahepatic portosystemic shunt  
*Yin L, Chu SL, Lv WF, Zhou CZ, Liu KC, Zhu YJ, Zhang WY, Wang CX, Zhang YH, Lu D, Cheng DL*

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## Key elements determining the intestinal region-specific environment of enteric neurons in type 1 diabetes

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### Abstract

Diabetes, as a metabolic disorder, is accompanied with several gastrointestinal (GI) symptoms, like abdominal pain, gastroparesis, diarrhoea or constipation. Serious and complex enteric nervous system damage is confirmed in the background of these diabetic motility complaints. The anatomical length of the GI tract, as well as genetic, developmental, structural and functional differences between its segments contribute to the distinct, intestinal region-specific effects of hyperglycemia. These observations support and highlight the importance of a regional approach in diabetes-related enteric neuropathy. Intestinal large and microvessels are essential for the blood supply of enteric ganglia. Bidirectional morpho-functional linkage exists between enteric neurons and enteroglia, however, there is also a reciprocal communication between enteric neurons and immune cells on which intestinal microbial composition has crucial influence. From this point of view, it is more appropriate to say that enteric neurons partake in multidirectional communication and interact with these key players of the intestinal wall. These interplays may differ from segment to segment, thus, the microenvironment of enteric neurons could be considered strictly regional. The goal of this review is to summarize the main tissue components and molecular factors, such as enteric glia cells, interstitial cells of Cajal, gut vasculature, intestinal epithelium, gut microbiota, immune cells, enteroendocrine cells, pro-oxidants, antioxidant molecules and extracellular matrix, which create and determine a gut region-dependent neuronal environment in diabetes.

**Key Words:** Enteric neurons; Neuronal environment; Gut region specificity; Type 1 diabetes, Hyperglycemia; Microbiota-gut interactions

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**Core Tip:** Diabetes-related intestinal motility disturbances result from multifactorial damage to the enteric nervous system. However, the diversity of the neuronal environment in different gut segments basically determines the regionality of diabetic enteric neuropathy. Therefore, in this review, we highlight the role of enteric glial cells, gut circulation, intestinal epithelium, gut microbiota, immune and enteroendocrine cells, pro-oxidants, antioxidant defence and extracellular matrix, which have great impact on the formation and maintenance of a region-specific enteric neuronal environment in diabetes.

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## INTRODUCTION

In the middle of last century, the general belief was that the neurons within the intestinal wall are parasympathetic neurons[1]. In recent decades, it has become evident that the neurons and glia cells of the gastrointestinal (GI) tract form a third, unique division of the nervous system besides the sympathetic and parasympathetic divisions[2]. The enteric nervous system (ENS) can function independently from the rest of the nervous system and at the same time are in a close, bidirectional connection with it [2,3]. The types and the proportion of enteric neurons were characterized by their morphology, neurochemical code, function and intestinal location in different species[1,4,5]. Nowadays specialized high-throughput “omics” technologies like single cell RNA sequencing even combined with spatially barcoded RNA sequencing can confirm and supplement previous data[6,7].

There is a large body of data on the structure and function of the ENS in physiological state, and it is clear that many pathological conditions strongly affect the enteric plexuses. Since the enteric plexuses are embedded in the histological layers of the intestinal wall (Figure 1), the projections of neurons and glia cells weave through the cross-section of the entire intestine, and because of the lack of blood-brain barrier in the periphery, the role of the environment surrounding the enteric ganglia and neuronal projections is increasingly evident in both health and diseases[2,8].

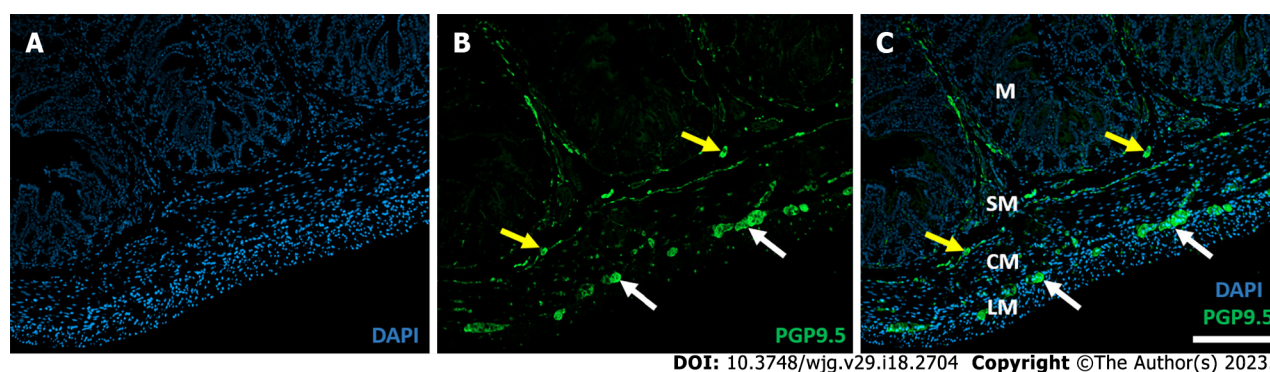
In this review, we provide a brief overview of the effects of type 1 diabetes (T1D) on the intestinal region-specific enteric neuronal environment. Unfortunately, the incidence of T1D is increasing and this incurable disease causes severe GI symptoms[8]. Chronic hyperglycemia influences the structural and functional features of the enteric neurons[9,10], it could change neurochemical code or even can cause neuronal cell death and thus lead to enteric neuropathy described by others and in our former review [11-13]. Hyperglycemia-related enteric neuropathy shows gut-region specific alterations. Therefore, the aim of this paper is to review the main environmental factors (Figure 2) in the intestinal tube from enteric glia cells (EGCs) to the luminal microbiota, which can play a crucial role in the region-specific damage of enteric neurons in the diabetic state. Some key factors like gut microbiota[14-16], GI immune [17-19] or epithelial cells[20-24] are highly emphasized in several papers, so here these are briefly summarized, while other, also critical components of the neuronal environment [e.g. EGCs, intestinal vasculature, pro-oxidant/antioxidant balance and extracellular matrix (ECM) molecules], are discussed in more detail.

## EGCs AND INTERSTITIAL CELLS OF CAJAL

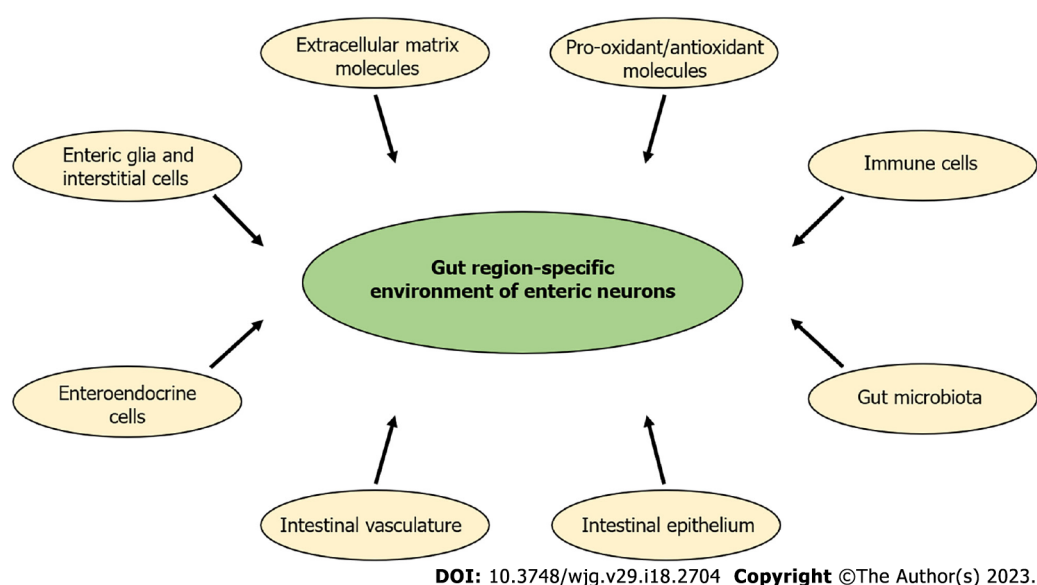
EGCs are not only supporting their neighboring neurons, but also actively regulate GI barrier function, immune homeostasis, or gut motility[25,26]. They directly interact with numerous cells in the gut wall, like enterocytes, immune cells, muscle cells, enteric neurons and vasculature, and these cross-talks influence their survival and functions in different intestinal layers and gut segments in health and disease[27].

Based on cellular morphology and location within different anatomical layers, EGC subtypes are classified into mucosal, intramuscular, submucosal and myenteric glia cells[28,29]. Glial fibrillary acidic protein (GFAP), S100 $\beta$  and Sox10 are among the main glial markers, but expression patterns of different EGCs inside and outside the ganglia can be varied and reflect dynamic gene regulation[30]. In summary, the variety of EGCs, as functional heterogeneity and phenotypic plasticity, fundamentally determine the cellular microenvironment within the gut wall[31,32].

Besides gut layer-dependent diversity, intestinal regional heterogeneity of EGCs is also demonstrated among GI segments. Unique developmental patterns derived from different enteric precursors and specialized functions of EGCs are associated with different GI regions (e.g. esophagus, stomach or intestine) and result in local environmental properties[32,33]. Different protein expression and transcrip-



**Figure 1 Representative fluorescent micrograph of a paraffin section of intestinal wall from control rat colon after Protein gene product 9.5 immunohistochemistry.** Protein gene product 9.5 (PGP9.5) (green) was used as a pan-neuronal marker to label neuronal elements and 4',6-diamidino-2-phenylindole (DAPI) (blue) labelled nuclei. A: DAPI; B: PGP9.5; C: DAPI + PGP9.5. M: mucosal layer, SM: Submucosal layer; CM: Circular muscle; LM: Longitudinal muscle; White arrows: Myenteric ganglia, Yellow arrows: Submucous ganglia; PGP9.5: Protein gene product 9.5; DAPI: 4',6-diamidino-2-phenylindole; Scale bar: 200  $\mu$ m.



**Figure 2 Main elements determining the gut region-specific neuronal microenvironment.** Enteric glia cells, interstitial cells of Cajal, intestinal vasculature and epithelium, enteroendocrine cells, intestinal microbiota and immune cells, balance of pro-oxidants and antioxidants and extracellular matrix molecules create and determine a strictly regional environment of enteric neurons in diabetes.

tional profiles of myenteric glia cells have been observed in mouse ileum and colon[31,34]. EGCs of myenteric ganglia displayed region-dependent responses to neuromodulators and glial regulation of gut contractility was also region- and pathway-specific in the duodenum and colon[35].

Development and function of EGCs and enteric neurons are in close interdependence[36]. Different neurotransmitters can activate EGCs and glial derived neurotrophic factors are crucial for neuronal survival and maintenance[27,37]. EGCs could also act as a critical link in the communication of enteric nervous and immune systems through the modulation of macrophages[38]. Because of the close neuron-glia relationship, it would be beneficial to investigate the involvement of EGCs in diabetes in addition to gut region-specific diabetic neuronal damage[39].

In the duodenum of type 2 diabetic mice with high-fat diet, a decline in the mucosa-associated glial network density was observed, however, neither the glial density and ultrastructure nor the expression of S100 $\beta$ , Sox10 and GFAP markers were changed in the EGCs of myenteric ganglia[40]. Meanwhile, in a distal direction, an intense reduction in the number of both the enteric neurons and S100-immunoreactive glia cells was seen in diabetic rat jejunum[41]. Expression of GFAP and neurotrophins, like glia cell-derived neurotrophic factor (GDNF) and neurotrophin-3 were decreased in the colon of diabetic rats [42]. Loss of enteric neurons and progressive decrease in GDNF expression was demonstrated with the course of diabetic state both in proximal and distal colon of Sprague-Dawley diabetic rats. Moreover, reduced Akt phosphorylation also accompanied these changes[43]. Also, hyperglycemia stimulated EGC apoptosis in culture by repressing the PI3K/Akt molecular pathway[44]. The down-regulation of

the PI3K/Akt pathway, an important mediator of neuronal survival, is heavily involved in the diabetic damage of enteric neurons[45,46].

Interstitial cells of Cajal (ICCs) are pacemaker cells in GI motility that generate spontaneous and rhythmic slow waves to promote the spontaneous contractions of smooth muscles[47]. The delayed gastric emptying both in diabetic patients and diabetic animal models is associated with ICC depletion [10,48]. Furthermore, damage of ICCs contributes to impaired motility in other GI regions causing constipation[49,50].

## INTESTINAL VASCULATURE

Blood vessels enmeshing the small and large intestine are important in nutrient transport and also responsible in supplying enteric cells. Macro- and microvascular anatomy of the GI tract fundamentally determine its regionality. Extramural circulation of the duodenum arises from the coeliac trunk, the jejunum and ileum are supplied by branches of superior mesenteric artery, while different parts of large intestine are supplied by the superior or inferior mesenteric arteries[51]. The impairment of large mesenteric vessels has been described in T1D[52], and substantial heterogeneity of endothelial dysfunction of different large arteries has been observed in a type 2 diabetic animal model[53]. Besides the variability of diabetic macroangiopathy, the impact of diabetes on the intestinal microvasculature can also be region-dependent[54-56].

Investigation of small capillaries in the close vicinity of myenteric ganglia revealed their different susceptibility to diabetic damage along the duodenum-ileum-colon axis[54]. Structural changes such as thickening of the endothelial basement membrane, caveolar hypertrophy and tight junction opening were confirmed in the ileum and colon, whereas only junctional alterations were visible in the duodenal capillaries. In addition, a severely impaired regulation of vascular permeability was shown in ileal and colonic capillaries, while an accelerated, but well-balanced albumin transport was indicated in the duodenum. Immediate insulin treatment prevented most of the diabetes-related changes of the capillary endothelium in the ileum, but not in the colon[54]. Increased thickening of arteriolar wall representing microangiopathy in colonic submucosal vessels was also shown in diabetic patients[56].

Naturally, distinct degrees of capillary damage in different gut segments strongly determine a segment-specific cellular environment and contribute to the diabetic fate of the cells they supply[8]. Close interaction between the capillary endothelial cells and migrating neural crest-derived cells has already been observed in intestinal neurovascular development and has an important role in creating a favorable neuronal microenvironment[57]. Therefore, the diabetes-related regional capillary impairments may greatly contribute to region-dependent enteric neuropathy in T1D[8].

However, not only the structural complications in the vascular system, but also the circulating microparticles can impair the endothelial function in diabetes[58]. Different gut segments feature their distinct microbial compositions and metabolites. Imbalance in the microbial composition accompanying diabetes results in changes of metabolites production, like short-chain fatty acids, bile acids, or tryptophan catabolites[59,60]. Enhancement of gut permeability related to dysbiosis may allow not only the release of different metabolites and endotoxin but also bacterial translocation from the gut to the venous circulation. These elements as integral mediators significantly contribute to vascular inflammation and immune activation[59-62].

## INTESTINAL EPITHELIUM

The lining of the GI tract is directly exposed to an ever-changing environment. This single layer of epithelial cells is crucial for preserving gut homeostasis and functions both as barrier and channel for the crosstalk between the GI immune cells and microbiota[23,63].

Epithelial tight junctions are the key components of the physical intestinal barrier along the GI tract [20]. Altered barrier function of enterocytes and colonocytes leads to several pathologic conditions, including obesity or diabetes[20,21,23]. The chronic hyperglycemia-related breakdown of barrier integrity leads to the systemic influx of microbial products and an enhanced incidence of enteric infection[64].

The intestinal epithelium also has an immunological role, as it contains pattern recognition receptors, such as the Toll-like receptors (TLRs)[20]. Recently, several studies demonstrated the expression of TLR4 in metabolic diseases[65-67]. When sensing microbial lipopolysaccharides of Gram-negative bacteria, TLR4 can activate pro-inflammatory pathways in the GI tract[16,22], thus TLRs may play a crucial role in diabetic enteropathy[65]. TLR4 not only affects ENS function, but also modulates neuro-immune interactions by mediating the effects of the intestinal microbiota[65].



## GUT MICROBIOTA

In the last two decades it has become clear that the imbalance of microbial species due to a reduction in microbial diversity, known as dysbiosis, is associated with several pathological conditions like autoimmune diseases[68], cancers[69], arteriosclerosis[70] depression[71,72], neurodegenerative diseases[73], obesity or diabetes[74-76]. Dysbiosis contribute to the formation of a proinflammatory milieu and gut leakiness[77,78].

Decreased microbiota diversity has been observed in T1D. At the phyla level, the proportion of *Firmicutes* decreased in patients compared to the healthy individual group, while *Bacteroidetes* abundance increased[16,79].

It is also obvious that the composition of microbiota and the number of microbes is different along the GI tract and each segment contains unique microorganism communities[80,81]. Unfortunately, only a very few studies performed longitudinal comparisons, but results showed that the mode and severity of dysbiosis has also been distinct in different gut segments[82-85]. Besides a longitudinal variability, a horizontal gradient also exists in the gut, with oxygen, redox and mucus gradients from the mucosal surface to the lumen[80] and these variables can contribute to the differences of luminal and mucosal microbiota both in health and disease[83,84,86].

By now, a sufficient amount of evidence has been gathered which show that probiotics have a beneficial influence on diabetes-related dysbiosis[78], and a plethora of studies investigate the effects of prebiotics, synbiotics and fecal microbiota transplantation on hyperglycemia and other diabetes-associated symptoms. Among others, *Roseburia intestinalis*, *Lactobacillus casei*, *Akkermansia muciniphila* and *Bacteroides fragilis* have been shown to ameliorate glucose metabolism and insulin sensitivity[75]. In the last 20 years, considerable progress has been made and the intestinal microbiota most certainly represents a promising target for T1D prevention and therapy; however, numerous unresolved concerns require further in-depth investigation.

## GI IMMUNITY

The GI tract is the largest immune organ in vertebrates, where the intestinal homeostasis is determined by the gut microbiota, intestinal epithelium and host immunity[21,87].

The complex and enormous amount of information available about the GI immune system is summarized in other reviews[17-19], here we would like to highlight only one aspect. In earlier studies, the GI immune system has been examined as small *vs* large intestine, based on obvious differences in structure and function. Recently it has become apparent that the immunological niches of the GI tract differ between more refined functional compartments, making it necessary to study them separately to understand the consequences on intestinal immune homeostasis[88].

Based on the review of Brown and Esterházy[88], the GI tube can be divided into the following five main parts: Proximal small intestine, gut-draining lymph nodes, distal small intestine, large intestine and mesentery. Each intestinal niche is influenced by a combination of intrinsic tissue properties, extrinsic environmental signals, and immune cell composition.

It would be beneficial if therapies would take into account the regionally different susceptibility of the GI tract to infections and diseases.

## ENTEROENDOCRINE CELLS

Enteroendocrine cells (EECs) not only play a role in humoral processes but also act as sensory cells in the GI mucosa next to the neurons and immune cells[89]. Therefore, microbial metabolites could stimulate or suppress hormone secretion by EECs, while endocrine and paracrine factors regulate GI functions and affect several metabolic processes in the body[90]. The diversity of EECs prompts the introduction of a new classification scheme. Earlier, EECs were classified based on producing a single hormone, but in the last decade it was shown that most EECs contain multiple hormones. Several hormones, like secretin and serotonin, are in separate storage vesicles at subcellular level[91]. The hormones produced by EECs might have a big potential in the future as novel microbiota-based therapies to alter metabolically active hormone levels, similarly to the use of the anorectic gut hormone, glucagon-like peptide 1, in the treatment of obesity and type 2 diabetes[90].

It is well established that EEC composition and proportion is different along the GI tract[92,93]. A recently published paper by Martin *et al*[93] has indicated that regional differences in nutrient sensing capability exist in mouse EECs. Colonic EECs has been shown to be more sensitive to glucose, while duodenal EECs to fructose and sucrose.

## PRO-OXIDANTS AND ANTIOXIDANTS

The intestinal redox state is critical in maintaining gut homeostasis and functional regulation. The maintenance of this delicate balance in redox state is influenced by the gut microbiota, immune cells and epithelium, which can all produce and respond to redox signals[94]. Numerous genera of bacteria has been identified as biomarkers for gut redox state[95]. Reactive sulfur species-producing bacterial families enhance the host's antioxidant capacity[96], however, sulfur metabolism can be distracted by opportunistic pathogens[94]. Large differences can be observed in different GI segments regarding the quantity and composition of microbiota, intestinal pH or partial pressure of oxygen within the luminal-facing epithelium[80]. There is a richer and more diverse microbial community and deeper anaerobic state from proximal to distal parts of the gut, therefore, it is not surprising that oxidant and antioxidant mechanisms have also been linked to strict region-dependency in health and disease[97]. Foods containing numerous antioxidants, such as vitamins, carotenoids, flavonoids, polyphenols, bioactive peptides or others, however, also include a lot of pro-oxidant molecules[98-100] and all of these can modulate the composition of microbial communities[101]. Consumed and endogenously produced antioxidants have varied strategies at different levels to maintain optimal redox balance[102,103]. Still, the accumulation of reactive oxygen species and/or decrease in antioxidant defence contribute to serious imbalance of intestinal pro-oxidant/antioxidant milieu[104].

Higher mucosal vitamin E and carotenoid concentration, higher total antioxidant activity, superoxide dismutase and catalase activity, as well as glutathione level were observed in the duodenum compared to the ileum and colon of different animal species[105-107]. The presence of probiotic *Lactobacillus* species also reflects a highly beneficial cellular environment in the duodenum[108]. Moreover, in diabetic rats, an increased abundance of the genus *Lactobacillus* has been observed relative to controls [83], which can result in enhanced antioxidant capacity[109]. While no significant changes in peroxynitrite production has been observed, a robust increase of metallothionein 2 and elevated glutathione level has been found in the duodenum of diabetic rats[110], which may contribute to cell survival in this particular gut segments.

In contrast to the duodenum, diabetes increased lipid peroxidation and catalase activity, as well as the percentage of nitrotyrosine-immunoreactive myenteric neurons in the jejunum[111]. Decreased superoxide dismutase and increased myeloperoxidase enzyme concentrations were also demonstrated in the diabetic jejunum[112]. Enhanced lipid peroxidation and protein oxidation accompanied with significantly lower superoxide dismutase levels, catalase and glutathione levels were also observed in the diabetic ileum[113,114]. However, a great increase in the activity of the endogenous heme oxygenase system was shown in myenteric neurons of diabetic ileum[115], maybe as an effect of microbial changes [116]. In the colon of diabetic rats, the doubled peroxynitrite level, reduced superoxide dismutase activity and the induction of the endogenous heme oxygenase system emphasizes the observation that distal gut segments have greater susceptibility to the diabetic oxidative environment, which is in correlation with diabetic neuronal cell loss[97,110,115].

## ECM

ECM structures composed of various proteins and polysaccharides are essential in the maintenance and well-regulated remodeling of tissues and have a key role in regulating different cellular events, like cell proliferation, differentiation or migration[117-119]. In the gut, numerous cells (*e.g.* epithelial, mesenchymal, stem cells) participate in the production of matrix molecules, and their precise composition is indispensable for the optimal cellular environment and normal intestinal function. Sensing the stiffness or the porosity of the ECM through specific receptors such as integrins, intestinal cells can change their intracellular state or dynamics[120,121].

Diabetes-related alterations of ECM is demonstrated in all parts of the gut, but with different extent in different regions and intestinal layers. In streptozotocin-induced diabetic rats, a significant increase in the amount of laminin-1 and fibronectin was observed in the small intestine by Western blotting and immunohistochemistry, and the strong labelling was restricted mainly to the intestinal smooth muscle and serous layers[122]. These hyperglycemia-mediated ECM accumulation was reversed by insulin treatment[122]. Additionally, in the distal colon, a marked increase of type 1 collagen was detected with no changes in type 3 and 4 collagen expression[123]. Besides of the well-marked pockets of collagen among the smooth muscle cells, formation of advanced glycation end-products was also observed in diabetic rats. Type 1 collagen deposits and glycation increase stiffness of the diabetic colon muscle, which contribute to limited colonic function[123]. There is a strict association between collagen content and mechanical properties, however, this varied in different parts of the small intestine [124]. Increased ECM deposition, as well as high levels of type 1 and 3 collagen and fibronectin mRNAs were also detected in diabetic colon mucosa[125]. The accumulation of ECM in the mucosa of the diabetic colon was associated with the deregulation of the transforming growth factor (TGF)- $\beta$ 1/Smad signaling pathway[125]. However, TGF- $\beta$  can also influence deposition of matrix molecules by upregulating several ECM receptors[126].

Structural alterations of basement membranes as specialized ECM structures have been characterized in diabetes mellitus. Thickening of capillary basement membrane is among the first histological hallmarks of the disease. Capillaries located in gut smooth muscle in different gut segments displayed region-specific thickening of their basement membranes in T1D[54]. Additionally, significant increase in mRNA levels of different matrix scaffold proteins, like fibronectin or procollagen type 1, was observed in the aorta and mesenteric artery of type 2 diabetic Goto-Kakizaki rats[127]. Moreover, gene expression was restored in the mesenteric bed but not in the aorta using an endothelin-1 antagonist[127]. Basement membrane thickening of smooth muscle cells was also demonstrated in the small intestine[122] and colon[123]. Moreover, the basement membrane surrounding the myenteric ganglia was also thickened in diabetic rats with strict regionality in different gut segments[128].

ECM accumulation can be due to the enhanced synthesis of matrix components, but also their decreased degradation, which in turn leads to the imbalance of ECM dynamics[129]. Matrix metalloproteinases (MMPs) and their tissue specific inhibitors (TIMPs) mainly produced by macrophages, neutrophils or epithelial cells have an essential role in tissue remodeling as a response to intestinal inflammation[130,131]. Growing molecular evidence support that these proteolytic enzymes are also targets of diabetic damage. In the diabetic ileum, MMP9 expression decreased in myenteric ganglia, capillary endothelial cells and intestinal smooth muscle cells, while these values did not change in the duodenum, which is in perfect agreement with the regionally distinct thickening of the ganglionic basement membrane. However, a specific, but great induction was revealed in MMP9 and TIMP1 at the mRNA level both in duodenum and ileum homogenates of diabetics[128]. Increased early expression of MMP2 and MMP9 mRNAs and MMP1 later on was also demonstrated in the diabetic colon mucosa. On the other hand, increased TIMP1 and TIMP2 expression could be the result of decreased MMPs degrading activities here[125].

## CONCLUSION

Because of its various functions, as food intake, mechanical and chemical breakdown, motility, absorption, regulation of blood flow, secretion, water reabsorption and immune functions, the GI tract has unique features. It has three detecting systems, which are more extensive than those of any other organ: (1) The ENS contains as many neurons as the spinal cord and different subpopulations of the EGCs cover all histological layers of the intestinal wall. Intrinsic primary neurons, interneurons and motoneurons can form local reflex circuits in the gut wall[1,2]; (2) There are more than 20 hormones produced by several types of EECs[89]; and (3) The GI tract is the largest immune organ with the cc. 70-80% of the body's immune cells[87,132].

In addition to the three systems listed above, other essential factors such as intestinal epithelial barrier, microcirculation of the gut wall, pro-oxidant/antioxidant milieu, ECM components and gut microbiota also play a crucial role in the formation of the enteric neuronal environment in both physiological and pathological states. Results demonstrated a clear relationship between intestinal microorganisms and the occurrence of T1D, but the correlation or causality remains an important question for several reasons. Altered gut microbiota-mediated redox imbalance and changes in cellular cross-talks may contribute to enteric neuropathy and also influence the function of gut-brain axis[15].

Considering these properties and the size of the GI tract, it is not surprising that it shows profound functional and structural differences along its length. When planning experiments, the gut should be regarded as a multiple organ, and in the case of illness, the applied therapies should take into account the intestinal segment-specific effects[88].

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## FOOTNOTES

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