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WORD COUNT	1166	TIME SUBMITTED	13-MAR-2024 05:35PM
		PAPER ID	107533767

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 91582

Manuscript Type: EDITORIAL

Bowel function and inflammation: Is motility the other side of the coin?

Panarese A. Inflammation and intestinal motility

Abstract

Digestion and intestinal absorption allow the body to sustain itself and are the emblematic functions of the bowel. On the flip side, functions also arise from its role as an interface with the environment. Indeed, the gut houses microorganisms, collectively known as the gut microbiota, which interact with the host, and is the site of complex immune activities. Its role in human pathology is complex and scientific evidence is progressively elucidating the functions of the gut, especially regarding the pathogenesis of chronic intestinal diseases and inflammatory conditions affecting various organs and systems. This editorial aims to highlight and relate the factors involved in the pathogenesis of intestinal and systemic inflammation.

Key Words: Motility; Inflammation; Pathogenesis; Vitamin D; Microbiota; Gut; Chronic intestinal pseudo-obstruction

Panarese A. Bowel function and inflammation: Is motility the other side of the coin? *World J Gastroenterol* 2024; In press

Core Tip: The pathophysiology and pathogenesis of inflammatory bowel diseases, functional bowel diseases and inflammatory diseases affecting other organs and systems is being defined. The gut is intended to be the site where inflammatory processes with systemic implications are triggered. A wide-ranging view is required to clarify these pathways with the aim of increasing differential diagnosis, early diagnosis, and treatment to improve prognosis of chronic bowel and systemic inflammation.

INTRODUCTION

Bowel disease is a substantial and growing factor driving access to medical care, with notable economic and social impacts, especially in the context of chronic inflammatory diseases[1]. These diseases encompass not only inflammatory bowel disease (IBD), but also other intestinal inflammations, such as diverticulosis and functional disorders[2].

Additionally, chronic systemic and organ inflammation is also increasing, carrying both epidemiological and clinical implications[3]. Currently, the pathogenetic role of the gut in chronic systemic inflammation depends on the function of the gut barrier. This functionality is related to the composition of the gut microbiota and the activity of tight junctions, influenced by inflammatory factors, diet, hormones, and the enteric system[4]. The gut barrier disruption, the "leaky gut", contributes to the development and progression of metabolic, ischemic, neoplastic, neurodegenerative and autoimmune systemic diseases with a substantial epidemiological impact[5-8].

The established role of gut microbiota/microbiome and intercellular junctions prompts a comprehensive exploration of all the factors influencing them. The rapidly accumulating volume of publications serves to enrich our understanding of biological processes and review data[9]. If environmental factors act unconditionally on all individuals, with variations across geographical area[2,5,9-11], among host factors, the genome is the most important. It determines intestinal nutrient absorption and availability, intrinsic intestinal motility, expression of structural proteins (including those of intercellular junctions), interaction with the gut microbiota, and immune response[3,7,8,12-14]. Gut and systemic inflammation, resulting from impaired gut immune activity, are primarily determined by genome[10,12-15]. The potential of intestinal inflammation to induce systemic inflammation may be attributed to the number of exogenous factors. These factors act over a very large surface, involving multiple types of cells and tissues[8-11,13,16]. The well-being of the human body depends on the homeostasis of the intestinal balance, which is unique in many respects. In the presence of favorable genetic characteristics exogenous factors have the potential to shift the immune response towards an inflammatory/autoimmune direction, carrying systemic implications[2-5,9,14,15,17].

RELEVANCE OF THE GENOME

Genome is the main determinant of gut biological processes for several reasons. First, the host genomics has an impact on the gut microbiota/microbiome[15-17]. Second, the

genome determines the gut barrier, a dynamic structure that serves as a defense mechanism by shielding the intestinal structures and processes from external aggression[12,13,18]. The microbiota, located in the intestinal lumen, at the interface with the intestinal epithelium, interacts with the gut barrier[16,19]. Third, intestinal immune activity, protected by the gut barrier, also has characteristics conferred by the genome[3,13,14,16,20]. Therefore, exogenous factors, as well as the microbiota, interact with a genetically set immune response[21,22]. The expression of structural, enzymatic and functional proteins, including those involved in the gut barrier, immune response, digestive function and absorption, and neuromuscular components, depends on genetic characteristics[23,24].

The fact that family history is relevant in the onset of intestinal and systemic/organ diseases (inflammation, malabsorption, allergies and neuromuscular diseases) confirms the relevance of the genome, for genetic syndromes such as idiopathic chronic intestinal pseudo-obstruction (mutation in ACTG2, ERBB2-3, *etc.*) and for diseases in which immune and oxidative stress is a determining factor[25]. Obviously, phenotypic expression is influenced by exogenous factors that interfere with the immune activities of the lamina propria by crossing the gut barrier, as well as the genome[2,5,9,26]. In the presence of these factors, including the microbiota and the intestinal barrier, stromal cells, fibroblasts, endothelial cells, and inflammatory and immune cells, alter their interactions[2,4,5,11,13,16,27].

CENTRALITY OF MICROBIOTA, MOTILITY AND NUTRIENTS

Among the factors that act on intestinal biological processes, a phenotypic manifestation of the genome, the microbiota play a crucial role in both physiological and pathological conditions[2,4,5,7]. Various factors modify the microbiota and intestinal activities (the intestinal barrier, immune response, neuromuscular activity). Ultimately, these modifications can amplify or inhibit the inflammatory cascade[2,5,9,28-30]. Among the factors, vitamin D plays an important protective role because vitamin D signaling strengthens the gut barrier by upregulating the tight junctions of intestinal epithelial

cells, and increasing the production of mucin and antibacterial peptides; downregulates dendritic cells activity; induces the differentiation and function of tolerogenic rather than pro-inflammatory T cells [increases the production of anti-inflammatory cytokines interleukin (IL)-4/IL-10 and decreases IL-17/IL-6/IL-2/interferon γ/tumor necrosis factor α][30]. Vitamin D/vitamin D receptor (VDR), by influencing both innate and adaptive immunity, plays a role in regulating the intestinal inflammation switch[30,31].

Scientific literature affirms the association between leaky gut and T cell dysfunction with the onset of conditions such as diabetes, cancers, depression and cardiovascular disease. Additionally, factors such obesity, diet, psychosocial stress, and early life stress are implicated in these associations[6,19,20]. Moreover, vitamin D signaling is related to type 2 diabetes, nonalcoholic fatty liver disease, multiple sclerosis and others autoimmune diseases, neurodegenerative diseases, allergies, cancers, IBDs, and chronic intestinal constipation[29,31-33]. Vitamin D deficiency may lead to gut dysbiosis and endotoxemia, potentially leading to systemic inflammation[22,30,31]. Essentially, vitamin D/VDR is involved in the pathogenesis of intestinal inflammation, with repercussions on systemic inflammation[30,31]. However, at the root of the pathogenetic sequence leading to diseases "related" to vitamin D deficiency there may be a defect in intestinal motility. Chronically reduced, whether idiopathic or secondary, intestinal motility can result in decreased absorption of vitamin D and other nutrients due to dysbiosis. Under favorable conditions, this scenario may lead to chronic intestinal and systemic inflammation[32]. By considering these premises, we can aim to prevent or treat diseases by modifying factors that reduce intestinal motility[25,34-41] (Figure 1).

CONCLUSION

Gut homeostasis depends on the balance between phenotype characteristics and exogenous factors, which collectively foster the stability of the microbiota. Clinical trials are required to validate the pathogenetic role of intestinal motility in impairing gut homeostasis consequently leading to inflammation with systemic involvement.

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