Genome Medicine

COMMENT

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The role of gut microbiota in the pathogenesis of diverticular disease: where are we now?

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Abstract

Diverticular disease (DD) is widespread worldwide. The role of gut microbiota (GM) in DD is not entirely understood. Here we discuss the significance of the current knowledge on GM in the different stages of DD and how crucial these acquisitions are for designing diagnostic and therapeutic trials in this field.

Keywords Diverticulosis, Symptomatic uncomplicated diverticular disease, Acute diverticulitis, Gut microbiota

Background

Diverticulosis of the colon is the most frequent anatomic alteration in adults aged 70 years or older [1]. Most remain asymptomatic, but about 15–20% of them may develop symptoms, the so-called diverticular disease (DD) [1]. Among these patients, about one-fourth will develop the most severe stage of the disease, called acute diverticulitis (AD). AD is a clinical-pathological entity characterized by inflammation of the diverticula associated or not with complications such as stenosis, diverticular perforation with possible formation of an abscess or fistula, and sometimes diverticular bleeding. DD has a significant impact on clinical practice since it has a rapidly increasing incidence worldwide, has managing costs of over 2 billion/year in the USA, and causes about 23,000 deaths/year in Europe [1]. Pathogenesis of DD is still not fully understood. Researchers have also focused on the gut microbiota (GM) in DD.

Hua et al. recently investigated the GM of patients with asymptomatic diverticulosis, comparing them with patients without diverticula. Although no significant differences in the overall diversity of GM between asymptomatic diverticulosis and controls were found, authors showed that *Roseburia intestinalis*, *Dorea* sp. CAG:317, and *Clostridium* sp. CAG:299 were more abundant in subjects with diverticulosis than controls (q values = 0.17, 0.24, and 0.10, respectively) [2]. Moreover, microbial function was significantly involved in different metabolic pathways in left- or right-sided diverticulosis (glycolysis and carbohydrate metabolism, and amino acid and carbohydrate metabolism in left- and right-sided, respectively) [2]. This means GM also plays a crucial role in the host's metabolic functions.

In light of these exciting results, we aimed to summarize current knowledge on the role of GM in the pathogenesis of DD.

Profiling the gut microbiota in diverticulosis

Several studies have profiled the GM composition in patients with diverticulosis, and none of these studies found significant changes in the overall diversity of GM

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between asymptomatic diverticulosis and controls [2, 3]. However, Alexandersson et al. found a higher abundance of genus *Comamonas* among subjects who later developed AD than those who did not ($P=0.027$) [3]. These last data have partially been confirmed by Hua et al.: no significant changes were found in alpha diversity between asymptomatic diverticulosis and controls, while some changes in beta diversity were recorded [2]. Moreover, this latter study provided interesting data about the metabolic pathways of left-sided and right-sided diverticulosis for the first time compared with controls [2]. Although the significance of these changes must be investigated more in-depth, these data suggest that some bacterial species may interact with lifestyle factors in the pathogenesis of diverticulosis.

Profiling the gut microbiota in symptomatic uncomplicated diverticular disease

GM has also been profiled in patients with symptomatic uncomplicated diverticular disease (SUDD). Microbial members with anti-inflammatory properties, such as *Clostridium cluster IV*, *Clostridium cluster IX*, *Fusobacterium*, and *Lactobacillaceae* [4], were depleted in patients with SUDD. At the same time, higher expression of *Akkermansia muciniphila* [5], *Ruminococcus*, *Cyanobacterium*, and *Faecalibacterium* was observed [6]. *Pseudobutyrivibrio* and *Bifidobacterium* were significantly more prevalent in patients with previous AD compared with those without previous AD episodes ($P=0.0040$ and $P=0.0056$, respectively), while the *Christensenellaceae* family and the *Mollicutes RF9* order were substantially more prevalent in patients with SUDD without history of AD ($P=0.0101$ and $P=0.0192$, respectively) [6]. However, all the studies mentioned above have relied on small cohorts, with limited impact on the comprehension of these results.

Recently, we found that a higher relative abundance of the family Streptococcaceae discriminated SUDD. Moreover, by stratifying the SUDD patients by the severity of abdominal pain (according to the visual analogue scale, VAS), we found that higher diversity and health-associated taxa (such as *Bifidobacterium*, *Eubacterium coprostanoligenes group*, and *Dorea*) characterized mild (VAS score 1–3) SUDD; *Proteobacteria*, *Veillonellaceae*, and *Blautia* characterized moderate (VAS score 4–7) SUDD; and *Prevotellaceae* and *Megasphaera* characterized severe (VAS score 8–10) SUDD. This study hypothesized that specific taxa may be related to SUDD, depending on the severity of abdominal pain [7]. Combining these data showed that GM profiling in SUDD patients could predict the severity of their symptoms, such as abdominal pain, thus facilitating the personalization of treatment.

Profiling the gut microbiota in acute diverticulitis

AD is the stage of the disease in which the GM is better profiled. This is probably because AD is the stage of DD with considerable morbidity and non-negligible mortality. Therefore, it is crucial to better understand the role of GM in its pathogenesis and the possible therapeutic implications. Three recent studies provided more exciting results because they all report significant GM perturbation.

O'Grady et al. enrolled 55 AD patients (44 with uncomplicated AD, UAD, and 11 with complicated AD, CAD) compared with 27 controls. Authors found that the *Actinobacteria* and *Proteobacteria* species were more abundant in AD than in controls; *Lachnospiraceae*, *Ruminococcus*, and *Faecalibacterium* decreased, while *Fusobacteria*, *Prevotella*, and *Paraprevotella* representation increased in AD [8]. More interestingly, *Prevotella*, *Fusicatenibacter*, and *Faecalibacterium* were more abundant in CAD than in UAD [8]. When comparing the mucosal-associated taxa in the AD tissues in patients with CAD vs. UAD, Portolese et al. found an increase in abundance of sulfur-oxidizers microbes (such as *Sulfurovum* and *Sulfurovaceae*) and sulfur-reducing microbes (such as *Bacteroidetes* spp., *Cloacibacillus evryensis*, and class *Synergistia*). Furthermore, an abundance of *Campylobacter ureolyticus* and *Clostridium cadaveris* species, the genus *Aggregatibacter*, and class *Methanobacteria* were found [9]. Ma et al. recently investigated the GM of patients with AD, comparing them with patients without AD. Authors found an increase of *Blautia*, *Ruminococcus gnavus*, and *Anaerotruncus colihominis*, a relatively newly described species involved in sulfur metabolism [10]. Furthermore, they discovered that *P. excrementihominis*, *Clostridium* species, *E. eligens*, *H. hathewayi*, and *R. gnavus* showed the greatest discriminative value between patients with AD and patients without [10]. Finally, metabolomic shifts in AD described the enrichments of metabolites related to histidine metabolism and depletions of microbially associated ceramides, changes linked to a clear inflammatory pattern [10]. All of these changes showed the crucial role of GM in the pathogenesis of AD and its severity, which may influence the host's metabolic activity.

The clinical significance of gut microbiota changes in diverticular disease: present and future

From a clinical point of view, all the modifications of GM described above must have a clear purpose: to clearly understand the role of these changes in preventing (or treating) the most frequent complication, i.e., AD. At present, three points are clear: (1) diverticulosis does not show significant changes in GM, and the potential

role of some single bacterial species as a risk factor for AD occurrence in these subjects must be confirmed; (2) SUDD shows mild but significant changes in GM. In particular, the taxa changes seem to be linked to the severity of the abdominal pain, and the role of increased abundance of mucin-degrading species, such as *Faecalibacterium* or *Akkermansia*, appears to be different compared to that occurring in inflammatory bowel diseases (IBD); (3) AD shows changes in GM that are similar to those reported in IBD. Furthermore, the abundance of microbial species involved in sulfur metabolism in AD cases could be considered a specific microbial characteristic of these patients.

However, several points must be addressed. First, are the GM changes a *continuum* from diverticulosis to AD? In other words, are the GM changes progressively increasing and worse through this continuum? If we look at the current results, the answer could be "yes": no significant changes in diverticulosis, mild changes in SUDD, significant changes in AD (Fig. 1). However, if it is so, it is unclear why not all SUDD patients develop AD. We know that the prevalence of AD in these patients is double that recorded in subjects with diverticulosis [1], but we know that no more than 8% of these patients develop AD. What about the other 92% of SUDD patients? Are there specific GM signatures that can predict the evolution towards AD? We don't know. Second, are these GM changes a reliable target for treating/preventing AD occurrence/recurrence? Preliminary data from controlled studies found probiotics promising as add-on therapy to control the evolution of in-hospital patients with AD [1]. However, these studies are still too preliminary to conclude, and further studies are needed. Furthermore, it must be noted that at least 50% of AD cases are genetically determined [1].

We think comprehending the metabolic activity arising from the relationship between host characteristics and GM will be necessary to define who is at risk of AD and, therefore, must be treated (and, of course, how it must be treated). Two studies conducted in SUDD

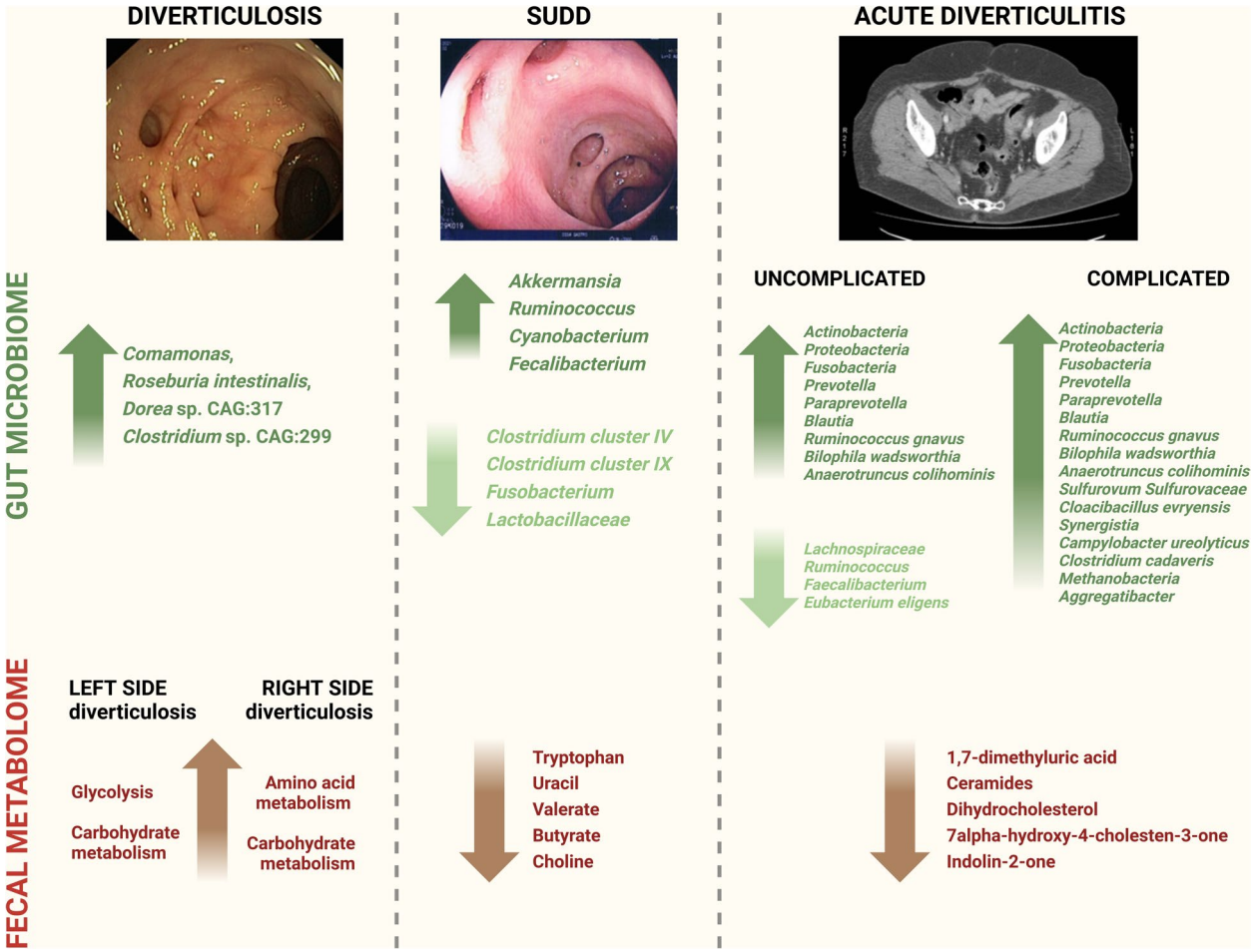

Fig. 1 Current knowledge about gut microbiota and fecal metabolome in diverticulosis and diverticular disease of the colon

patients [4, 5] and the recent studies by Ma et al. in AD [10] and Hua et al. in asymptomatic diverticulosis [2] found that specific metabolomic signatures are linked to GM signatures. Therefore, microbiomics and metabolomic studies could be the future in this setting, which may aid physicians in selecting patients at risk (such as those obesity or specific endoscopic damage) who need to be treated and followed up.

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AT wrote the initial version of the manuscript, and AT and AP revised and edited it. AT and AP read and approved the final manuscript.

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Data availability
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Not applicable.

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Competing interests
Antonio Tursi served as speaker and/or consultant for AbbVie, Bayer, Fenix Pharma, Galápagos, Janssen, Nalkein, and Omega Pharma; Alfredo Papa served as a speaker for Janssen.

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