

COMMENTARY

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The interaction between gut microbiota and age-related changes in immune function and inflammation

Thea Magrone* and Emilio Jirillo

Abstract

Intestinal microbiota and gut immune systems interact each other, maintaining a condition of homeostasis in the context of the intestinal habitat. However, both systems undergo modifications in elderly, thus accounting for a low grade inflammatory status which, in turn, may evolve toward more severe pathological conditions such as inflammatory bowel disease and colon rectal cancer. In addition, in western societies dietary habits may negatively influence the microbiota composition, also altering gut immune response which is *per se* impaired in elderly. In order to prevent the outcome of aged-related disease, supplementation of nutraceuticals able to correct abnormalities of both immune system and microbiota has become more frequent than in the past. In this respect, a better identification of components of the aged microbiota as well as a deeper analysis of gut mucosal immunity function should be pursued.

Keywords: Ageing, Gut, Immunity, Microbiota

Introduction

The intestinal microbiota is mostly confined in the colon where resides 1.5 Kg of microbes that is equal to about 10^{14} microorganisms [1]. Human microbiota represents a “superorganism” possessing more genes than the human genome [2]. It undergoes individual variations in its composition and, in the same individual, variations in the different segments of the bowel have been reported [3]. Moreover, the microbiota of the mucosa seems to differ from that of the lumen and not always a direct interaction between microbiota and epithelial cells does occur [4]. Actually, two major *phyla* have been identified in the animal and human microbiota, such as Bacteroidetes (Gram-negative bacteria) and Firmicutes (Gram-positive bacteria). However, Actinobacteria and Protobacteria can predominantly colonize the intestine in some people [5,6].

In the context of the gut associated lymphoid tissue (GALT), enterocytes or intestinal epithelial cells (IECs) represent the first barrier against invading microorganisms either secreting mucin or defensins (a class of antimicrobial peptides) or sensing pathogens *via* Toll-like

receptors (TLRs) [7]. Furthermore, microfolded (M) cells, specialized IEC, are able to sample microbial antigens and transfer them to lamina propria (LP) immune cells [e.g., dendritic cells (DCs)] [8]. In turn, DCs act as presenting antigen cells (APCs), thus triggering both harmful and protective responses in the host [9]. DCs in the presence of a milieu enriched in interleukin (IL)-6, IL-1 β and transforming growth factor (TGF)- β are able to polarize the immune response towards T helper (h)17 cells which, in turn, release IL-17A, IL-17 F, IL-21 and IL-22, thus becoming inflammatory in the presence of IL-23 [10]. This immune pathway is mainly activated in the course of inflammatory bowel disease (IBD).

On the other hand, CD103+ cells are tolerogenic and in the presence of IL-10, TGF- β , thymic stromal lymphopoietin and vasoactive intestinal peptide induce T regulatory (Treg) cells [11]. These CD4 + CD25 + FoxP3+ cells release IL-10 in the bowel, counteracting the activity of Th17 cells [12]. This tolerogenic anti-inflammatory activity is favored by retinoic acid (RA), a metabolite of vitamin A, produced by CD103+ tolerogenic DCs [13]. Of note, RA seems to directly interfere with Th17 polarization. In the context of intestinal mucosa, secretory

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(s) IgA production by B cells prevents bacterial adhesion to mucosal surfaces and neutralize toxins.

Regulation of the intestinal immune homeostasis by the microbiota is illustrated in Figure 1.

In aged GALT, a marked multiple impairment of the immune response has been reported as evidenced by several studies conducted in animal models [14]. Major alterations are represented by [15]:

1. Reduced secretion of mucus and α -defensin;
2. Easy entry of pathogens into the mucosal layers and generation of a low grade inflammatory response (the so-called "inflamm-aging") [16] with Th1, Th2 and Th17 cell polarization.

This condition of inflamm-aging [16] is perpetuated by overgrowth of intestinal pathobionts.

Interactions between intestinal microbiota and immune system

Microbiota and immune cells actively interact within the gut [17]. Evidence has been provided that *Bacteroides fragilis* induces production of IL-10 by Treg cells via

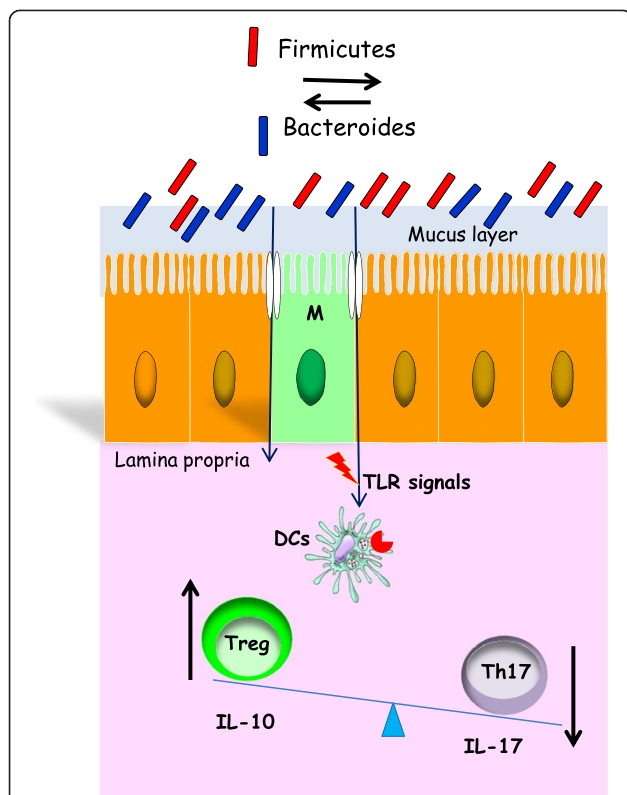


Figure 1 Immune homeostasis maintained by the intestinal microbiota. The equilibrium between Bacteroidetes and Firmicutes leads to the activation of T regulatory cells with production of the anti-inflammatory cytokine IL-10. On the other hand, release of IL-17 by Th17 cells is reduced.

recognition of the polysaccharide A by TLR-2 [18]. In addition, lactobacilli and bifidobacteria play a tolerogenic role, rendering DCs less undifferentiated [19]. Conversely, segmented filamentous bacteria (SFB), component of the animal microbiota, are able to induce production of IL-17 from Th17 cells in mice [20]. Therefore, a fine balance is required in the daily interplay between microbiota and innate and adaptive immune cells to avoid noxious reactions to the host. According to the two-hit model [21] alteration of the microbiota triggers IL-6 production by lamina propria DCs, thus leading to activation of T0 cells. Differentiation of T0 cells into Th1 cells and Th17 cells creates an inflammatory milieu which culminates in colitis (Figure 2).

Studies on the aged intestinal microbiota have led to conflicting results. A decline of bifidobacteria and lactobacilli has been reported in the elderly with an increase of *Bacteroides* and facultative anaerobes [22,23]. In contrast, others reported higher levels of *Ruminococcus* and

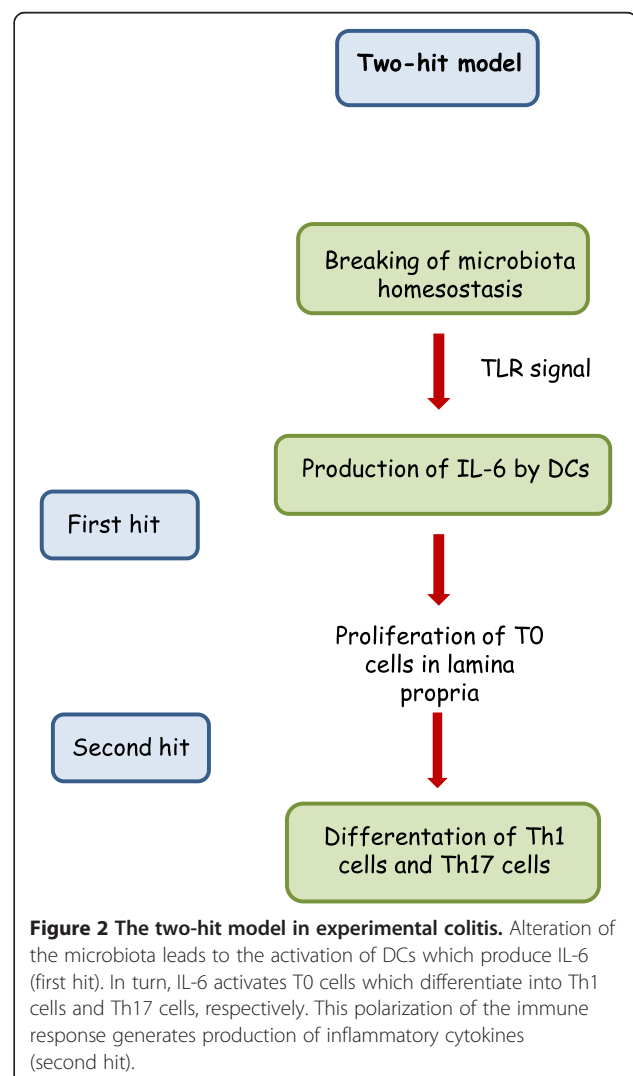


Figure 2 The two-hit model in experimental colitis. Alteration of the microbiota leads to the activation of DCs which produce IL-6 (first hit). In turn, IL-6 activates T0 cells which differentiate into Th1 cells and Th17 cells, respectively. This polarization of the immune response generates production of inflammatory cytokines (second hit).

lower levels of Eubacterium and Bacteroides [24] with higher levels of bifidobacteria in comparison with the younger counterpart [25]. Finally, no differences between aged and younger individuals have been reported by others except for higher numbers of aerobes in elderly [26]. Also differences in aged microbiota were found depending on the country examined. In this respect, in a small population of aged Italian subjects an unchanged level of Bacteroidetes and an increase in *Faecalibacterium* spp. were observed [27]. *Viceversa* in a large cohort of Irish elderly people Bacteroidetes and *Faecalibacterium* spp. remarkably increased [22]. In the above mentioned group of Italian people no differences in microbiota were found when young adults (30 yrs old) and elderly (70 yrs old) were compared. Conversely, in the same group, centenarians exhibited a different composition of their microbiota. While Bacteroidetes and Firmicutes were still present with levels comparable to those of younger adults, a decrease of Clostridium cluster XIVa, an increase in bacilli and rearrangement of Clostridium cluster IV were reported [27]. In addition, in centenarians the observed increase in Proteobacteria, the so-called “pathobionts”, may explain the high frequency of infections once these bacteria have escaped from the host immune response [28].

Microbiota components account for the production of short chain fatty acids (SCFA) and, in particular butyrate, acetate and propionate. SCFA are endowed with anti-inflammatory (inhibition of NF- κ B) and anti-neoplastic activities, also exerting a protective function in favor of intestinal epithelia [29]. In fact, butyrate has been shown to provide energy to the intestinal epithelium, as suggested by epithelial atrophy and inflammation in diversion colitis owing to SCFA deficiency [30]. In aged people, evidence has been provided that reduction of butyrate levels is depending on the decreased number of *Faecalibacterium* (*F.*) *prausnitzii*, *Eubacterium hallii* and *Eubacterium rectal*/Roseburia group [27]. Therefore, SCFA decrease may lead to an impaired secretion of mucins by the IECs and, therefore, easier entry of pathogens into the intestinal mucosa, especially Enterobacteriaceae. These Gram-negative bacteria are able to release lipopolysaccharides or endotoxins, which, in turn, aggravate the inflammatory condition [31]. In general terms, patients with IBD exhibit an abnormal microbiota with instability of dominant species which is higher than in healthy controls. In particular, *F. Prausnitzii* is severely reduced in Chron's disease and in ulcerative colitis with an increased prevalence of adherent-invasive *E. coli* strains. However, the question is still open whether this alteration of microbiota is the cause or the consequence of IBD [32]. Moreover, evidence has been provided for a decreased content of SCFA in colon rectal cancer (CRC) with an increase of CRC in the western elderly population. A condition of chronic inflammation dependent on the change of microbiota leading to

TLR-mediated NF- κ B activation and colonization of the bowel by toxigenic bacterial strains, such as *Helicobacter pylori*, *Bacteroides fragilis* and *Escherichia coli* seems to contribute to the pathogenesis of CRC [33]. In this framework, in a recent study a comparison of aged microbiota was made between community-dwelling individuals and long-stay individuals. Actually, SCFA fecal content was more pronounced in community group than in long-stay patients [34]. In the latter, IL-6, IL-8 and C-reactive protein levels were higher than in the former group, as expression of a status of systemic inflammation. All these evidences correlated to a change in microbiota since in community individuals a higher numbers of Firmicutes and lower numbers of Bacteroidetes than those observed in long-stay patients were detected [34]. This situation is depicted in Figure 3 where the activation of Th17 cells leads to a condition of inflammation.

In this context, one should emphasize that obesity leads to an alteration of intestinal microbiota with an increase of Firmicutes [35], thus provoking a further aggravation of inflamm-ageing.

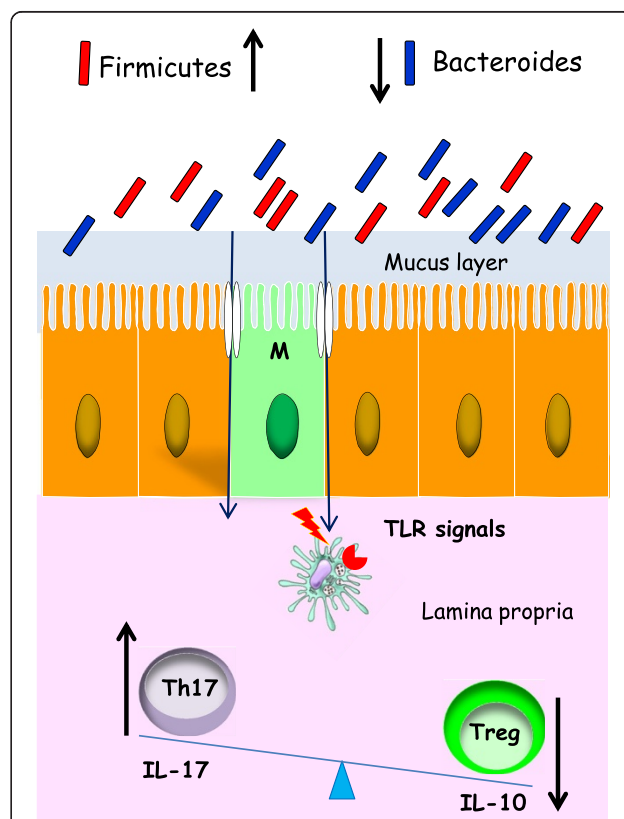


Figure 3 Effects of altered microbiota in the intestinal immune response in elderly people. Even if data on the aged microbiota are still controversial, in some cases increase of Firmicutes and decrease of Bacteroidetes may lead to a switch of the immune response towards an inflammatory profile with activation of Th17 cells.

Nutraceutical interventions in elderly

Nowadays, an arsenal of dietary products is available for the restoration of microbiota in young and elderly population [36]. Prebiotics, as non digestible components of fruits, vegetables and grain, are oligosaccharides able to accelerate the growth of gut anaerobes with production of SCFA [29,37]. Probiotics are viable bacteria [38] which enhance intestinal epithelial functions such as production of mucus, defensins and sIgA [39]. Moreover, probiotics upregulate phagocytic and natural killer (NK) cell functions, also inducing activation of Treg cells [40-42]. Probiotics and symbiotics (a mix of prebiotics and probiotics) have been proven to be beneficial when administered to aged people. For instance, supplementation of *Bifidobacterium (B.) lactis* HN 019 to aged individuals led to the recovery of granulocyte and NK cell activities [43]. Oral intake of *Lactobacillus (L.) pentosus* strain b240 (b240) has been shown to augment sIgA secretion in elderly people. Moreover, b240 was able to reduce frequency of common cold in aged individuals, likely acting *via* mucosal immunity [44]. In a double-blind trial *B. lactis* BL-01 and *B. bifidum* BB-02 along with inulin as a prebiotic could increase numbers of *B. bifidum* and total bifidobacteria and lactobacilli in the microbiota of elderly subjects [45]. Modification of microbiota seems to represent an essential event for less frequency of winter infections to occur. In a recent trial, administration for one month of fermented cow milk containing *L. rhamnosus* and oligofructose (a symbiotic) to free-living elderly increased serum levels of IL-1, IL-6, and IL-8, while reduced basal levels of IL-12, IL-10 and tumor necrosis factor (TNF)- α were not modified by this treatment [46]. It is likely that induction of a more vigorous acute phase response in these subjects may compensate the impaired adaptive immune response in the case of pathogen invasion.

Main functions of prebiotics and probiotics are represented in Figure 4.

Polyphenols, compounds widely present in the vegetal kingdom, have been shown to influence the composition

of the gut microbiota. Consumption of blueberry [47], grape juice [48] and red wine or gin [49], respectively, mainly increased *Bifidobacterium* spp. in fecal samples from human volunteers. In addition, our recent studies have demonstrated that polyphenols contained in red wine or in fermented grape marc exhibit an anti-inflammatory role both *in vitro* [50] and *in vivo* [51]. Particularly, *in vitro* induction of human Treg cells and *in vitro* attenuation of colitis in mice with decrease of IL-1 β and TNF- α content in homogenized colon seem to sustain the anti-inflammatory activities of polyphenols. Therefore, intake of dietary polyphenols in the elderly may beneficially act either on microbiota restoration and, consequentially, on attenuation of chronic inflammatory conditions.

In this framework, deficiencies of micronutrients (*e.g.*, zinc) as well as vitamin B12 have been reported in the elderly, thus accounting for frailty in the host [52,53]. However, the relationship between oligoelements and vitamin B12 and intestinal microbiota deserves further investigation in elderly.

Conclusion

In conclusion, more studies are needed for a better comprehension of the interplay between human microbiota and gut immune cells in elderly. In fact, inter individual variations of microbiota composition mostly depending on the type of diet, life style as well use of different molecular techniques of bacterial identification seem to represent the major difficulties in this area of research. In this direction, in a very recent editorial Sartor [54] has pointed out the emergence of certain strains of sulphate-reducing Deltaprotobacteria, *e.g.*, *Bilophila (B.) wadsworthia*, which induces colitis in mice through release of interferon- γ by Th1 cells. Quite interestingly, *B. wadsworthia* is increased in patients with ulcerative colitis, thus suggesting the need to identify new subsets of patients with IBD using Deltaprotobacteria as biomarkers [55]. It appears that consumption of saturated milk fat led to expansion of *B. wadsworthia* in mice [55]. Therefore, the possibility that also in humans changes of

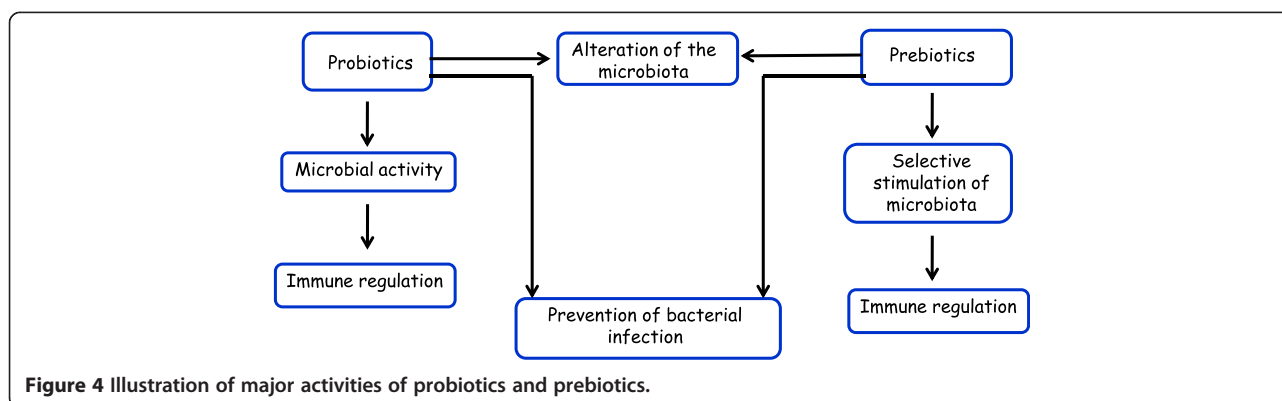


Figure 4 Illustration of major activities of probiotics and prebiotics.

microbiota could be induced by milk-fat intake should be taken into consideration. On the other hand, in spite of many advances in the field of mucosal immunity, age-related changes, which occur at mucosal surface, are still not completely explored. Most of the present knowledge is related to studies in rodent models, while a few investigations have been conducted on the human aged mucosal immunity. In order to overcome this problem the use of humanized mice may help in the understanding of mucosal immunity in elderly and, for instance, constructing effective vaccines to combat infectious diseases, as well as targeting specific components of the intestinal microbiota with the supplementation of nutraceuticals seem to represent the major therapeutic intervention [56,57].

Abbreviations

APCs: Antigen presenting cells; b240: *Lactobacillus pentosus* strain b240; CRC: Colon rectal cancer; DCs: Dendritic cells; GALT: Gut associated lymphoid tissue; IECs: Intestinal epithelial cells; IL: Interleukin; IBD: Inflammatory bowel disease; LP: Lamina propria; M: Microfolding cell; NK: Natural killer; RA: Retinoic acid; SCFA: Short chain fatty acids; SFB: Segmented filamentous bacteria; slg: Secretory immunoglobulin; TGF: Transforming growth factor; Th: T helper; TLR: Toll-like receptor; Treg: T regulatory; TNF: Tumor necrosis factor.

Competing interests

Both authors declare that they have no competing interests.

Authors' contributions

TM and EJ equally contributed. Both authors read and approved the final manuscript.

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