Is inflammeing influenced by the gut microbiota in older people? A systematic review

Cabirou M. Shintouo¹,²,³, Tony Mets¹,²,⁴, David Beckwee¹,²,⁶, Ivan Bautmans¹,²,⁴, Stephen M. Ghogomu³, Jacob Souopgui⁵, Lynn Leemans⁶, Henry D. Meriki³, Rose Njemini¹,²*¹

¹Frailty in Ageing Research Group, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium.
²Gerontology Department, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090, Brussels, Belgium.
³Department of Biochemistry and Molecular Biology, Faculty of Science, University of Buea, P.O Box 63, Buea, Cameroon.
⁴Department of Geriatric Medicine, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium.
⁵Department of Molecular Biology, Institute of Biology and Molecular Medicine, IBMM, Université Libre de Bruxelles, Gosselies Campus, Belgium.
⁶Rehabilitation Research Department, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090, Brussels, Belgium.

*Corresponding author:

Rose Njemini

Vrije Universiteit Brussel

Gerontology (GERO) & Frailty in Ageing research (FRIA) departments

Laarbeeklaan 103, B-1090 Brussels (Belgium)

Tel: +32 2 477 42 41, Fax: 32 2 477 63 64, E-mail: Rose.Njemini@vub.be
Keywords

Gut microbiota, Inflammation, Cytokines, Ageing
Abstract

Ageing is characterized by a low-grade chronic inflammation marked by elevated circulating levels of inflammatory mediators. This chronic inflammation occurring in the absence of obvious infection has been coined as inflammageing and represents a risk factor for morbidity and mortality in the geriatric population. Also, with ageing, important perturbations in the gut microbiota have been underlined and a growing body of literature has implicated age-related gut dysbiosis as contributing to a global inflammatory state in the elderly. Notwithstanding, very little attention has been given to how gut microbiota impact inflammageing in older persons. Here, we investigate the available evidence regarding the association between inflammageing and gut microbiota during ageing. PubMed, Web of Science and Scopus were systematically screened, and seven relevant articles in humans or animals were retrieved. The study on humans demonstrated that bacteria of the phylum Proteobacteria exhibited a positive correlation with IL-6 and IL-8 while Ruminococcus lactaris et rel. portrayed a negative correlation with IL-8. The animal studies reported that Parabacteroides, Mucispirillum, Clostridium and Sarcina positively associate with the pro-inflammatory MCP-1 while Akkermansia, Oscillospira, Blautia and Lactobacillus negatively correlate with MCP-1. Furthermore, “aged”-type microbiota were associated with increased level of IL6, IL-10, Th1, Th2, Treg, TNF-α, TGF-β, p16, SAMHD1, Eotaxin, RANTES and activation of TLR2, NF-κB and mTOR with a decrease level of cyclin E and CDK2. We conclude that changes in “aged”-type gut microbiota are associated with inflammageing.
1. **Introduction**

The elderly population, particularly the oldest old group, is growing very rapidly. It was estimated that in 2020, for the first time in human history, people aged 60 and older will outnumber the children aged five and younger (https://www.thelancet.com/series/ageing). Moreover, by 2050, the elderly are expected to comprise more than one-fifth of the world’s population [1]. These unprecedented demographic transformations have resulted in the emergence of new trends in epidemiology, with the rise of chronic diseases [2]. Indeed, one of the most prominent manifestations of ageing is low grade chronic inflammation (LGCI), known as inflammageing [3, 4]. Serum levels of pro-inflammatory cytokines including, but not limited to, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are commonly elevated in the elderly when compared to young persons, even in healthy persons, in the absence of overt infection [5]. This LGCI is thought to underlie many age-related manifestations, including increased vulnerability for diseases, morbidity, and mortality [6]. There is supportive evidence for a direct role of LGCI in the development of disability and dependence in elderly persons [7, 8]. As a result, chronic inflammatory conditions commonly encountered in the geriatric population have become major health concerns.

Several possible sources of LGCI observed during ageing have been postulated, including, amongst others, cell senescence, dysregulation of innate immunity, and changes in gut integrity [9, 10, 11]. In the gut, the intestinal epithelial cells represent the first barrier against invading microorganisms. They secrete antimicrobial substances such as mucins and defensins, and are able to sense pathogens (via recognition by Toll-like receptors), sample them and transfer the information to immune cells [12, 13]. However, several studies have reported major alterations in immune responses in the aged gut [14, 15, 16]. For instance, a reduction in the secretion of
mucin by intestinal epithelial cells and a greater permeability of mucosal membranes have been observed in older persons [17]. This condition facilitates the entry of microorganisms into the mucosal layers, resulting in the release of heightened levels of lipopolysaccharides, which, in turn, may lead to pro-inflammatory signaling through pattern recognition receptors [18, 19, 20, 21]. In this perspective, increasing evidence has implicated age-related deterioration of the gut barrier against bacteria as contributing to a global inflammatory state in older persons [18].

Thus far, our understanding of the effects of multiple deregulations in the gut microbiota in mediating inflammation with advancing age is incomplete. Toward et al. [22] reported an age-related decrease in the abundance of anti-inflammatory microbiota including *Bifidobacterium spp.* and *Faecalibacterium prausnitzii*. In contrast, the presence of pro-inflammatory microbiota, such as *Streptococcus spp.*, *Staphylococcus spp.*, *Enterococcus spp.*, and *Enterobacter spp.* was found to increase with age [22]. Also, a decline of bifidobacterial with a corresponding increase of Bacteroides has been observed with ageing [23, 24, 25, 26]. On the other hand, He et al. [27] reported an age-related upregulation of Ruminococcus, Eubacterium, Lactobacillus and Enterococcus, contrasting with a reduction of Faecalibacterium and Bacteroides — both anti-inflammatory microbiota — reported to prevent intestinal inflammation [28] through suppression of the pro-inflammatory IL-17 production and the induction of Foxp3+ regulatory T cells that produce IL-10 [29]. In this framework, the current systematic review aimed at evaluating the literature on the effects of the gut microbiota on inflammation.
2. Method

2.1. Literature Search

The literature databases including PubMed [search key: (("Inflammation"[Mesh]) OR Inflammation) OR Interleukin*) OR Cytokine) OR infection) OR IL6) OR IL10) OR IL1) OR IL17) OR IL8) OR IL23) OR Interferon*) OR "tumor necrosis factor alpha") OR "Granulocyte macrophage colony stimulating factor") OR Lymphokine) OR Chemokine) OR Prostaglandin)) AND (("Immunity"[Mesh]) OR Immunity) OR "Immune system") OR ("T cell" OR "T cells") OR ("B cell" OR "B cells") OR ("dendritic cell" OR "dendritic cells") OR ("White blood cell" OR "White blood cells") OR Phagocyte) OR Macrophage) OR immnosenescence) OR Lymphocyte)) AND (("Microbiota"[Mesh]) OR Microbiota) OR "Gut bacteria") OR Prevotella) OR "Gut microbiota") OR Bacteroides) OR Ruminococcus) OR "gut flora") OR "Intestinal microbiota") OR Microbiome) OR "gastrointestinal microbiota") OR Enterotype) OR clostridium) OR clostridia) OR clostridioides)) AND (("Aged"[Mesh]) OR "Older adult") OR "Older adults") OR senescence) OR geriatric) OR elderly) OR "Older people") OR "Older peoples")], Web of Science, and Scopus [search key: Inflammation OR Interleukin* OR Cytokine OR infection OR IL6 OR IL10 OR IL1 OR IL17 OR IL8 OR IL23 OR Interferon* OR "tumor necrosis factor alpha" OR "Granulocyte macrophage colony stimulating factor" OR Lymphokine OR Chemokine OR Prostaglandin AND Immunity OR "Immune system" OR "T cell" OR "T cells" OR "B cell" OR "B cells" OR "dendritic cell" OR "dendritic cells" OR "White blood cell" OR "White blood cells" OR Phagocyte OR Macrophage OR immunosenescence OR Lymphocyte AND Microbiota OR "Gut bacteria" OR Prevotella OR "Gut microbiota" OR Bacteroides OR Ruminococcus OR "gut flora" OR "Intestinal microbiota" OR Microbiome OR "gastrointestinal microbiota" OR Enterotype OR clostridium OR clostridia OR clostridioides
AND Aged OR "Older adult" OR "Older adults" OR senescence OR geriatric OR elderly OR "Older people" OR "Older peoples"] were systematically screened for relevant articles until January 2020 (last search on January 25th 2020).

Studies were included if they were written in English and analysed the relationship between inflammation and gut microbiota either in humans or in animals; all subjects were older adults. Letters to editors, reviews, and comments to other articles were excluded. Two independent researchers assessed the eligibility of articles for inclusion in this systematic review using Rayyan software [30]. A third researcher was involved in case of disagreement and the article in question was included only if a consensual agreement was achieved. After analysis of the full texts, 5 articles were included. The reference lists of the 5 included articles were screened, which did not reveal additional relevant studies. After performing a forward search using articles that have cited the 5 articles included, 2 articles were added giving a total of 7 articles for the systematic review (see Figure 1).

2.2. Quality assessment

The study on humans was analysed using the National Heart, Lungs and Blood Institute study quality assessment tools for observational cohort and cross-sectional studies [31]. Animal studies were analysed using the SYRCLE’s risk of bias tool for animal studies [32]. Assessments were performed independently by two reviewers, and if assessments were conflicting, a consensus-based final score was assigned.
2.3. Data extraction

First, the main characteristics of the participants were identified (human or animal subjects, type of study population, age, gender). Next, the inflammatory markers that were analysed and the microorganisms of the gut were recorded.
3. Results

3.1. Literature search

A potential total of 2,973 articles were generated: 927 in PubMed, 921 in Web of Science, and 1,125 in Scopus. Duplicates (n = 871) were removed and, excluding articles based on title and abstract, a total of 10 articles were retained. After analysis of the full texts, 5 articles were included. The reference lists of the included articles were screened, and a forward search was also performed using articles that have cited the included articles, bringing the total number to 7 articles.

3.2. Quality of study designs

The included studies showed moderate to good quality. The study on humans [25] was of good quality with a low risk of bias; however, outcome assessors were not blinded (see Figure 2). The study on humans was the only study that amplified the total bacterial 16S rRNA genes of the gut microbiota. The studies on animals amplified just portions of the gut microbiota (see Table 1) and were generally of good quality [33, 34, 35, 36, 37] except one [38] which was of moderate quality. With regard to selection bias, 5 articles [33, 34, 35, 36, 37] showed appropriate methods of randomization and none reported adequate concealment of allocation (see Figure 3). The groups were comparable at baseline in all included studies. In terms of performance bias, 3 studies reported on random housing [33, 35, 37] and most of the investigators were not kept blinded to treatment allocation. Concerning detection bias, all the animals used in the studies were selected at random for outcome assessment. However, the outcome assessors were not blinded from knowing which intervention each animal received except for one of the studies [36]. For attrition bias, all groups in every study were followed up for an equal length of time.
Figure 2. Risk of bias summary Human study

The study on humans was analyzed using the National Heart, Lungs and Blood Institute (NHLBI) study quality assessment tools for observational cohort and cross-sectional studies [31]. Green, red and yellow were respectively marked as Yes, No and Unclear on the NHLBI checklist.
Figure 3. Risk of bias summary Animal studies
Animal studies were analyzed using the SYRCLE’s risk of bias tool for animal studies [32].
Green, red and yellow were respectively marked as Yes, No and Unclear on the SYRCLE checklist.
Table 1. Summary of study results

<table>
<thead>
<tr>
<th>Study type/Author</th>
<th>Participants</th>
<th>Mean age + SD</th>
<th>Inflammation</th>
<th>Gut microbiota</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baigi et al., 2010</td>
<td>21 centenarians (20 women, 1 man)</td>
<td>100.5 years</td>
<td>B lymphocytes, T lymphocytes, virgin T lymphocytes, memory T lymphocytes, NK cells</td>
<td>Bacteria in the gut: Total bacterial 16S rRNA genes</td>
<td>Positive correlation: Phylum Proteobacteria with either IL-6 or IL-8 , (0.41 to 0.55) p = NR</td>
</tr>
<tr>
<td></td>
<td>22 elderly (11 women, 11 men) genetically unrelated to the centenarians</td>
<td>72.7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 young adults (9 women, 11 men)</td>
<td>31 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 elderly people - offspring of the centenarians (10 women, 11 men)</td>
<td>67.5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Animals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conley et al., 2016</td>
<td>5 young female C57Bl/6 mice</td>
<td>2 months</td>
<td>MCP-1</td>
<td>Bacteria in the gut: V4 region of 16S rRNA</td>
<td>Positively associate with MCP-1: Parabacteroides (0.84) , Mucispirillum (0.69) , Clostridium (0.69) and Sarcina (0.69)</td>
</tr>
<tr>
<td></td>
<td>5 aged female C57Bl/6 mice</td>
<td>26 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Subject Details</td>
<td>Age/Duration</td>
<td>CD4+ T, Treg, Th1, Th2, Th17 and TNF-α</td>
<td>Bacteria in the gut:</td>
<td>“Aged” microbiota:</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Fransen et al., 2017</td>
<td>10 young C57BL/6JRccHsd female mice, 10 young germ free old microbiota recipient female mice, 10 young germ free young microbiota recipient female mice, 5 young germ free control female mice, 10 aged C57BL/6JRccHsd female mice</td>
<td>7 - 10 weeks, 12 - 14 weeks</td>
<td>CD4+ Th, Treg, Th1, Th2, Th17 and TNF-α</td>
<td>Bacteria in the gut: V1 - V2 region of 16S rRNA genes</td>
<td>↑ Th1, Th2, Treg in the spleen, Th1 in Peyer’s patch and TNF-α (p &lt; 0.05) ↑ activation of TLR2 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Kim et al., 2016</td>
<td>8 young male C57BL/6J mice, 8 TLR4-deficient C57BL/10ScNJ young mice, 8 old male C57BL/6J mice</td>
<td>4 months, 4 months, 18 months</td>
<td>TNFα, IL-1β, and IL-6, p16, beclin-1, ATG7, LC3, NF-κB, mTOR, phosphorylated p65, p65, SAMHD1, cyclin E, CDK2, and β-actin proteins</td>
<td>Bacteria in the gut: V1 - V3 regions of 16S rRNA gene.</td>
<td>“Aged” microbiota: ↑ p16 and SAMHD1, activation of NF-κB and mTOR (p &lt; 0.05) ↓ cyclin E and CDK2 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Thevaranjan et al., 2017</td>
<td>WT young C57BL/6 mice, WT C57BL/6 old mice, Young SPF mouse, Old SPF mice, TNF−/− mice</td>
<td>10 - 16 weeks, 18 - 22 months, 8 - 14 weeks, 18 - 22 months</td>
<td>IL6, TNF</td>
<td>Bacteria in the gut: V3 region of 16S rRNA</td>
<td>“Aged” microbiota: ↑ TNF and IL6 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Sphychal et al., 2017</td>
<td>Young C57BL/6 male mice, Aged C57BL/6 male mice</td>
<td>8 - 12 weeks, 18 - 20 months</td>
<td>Circulating inflammatory cytokines: Multiplex assay kits</td>
<td>Bacteria in the gut: V4 to V5 region of 16S rRNA</td>
<td>“Aged” microbiota: ↑ IL6, TNF-α, Eotaxin, and RANTES (P ≤ 0.04)</td>
</tr>
<tr>
<td>Zhang et al., 2019</td>
<td>Female Holstein cattle (n = 180): L1 (n = 60, 1st lactation), L3 (n = 60, 3rd lactation)</td>
<td>NR</td>
<td>TNF-α, IL6, TGF-β, and IL-10: ST-360 Microplate Reader and cytokine diagnostic reagents</td>
<td>Bacteria in the gut: V3 - V4 region of 16S rRNA</td>
<td>“Aged” microbiota: ↑ TNF-α, IL6, TGF-β, and IL-10 (p &lt; 0.05) Cellulosilyticum: ↑ TNF-α (p &lt; 0.01)</td>
</tr>
</tbody>
</table>
L5+ \( [n = 60, 5\text{-}9\text{th lactation}] \)

Note: 1 = Pearson correlation, 2 = Tau, NR = not reported, HITChip = Human Intestinal Tract Chip, IL = Interleukin, IFN = Interferon, TNF-\( \alpha \) = Tumor necrosis factor alpha, TGF = Transforming growth factor, NK cells = Natural killer cells, MCP-1 = monocyte chemoattractant protein-1, Treg = Regulatory T cells, Th = T helper cells, TLR2 = Toll-like receptor 2, p16 = multiple tumor suppressor 1, ATG = Autophagy regulator, NF-\( \kappa \)B = nuclear factor-kappa B, mTOR = mammalian target of rapamycin, SAMHD1 = sterile \( \alpha \)-motif domain and HD domain-containing protein 1, CDK2 = Cyclin-dependent kinase 2, and RANTES = regulated on activation, normal T-cell expressed and secreted.

3.3. Participants

As can be seen in Table 1, of the 7 included articles, one described a study on humans which involved 21 centenarians, 21 elderly people who were offsprings of the centenarians, 22 elderly persons who were genetically unrelated to the centenarians, and 20 young adults [25]. Six articles described studies on animals [33, 34, 35, 36, 37, 38, 39].

3.4. Results of the various studies

The article on humans explored the age-related differences both in the inflammatory status and in the gut ecosystem composition, by using the Human Intestinal Tract Chip (HITChip) analysis [25]. The difference between the gut microbiota of young adults and elderly, separated by more than 40 years on average, was remarkably small when compared to that observed between centenarians and the younger elderly, separated by less than 30 years of life span. Also, centenarians’ microbiota portrayed a marked decrease in \textit{Faecalibacterium prausnitzii} anti-inflammatory species with an upregulation of the proinflammatory cytokines in the peripheral
blood that correlated with changes in their gut microbiota profile. The log-transformed results of pro-inflammatory cytokines quantification and HITChip profiling of the gut microbiota were used in a multivariate analysis to get the possible correlations between the microbiota composition and the cytokines pattern using cytokines plasma levels and the age groups as “environmental variables”. Bacteria of the phylum Proteobacteria exhibited a positive correlation with IL-6 and IL-8 (ranging between 0.41 and 0.55) while Ruminococcus lactaris et rel. were the only bacteria group to have a negative correlation with IL-8 (-0.44, P = 0.0001; see Table 1).

The influence of the aged gut microbiota on the immune system was evaluated by Fransen et al. [34], via the transfer of gut microbiota from young or old conventional mice to germ-free (GF) mice. They demonstrated that the aged microbiota induced higher frequencies of Th1, Th2, Treg in the spleen, and Th1 in Peyer’s patch (p < 0.05) in GF mice, which received the “old” microbiota. Moreover, the expression of TNF-α was significantly elevated in the ileum after transferring microbiota of aged mice (p < 0.05; see Table 1). More so, “old” microbiota transfer lead to increased translocation of inflammatory bacterial products into the circulation as GF mice which had received “old” microbiota showed significantly higher activation of Toll-like receptor 2 (p < 0.01). Spychala et al. [38] also tested the hypothesis that a heightened inflammatory response accompanies the aged microbiome when transplanted into young mice. Young mice with aged microbiota had a greater increase in proinflammatory cytokines following stroke compared to adult mice with young microbiota. Aged microbiota were associated with an increase in IL6, TNF-α, Eotaxin, and RANTES (P ≤ 0.04) while the young microbiota were associated with an increased level of IL4 and granulocyte colony-stimulating factor (p < 0.05).
Thevaranjan et al. [36] reported that intestinal permeability increases with age in mice due to age-related microbial dysbiosis that might drive intestinal permeability and decrease macrophage function. The microbial products that enter the bloodstream of aged mice trigger systemic inflammation leading to increased levels of TNF-α and IL6 (p < 0.05). Moreover, Conley et al. [33] investigated the relationship between age, the microbiome, and serum monocyte chemoattractant protein-1 (MCP-1) as a surrogate marker of inflammation in a mouse model. It was anticipated that if a specific taxon interacts with the immune system, its relative abundance in the microbiome would be associated with cytokine abundance. They tested for such associations by correlating Operational Taxonomic Units (OTUs) abundance and MCP-1. They identified 293 OTUs that significantly associated with MCP-1 status (q < 0.15, tau > 0.5). A total of 117 OTUs positively associated with MCP-1, with the strongest correlations from OTUs within Parabacteroides, Mucispirillum, Clostridium, and Sarcina (Kendall’s tau = 0.84, 0.69, 0.69, and 0.69; respectively). Conversely, 176 OTUs negatively correlated with MCP-1. Those with the strongest negative correlations were within Akkermansia, Oscillospira, Blautia, and Lactobacillus (Kendall’s tau = - 0.75, - 0.78, - 0.76, and - 0.75; respectively) (see Table 1).

The relationship between ageing and gut microbiota lipopolysaccharide - induced inflammation was investigated by Kim et al. [35]. The levels of p16 (as a senescence marker), and cyclin E and CDK2 (cell cycle regulators) were measured. The expression of p16, SAMHD1, and the activation of NF-κB and mTOR were higher in aged mice, while the expression levels of cyclin E and CDK2 were rather decreased (p < 0.05).

Further, the bacterial communities in the rumen of cows were analysed by Zhang et al. [37], with the aim of finding an explanation for the fragility of older dairy cows, and the relationship between the cow gut microbiota and inflammation, as well as longevity. They observed a low-
level inflammation among cows that have lactated for at least five different periods. The levels of all the measured cytokines - TNF-α, IL6, TGF-β, and IL-10 - were significantly higher in cows with a lactation period of five and above compared with those with first lactation period (p < 0.05). More so, Cellulosilyticum, which was more abundant in cows with a lactation period of five and above, was strongly and positively correlated to TNF-α (p < 0.01, see Table 1).
4. Discussion

With ageing, important perturbations in the gut microbiota has been underlined and a growing body of literature has implicated age-related gut dysbiosis as contributing to a global inflammatory state in the elderly. This age-related LGCI is the leading cause of morbidity, mortality and health-care related costs in older persons [6]. Therefore, a deeper understanding of the underlying processes of age-related chronic inflammation is mandatory to improve well-being in older age.

This systematic review provides an overview of the relationship between inflammation and gut microbiota. Baigi et al. [25] analysed human gut microbiota that might have been coexisting with their host for over 100 years and reported differences in terms of composition and diversity, which did not follow a linear relation with the age of the host. Indeed, the difference between the gut microbiota of young adults and elderly, separated by more than 40 years on average, was remarkably small when compared to that observed between centenarians and the younger elderly, separated by less than 30 years of life span. This comprehensive approach appears to indicate that the threshold for a switch towards an “aged” type of microbiota is situated around the age of 75 – 80 years. The analysis of the gut microbiota composition and the inflammatory parameters portrayed an upregulation of the proinflammatory cytokines in the peripheral blood of centenarians that correlated with changes in their gut microbiota profile. In particular, the increase of IL-6 and IL-8 was linked with an enrichment in Proteobacteria and a decrease in the levels of Ruminococcus lactaris et rel. [25]. This association between “aged” type gut microbiota and inflammation was confirmed in studies in rodent models [33, 34, 35, 36, 37, 38], suggesting that age-related changes in the gut microbiota composition may be relevant in age-related inflammation.
To investigate whether “aged” type microbiota is a cause or consequence of inflammageing, aged microbiota were transferred from old to young mice [34, 38]. This led to an exaggerated systemic inflammatory response, and higher frequencies of several T-helper cell subsets. Moreover, in young mice, the expression of several inflammatory markers, particularly TNF-α, increased while short-chain fatty acids decreased, after receiving microbiota from old mice. TNF-α is well known for its role in pro-inflammatory responses and has been shown to increase intestinal epithelial permeability [40, 41], provoking a further aggravation of inflammageing. Likewise, Thevaranjan et al. [36] demonstrated that exposure to microbial products including Toll-like receptor ligand or Th1 cytokines, such as TNF-α and IFN-γ, polarizes macrophages into the proinflammatory phenotype - leading to increased production of proinflammatory cytokines and reactive oxygen species - which ultimately contribute to the inflammatory state of the aged host [42]. Moreover, Zhang et al. [37] observed that dysbiosis of faecal microbiota of cows is related to inflammation. In their study, cellulosilyticum, a bacterial genus from the family of Lachnospiraceae - which was strongly and positively related to TNF-α - was more abundant in older cows. Also, the reconfiguration of older cows’ microbiota led to changes in the metagenome: older cows metagenome contained more functions related to protein metabolism and fewer functions related to carbohydrate and lipid metabolism. Moreover, the fermentation of proteins results in the production of toxic chemical substances while the loss of lipid and carbohydrate related genes may decrease the potential to generate beneficial compounds, such as short-chain fatty acids, which can exert anti-inflammatory effects through blocking the activation of NF-B [37].

Serum MCP-1 - a surrogate marker of inflammation - was used by Conley et al. to further elaborate on the relationship between inflammageing and “aged” type gut microbiota [33]. They
observed that young and aged groups of mice had distinct gut microbiomes but also that aged mice exhibit elevated serum MCP-1, which correlated with “aged” type microbiota. The correlation between gut microbiome and serum MCP-1 in their study is indicative that the gut microbiome may play a modulating role in age-related immunological processes. Also, Kim et al. [35] investigated the relationship between ageing and gut microbiota lipopolysaccharide (LPS)-induced inflammation and concluded that advancing age could cause gut microbiota dysbiosis, increase LPS production in the gut microbiota, increase the intestinal permeability, and thereby accelerate systemic inflammation. The identification of mechanisms that mediate age-related inflammation will be of significant impact on improving the quality of life of the elderly [35, 43].

Studies have been carried out to alter the composition of the gut microbiota - using probiotics - and assess the possible role of such treatment in ameliorating gut immunity in aged mice [44, 45]. They demonstrated that alteration of aged microbiota leads to changes in the inflammatory status. However, these intervention studies were not included as part of this systematic review. Our literature search was designed to identify associations between inflammation and “aged”-type gut microbiota. Consequently, our results reflect the present situation regarding the role of aged microbiota in inflammation.

5. Conclusion

In conclusion, ageing perturbs the gut microbiota with a shift in bacterial composition toward pro-inflammatory phenotypes. Hence, these aged-related changes in the gut microbiota can be considered as associated with inflammation, which represents a risk factor for morbidity and mortality in the geriatric population. With the increasing life-expectancy and the exponential
ageing of the population, the burden due to inflamming is expected to increase steeply in the near future. Therefore, interventions directed at the composition of the gut microbiota might contribute to alleviate inflammation, improve well-being in older persons and reduce health-care related costs.
References


