Dysbiosis, malnutrition and enhanced gut-lung axis contribute to age-related respiratory diseases

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Abstract

Older people are at an increased risk of developing respiratory diseases such as chronic obstructive pulmonary diseases, asthma, idiopathic pulmonary fibrosis or lung infections. Susceptibility to these diseases is partly due to the intrinsic ageing process, characterized by genomic, cellular and metabolic hallmarks and immunosenescence, and is associated with changes in the intestinal microbiota. Importantly, in the lungs, ageing is also associated with a dysbiosis and loss of resilience of the resident microbiota and alterations of the gut-lung axis. Notably, as malnutrition is often observed in the elderly, nutrition is one of the most accessible modifiable factors affecting both senescence and microbiota. This article reviews the changes affecting the lung and its resident microbiota during ageing, as well as the interconnections between malnutrition, senescence, microbiota, gut-lung axis and respiratory health. As the communication along the gut-lung axis becomes more permissive with ageing, this review also explores the evidence that the gut and lung microbiota are key players in the maintenance of healthy lungs, and as such, are potential targets for nutrition-based preventive strategies against lung disease in elderly populations.

1. Introduction

Population worldwide is getting older; more than 1 billion people are over 60 and this number will continue to increase in the future, especially in developing countries. Failing to ensure healthy ageing in these elderly populations would lead to multiple negative consequences (personal, economic and societal) and it is, therefore, essential to prepare societies to meet their specific needs. This has been made a priority of the World Health Organization (WHO), which has elaborated the plan for a Decade of Healthy Ageing 2020-2030.

Ageing reflects all the changes taking place over the course of life. Its process has a high inter-individual variability with respect to its rate and affected organs, and is characterized by a decrease in physical capacity, an increased vulnerability to environmental challenges, and a growing

Abbreviations: AECII, Alveolar epithelial type II cells; AMDC, airway mucosal DC; ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; BAL, bronchoalveolar lavage; BCR, B cell receptor; Blimp, B-lymphocyte-induced maturation protein; CAF, cancer-associated fibroblast; CAP, Community Acquired Pneumonia; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, coronavirus disease 2019; CR, Calorie restriction; CsA, cyclosporine A; DAI, Disabling Event Years; DC, Dendritic cell; DDR, DNA damage response; DRCII, Alveolar epithelial type II cells; EEC, epithelial-to-epithelial cell; EGIS, Epidemiological and Genomic Indicators of Senescence; EMT, epithelial-to-mesenchymal transition; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; ER, endoplasmic reticulum; GATA, GATA binding protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; HbA1c, glycated hemoglobin; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HOMA, homeostasis model assessment; HPA axis, hypothalamic-pituitary-adrenal axis; HUA, hyperuricemia; ICAM, intercellular adhesion molecule; IAV, influenza A virus; IAV, influenza A virus; IFN, interferon; Ig, immunoglobulin; IIS, insulin and IGF-1 signaling; IL-1, interleukin; IPF, idiopathic pulmonary fibrosis; LPS, lipopolysaccharide; MACS, multiple use respiratory cell cultures; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; MHC, major histocompatibility complex; miRNA, microRNA; MRS, Methicillin-resistant Staphylococcus aureus; mTOR, mammalian target of rapamycin; NET, neutrophil extracellular trap; NOS, nitric oxide synthase; NSCLC, non-small cell lung cancer; OTU, Operational Taxonomic Units; PAX, paired box; PI3K, phosphoinositide 3-kinase; PINK1, PTEN-induced putative kinase 1; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; RSV, Respiratory syncytial virus; SASP, senescence-associated secretory phenotype; SCFA, short-chain fatty acids; SFB, segmented filamentous bacteria; SP, surfactant protein; T2D, Type 2 Diabetes; Tc, cytotoxic effector T cell; TCR, T cell receptor; TGF, Transforming growth factor; TLR, toll-like receptor; TNM, tumor, node, metastasis; Treg, regulatory T cell; UPR, unfolded protein response; URT, upper respiratory tract; WHO, World Health Organization; YDL, Years Lost to Disability; YLL, Years of Life Lost.

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risk of disease and death. Physiologically, loss in muscle mass, decline in strength (Leong et al., 2015; Rantanen et al., 2003), and increased risk of fracture, are commonly associated with ageing. Impairments in sensory functions, increased frequency of infections, falls, pressure ulcers and deterioration in cognitive functions (Fernández-Garrido et al., 2014; Fried et al., 1991; Inouye et al., 2007), are negatively correlated with survival (Kane et al., 2012; Lordos et al., 2008). Particularly, the elderly population is at risk of developing lung infections. The prevalence of other pulmonary diseases, (e.g. tuberculosis, chronic obstructive pulmonary diseases, asthma), increases with age and contributes to morbidity and mortality in older individuals. At a cellular level, ageing is associated with immunosenescence (Lang et al., 2012) and with chronic low-level inflammation, known as inflamm-ageing (Ferrucci and Fabbri, 2018).

Malnutrition is defined by the European Society for Clinical Nutrition and Metabolism as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” (Cederholm et al., 2017). Importantly, it is also one of the first signs of a degrading health condition in the elderly population. Undernourished old people are at increased risk of falls, long hospital stays, infections, impaired respiratory function and death (Rasheed and Woods, 2013; Tappenden et al., 2013). Interestingly, an early study by Heymsfield et al. showed an association between malnutrition and the apparition of further pathologies, including bronchopneumonia (Heymsfield et al., 1979). Thus, because nutrition is one of the most accessible modifiable factors, it can be considered as a lever of action to promote healthy ageing in older people (Rodgers and Collins, 2020).

Many clinical issues observed in ageing individuals are associated with changes in the microbiota composition and functionality in the gut and other organs (Claesson et al., 2012, 2011; Jackson et al., 2016; Jeffery et al., 2016; O’Sullivan et al., 2011). Although there is a very high inter-individual variability, multiple studies have shown that the diversity of gut microbiota and genera such as *Bifidobacteria* and *Lactobacilli* are reduced in older individuals, whereas certain opportunists (e.g. *Clostridoides difficile*) are increased (Claesson et al., 2011; Milani et al., 2016; Rea et al., 2012). Moreover, specific microbial profiles have been identified as longevity signatures in centenarians (Biagi et al., 2017; Catoire et al., 2020; Kong et al., 2016; Naito et al., 2019; Rampelli et al., 2020; Santoro et al., 2018; Wang et al., 2019a; Wu et al., 2020). In the lungs, due to the invasiveness of the procedure, no study has been performed on lower respiratory tract microbiota and only a few studies have described the composition of the upper respiratory tract (URT) microbiota in the elderly (de Steenhuijsen Pieters et al., 2016; Lee et al., 2019a; Stearns et al., 2015; Whelan et al., 2014). It is not fully understood how the microbiota impacts ageing processes, but it is likely that dysbiosis plays a central role in the progression of ageing-related disorders and that restoration of eubiosis would promote healthy ageing (Fig. 1).

Here, we review the hallmarks of the ageing lung and interconnections between malnutrition, ageing, specifically cellular senescence, microbiota and lung health. The evidence of the gut-lung axis and its specificities in the elderly population prompt us to propose that both gut and lung microbiota are main players in the maintenance of healthy lungs and, therefore, are central targets for nutrition based preventive strategies in elderly populations.

2. Ageing in the lungs

2.1. The ageing lung and the most prevalent age-related pulmonary diseases

According to the European Respiratory Society (ERS), the status of...
lung function is considered a predictor of healthy ageing (Meiners et al., 2015). For instance, elder individuals with poor lung function are prone to develop cardiovascular disease, type 2 diabetes (T2D) and cognitive decline, when compared to those individuals with robust lung function (Bowdish, 2019; Hole et al., 1996; Lange et al., 1990; Weiss et al., 1995). Conversely, in older adults, a robust lung function correlates with a higher metabolic rate, which is a well-known parameter for fitness, activity and physical performance in the elderly (Bowdish, 2019; Choi and Pai, 2004; Simpson et al., 2005).

Although the ageing of the lung is inevitable, and leads to a natural decline in its function, there are intrinsic (e.g., genetic components) and extrinsic (e.g., environment) factors that may accelerate or slow down the process.
this process. There are ten hallmarks thought to contribute to physiological changes associated with ageing and particularly with the ageing lung (Fig. 2) (López-Otín et al., 2013; Meiners et al., 2015). These include 1) genomic instability, 2) telomere attrition, 3) epigenetic alterations, 4) loss of proteostasis, 5) deregulated nutrient sensing, 6) mitochondrial dysfunction, 7) cellular senescence, 8) stem cell exhaustion, 9) altered intercellular communication and 10) dysregulation of extracellular matrix (ECM). These alterations can occur in conducting airway epithelial cells, alveolar epithelial cells as well as airway smooth muscle cells and resident immune cells, and result in both structural and physiological changes. For instance, the increased apoptosis of epithelial cells, together with abnormalities of the microtubular structure of the cilia of multiciliated cells, the altered mucins and antioxidants content of the epithelium lining fluid and the decreased respiratory muscle and diaphragm strength, lead to defects in the mucociliary clearance machinery and a decreased ability of the lungs to clear mucus and inhaled particles and pathogens (Cho and Stout-Delgado, 2020; Ho et al., 2001; Wansleben et al., 2014). The size of alveoli is also increased in the aged lungs, due to changes in the ECM and this leads to decreased elastic recoil and increased end expiratory lung volume (Cho and Stout-Delgado, 2020; Janssen et al., 1999). These physiological changes that occur in the ageing lung collectively lead to poor lung functional capacity and a decreased ability to maintain homeostasis.

As a consequence of the natural accumulation of age-related physiological changes in addition to exposure to toxic environmental factors, this organ becomes susceptible to chronic disorders such as Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), Lung cancer and asthma, and infectious diseases like Community Acquired Pneumonia (CAP). In particular, the age-associated alterations of the immune system, called immunosenescence and discussed in the next section, are thought to be a key driver of asthma exacerbation in the elderly (Cho and Stout-Delgado, 2020; Li et al., 2017b; Metcalf et al., 2015; Shaw et al., 2011). Similarly, immunosenescence is thought to be the main culprit for predisposing the ageing lung to immunopathology in response to infectious stimuli (Chen et al., 2020; Cho and Stout-Delgado, 2020; Goldstein, 2012) and consequently, the ageing lung is more predisposed to secondary bacterial infections consecutive to viral pneumonia (Akgün et al., 2012; Castle et al., 2007; Chen et al., 2020; Cho and Stout-Delgado, 2020; Goldstein, 2012). According to the WHO-Europe, older adults are at a significant increased risk of severe disease from SARS-CoV-2 infection; over 95% of the reported fatalities occurred in those individuals over 60 years old and with comorbidities. Recent data indicate clear effects on the immune system, which may be worsen in older individuals (Wang et al., 2020b).

2.2. Immunosenescence and its impact on age-related pulmonary diseases

Immunosenescence is defined as the age-associated decline in the immune system capacity to respond to infections and generate long-term immune memory (Cho and Stout-Delgado, 2020). As a consequence, older individuals are prone to infection, cancer, autoimmunity and chronic inflammation, and exhibit a poor vaccine response (Al-Alawi et al., 2014; Fulop et al., 2014; Murray and Chatirmall, 2015). Globally, immunosenescence has the following traits: poor capacity to respond to new antigens, accumulation of memory T cells in detriment of a diminished naïve T cell repertoire, and chronic low-grade inflammation state known as inflam-aging (Alessio et al., 2019). Both innate and adaptive immunity are affected by immunosenescence.

Immunosenescence of alveolar macrophages causes a decrease in their total numbers and capacity to perform phagocytosis and clearance of foreign particles, provoking susceptibility to bacterial and viral infections causing CAP (Chen et al., 2020; Volkova et al., 2012; Wong et al., 2017). It also diminishes the capacity of these cells to produce pro-resolution mediators, such as resolvins (Arnardottir et al., 2014), antioxidant/detoxification factors in response to cigarette smoke in COPD disease (Suzuki et al., 2008), or to clear away apoptotic airway epithelial cells generated during COPD (Chen et al., 2020; Hodge et al., 2003). Immunosenescence of airway mucosal Dendritic Cells (DCs) is reflected by lower expression and function of Toll-like receptors (TLRs), decreased phagocytosis capacity, and diminished/delayed migration potential towards draining lymph nodes upon activation (Agrawal et al., 2007; Agrawal and Gupta, 2011; Volkova et al., 2012). In the context of viral pneumonia, the capacity of DCs to prime naïve T cells against influenza is deficient due to a delayed infiltration kinetics of DCs into the aged lungs, and a defect of DCs migration from the lung into the draining lymph nodes (Valkenburg et al., 2012; Zhao et al., 2011). DCs also display age-associated defects in their ability to prime CD8+ T cell responses through MHC-I-dependent antigen presentation (Zacca et al., 2013), and inflammasome activation and production of IL-1β (Chen et al., 2020; Stout-Delgado et al., 2012). Immunosenescence of neutrophils, the most abundant innate immune leukocyte, provokes an unregulated production of superoxide, deficient phagocytosis (Chen et al., 2014; Cho and Stout-Delgado, 2020; Corberand et al., 1981) and deficient formation of neutrophil extracellular traps (NETs) that correlates with defective bacterial clearance (Brinkmann and Zychlinsky, 2007). Immunosenescence also impacts neutrophil migration to the lung in response to stimuli but these cells tend to accumulate and prolong their stay in this organ (Kahlich et al., 1975). Together, these age-related alterations in neutrophil functions can have devastating consequences, as best exemplified in the current SARS-CoV-2 pneumonia epidemic (Barnes et al., 2020; Chen et al., 2020). Indeed, not only is the neutrophil accumulation well-documented across mouse and large animals during influenza infection, but COVID-19 patients who succumb, display a two-fold increase in neutrophilia, contributing to the age-enhanced mortality to SARS-CoV-2 infection (Barnes et al., 2020; Liu et al., 2020; Wang et al., 2020a).

In the adaptive immune system, immunosenescence is best reflected in the T cell compartment, which increases the ratio of CD4+ to CD8+ T cells in the bronchoalveolar fluid, suggesting that the pool of lung resident memory CD4+ T cells also augments as a function of age (Haynes and Swain, 2006; Kovaiov and Grubeck-Loebenstein, 2006). The systemic and local increases in memory T cells are thought to contribute to the T cell-driven asthma in the elderly (Murray and Chatirmall, 2015). In viral-driven pneumonia, immunosenescence causes a decrease in the diversity of the CD8+ T cell compartment and in the global immune response to influenza infection (Zhang et al., 2002). In SARS-CoV-2 pneumonia, the total number of peripheral lymphocytes is reduced, displaying a clear defect in CD8+ T cell abundance, shifting the CD4+ to CD8+ T cell ratio (Wang et al., 2020b). Beyond alteration in abundance, it appears that the function of CD8+ T cells in COVID-19 patients becomes exhausted (Zhang et al., 2019; Zheng et al., 2020). Immunosenescence also impairs B cell development at all stages, leading to a net reduction of the total numbers and diversity of immature B cells (Holodick and Rothstein, 2015). Consequently, the antibody specificity and antigen affinity are diminished, resulting in poor vaccination efficacy and susceptibility to lung infections in older people (Holodick and Rothstein, 2015). In SARS-CoV-2 pneumonia, the total number of peripheral B lymphocytes is reduced, a phenomenon that is reversed upon treatment (Wang et al., 2020b). In the context of influenza infection, aged mice exhibit a defect in the cooperation between T follicular and B cells due to low expression of CD40 L (Chen et al., 2020; Lefebvre et al., 2016). This is important because B cells require activation signalling through the CD40 receptor (by CD40 L expressed in T cells) to undergo activation, differentiation, cytokine production and differentiative into plasma cells (Chen et al., 2020; Lefebvre et al., 2016). Immunosenescence also induces B cell-intrinsic effects, such as low expression of the transcription factors paired box 5 (Pax 5) and B-lymphocyte-induced maturation protein 1 (Blimp1), which are crucial for the development and differentiation of these B lymphocytes (Chen et al., 2020; Frasca et al., 2016; Nipper et al., 2018). Not too surprisingly, there is a poor production of influenza-neutralizing antibodies in aged mice, non-human primates and humans (Chen et al., 2020; Frasca et al., 2016; Josset et al., 2012;
Table 1
Summary of the results of publications comparing respiratory tract microbiome from elderly to younger adults. Arrows indicate an increase (↗) or decrease (↘) in relative abundance of the microbiome.

| Study                  | N  | Population | Age | Sample origin | Results                                                                 |
|------------------------|----|------------|-----|---------------|-------------------------------------------------------------------------|
| Whelan et al., 2014    | 242| Publicly available data (NIH’s Human Microbiome Project) | 18-40 | Anterior nares and oropharynx | Elderly vs. mid-aged, Streptococcus pneumoniae in anterior nares, Prevotella, Veillonella in anterior nares, Prevotella, Lachnospiraceae in oropharynx, Rothia and Lactobacillus, overall bacterial density, species richness (not in young cohorts) |
| de Steenhuijsen Piters et al., 2016 | 91 | Healthy elderly (HE) | 75,3 | Oropharynx | Shannon diversity indices (not in young cohorts), Streptococcus OTUs, Rothia, Gemellales, Prevotella melaninogena, Veillonella dispar, Paracoccus and Leptotrichia |
| Lee et al., 2019a      | 30 | Asthmatic elderly (AE) | 72,5 ± 5,4 | Nasopharynx | AE vs. AA, Staphylococcus, Propionibacterium, Moraxella |
|                        | 10 | Healthy adults (HA) | 67,3 ± 3,5 | HE vs. HA | Proteobacteria, Propionibacterium, Corynebacteriales |
|                        | 30 | Asthmatic adults (AA) | 34,1 ± 7,0 | AA vs. HA | Proteobacteria |
| Lee et al., 2019b      | 24 | Elderly | 63 | Sputum | Elderly vs. young, Firmicutes and Bacteroidetes associated with arterial stiffness in elderly subjects |
|                        | 24 | Young | 29 | young | Firmicutes and Bacteroidetes associated with arterial stiffness in elderly subjects |

Toapanta and Ross, 2009). Collectively, immunosenescence affects the humoral immunity in the airways, creating an environment prone to infections and susceptible to other age-related pulmonary diseases.

2.3. Microbiota in the ageing lung

The microorganisms populating this issue have a low density, which appears to be critical for the maintenance of healthy lungs (Mathieu et al., 2018) and these bacteria can exert distinct effect on the pathogenesis of lung diseases such as asthma (Mathieu et al., 2018; Remot et al., 2017). Due to the difficulty to access resident lung microbiota, to date, no study has been performed on lower respiratory tract microbiota in the elderly population and only few studies have compared the composition of the upper respiratory tract microbial ecosystem in the elderly to the one in younger adults (Table 1, de Steenhuijsen Piters et al., 2016; Lee et al., 2019a; Stearns et al., 2015; Whelan et al., 2014)).

Advanced age decreased the relative abundance of Corynebacterium and Propionibacterium in the nose and of Prevotella in the oropharynx. Importantly, Whelan et al. demonstrated that, although the microbiota from the anterior nares is distinct from that of the oropharynx in mid-aged adults, this distinction is abolished in elderly subjects (Stearns et al., 2015), suggesting that ageing in the upper airways is accompanied by a loss in the geodistribution of the microbial ecosystem. Another study by the same group, comparing URT microbiota from children to that of adults, reported similar high inter-individual variability, as was shown in elderly individuals. Therefore, it is possible that the absence of a more stable URT microbiota in these aged groups is related to a higher susceptibility to respiratory infections and other lung diseases, such as asthma as seen in children for whom the prevalence of these diseases is also increased compared to adults. This is supported by mouse-based studies in which the age altered the recovery from pulmonary infection with Streptococcus pneumoniae. Indeed, older mice were less efficient to clear the pathogen and showed an increase in the abundance of OTUs from the Firmicutes phylum compared to the younger counterparts. The composition of URT microbiota from older mice also failed to return to their original composition, up to 4 weeks after the infection (Krone et al., 2014; Thevaranjan et al., 2016), suggesting a loss of resilience of their microbiota.

3. Impact of nutrition on ageing/senescence and role of the microbiota

Lifestyle and more particularly certain diets/dietary patterns have been associated with changes in Years of Life Lost (YLL) and Years Lost due to Disability (YLD), thus modulating Disability-Adjusted Life Years (DALYs), which represents years of healthy life (GBD, 2017 Diet Collaborators, 2019; May et al., 2015; Struijk et al., 2014).

3.1. Nutrition and cellular senescence

As described above, at the cellular level, the ageing process, called senescence, is characterized, among others, by shortening of telomeres and the SASP (Senescence-Associated Secretory Phenotype). One current area of interest is whether diet can influence senescence process. This has now been studied by many groups and reviewed recently (Bal as et al., 2018), although no consensus has emerged. Some studies have reported a positive association between a longer telomere length, measured in leukocytes, and certain types of food, including nuts, seaweed, fruits or coffee, whereas consumption of alcohol, and red or processed meat was associated with a shorter leukocyte telomere length (Bal as et al., 2018; Lee et al., 2015; Leung et al., 2014; Liu et al., 2016; Pavan ello et al., 2011; Tucker, 2018). Consumption of certain diets, foods and nutrients have also been positively or negatively associated SASP in different tissues (Sone and Kagawa, 2005; Wang et al., 2019b; Yang et al., 2020). On the other hand, a meta-analysis from 2017 (Pérez et al., 2017), which included 533 participants under 9 different diets in 5 randomized controlled trials, showed that there was no effect of diet on telomere length. However, there was a high heterogeneity in the types,
length of studies and in the dietary interventions, which might have affected the conclusion of this meta-analysis. One of the hypotheses that could explain how diet impacts senescence process is through the regulation of ROS production and oxidative stress coming from endogenous and exogenous sources. Indeed, it is known, for example, that unhealthy diets, such as high fat diets, can induce an increase in ROS production in certain tissues (Matsuzawa-Nagata et al., 2008; Vial et al., 2011). Of interest, a healthy diet with reduced calorie intake (calorie restriction diet – CR), reduced mitochondrial activity and ROS production, and this has shown some promising results in certain studies. In animals, CR diet delayed the onset on some ageing-associated diseases such as diabetes (Cheng et al., 2017; Colman et al., 2009), cardiovascular diseases (Colman et al., 2009) or cancer (Weindruch et al., 1986), and it even prolonged life in non-human primates (Colman et al., 2014, 2009), although it did not appear to affect telomere length (Smith et al., 2011). In humans, while such studies are difficult to implement, similar health benefits have been reported in certain population, such as the Okinawan adult population. This population eats an average of 17 % less calorie-intake compared to that of the rest of Japan, and has a higher rate of centenarian people and a lower mortality due to cardiovascular diseases, cancer and other diseases around the globe (Kagawa, 1978; Suzuki et al., 2001). The CALERIE 1 & 2 studies have also demonstrated the beneficial effect of a CR diet on general health and the prevention of ageing associated diseases (Most et al., 2018; Redman et al., 2018; Weiss et al., 2006). Interestingly, intermittent fasting has also been shown to reduce insulin resistance and cholesterol levels in humans, suggesting that this type of diet could also be beneficial against the development of ageing associated pathologies by modulating oxidative stress associated with ageing (Harvie et al., 2013, 2011; Klempel et al., 2012; Stekovic et al., 2019; Varady et al., 2015).

3.2. Involvement of the microbiota in the effect of nutrition on ageing processes

It is now widely accepted that the composition and function of the gut microbiota are clearly influenced by dietary intake and can be modulated by specific diets (e.g., meat, vegetarians, rich in fiber) and the type of food matrices, which includes both the composition and interactions between the constituents (Aguilera, 2019; David et al., 2014; Derrien and Veiga, 2017; Duncan et al., 2007; Ley et al., 2006; Muegge et al., 2011; Walker et al., 2011; Wu et al., 2011). Consequently, the effect of particular diets on molecular and cellular processes involved in ageing could be mediated by the modulation of microbiota.

3.2.1. Impact of nutrition on microbiota

Our diet feeds the microbiota by supplying substrates for microorganisms, especially non-digestible sugars, known as prebiotics (Gibson et al., 2017). Food is also a source of microorganisms, seeding our ecosystems in the gut and the lung. The overall microbial biomass ingested per day has been estimated around 10^{10} (Derrien and van Hylckama Vlieg, 2015), ranging from 10^3 to 10^12 in function of the diet considered. In addition to fermented foods, that are especially rich in microorganisms, it is important to realize that raw food we ingest (e.g., fruits, vegetables) also contains their own microbial communities that could impact the composition and functionality of gut microbiota. Thus, modifying the diet for elderly people also impacts the microorganisms they ingest. Since the early 2010’s, it is known that these food microorganisms survive through the GI tract and associate, at least temporarily, with the resident gut microbiota (David et al., 2014; Walker et al., 2011), although whether they “durably” colonize the digestive tract remains uncertain (McNulty et al., 2011).

Distinct types of food, such as non-digestible starch, and particular diets like the Mediterranean diet, affect the microbiota composition in a specific manner. It has been extensively reviewed in recent years (Barber et al., 2020; Burr et al., 2020; Dogra et al., 2020; Fassarella et al., 2020; Kolodziejczyk et al., 2019; Vandeputte and Joossens, 2020). Although there exists a very high inter-individual variability, due to host and microbe own characteristics, the microbiota appears as a strong malleable therapeutic target that can be reshaped using specific diets. For instance, a high-fat and low-fibre diet in mice decreased microbiota composition in Bacteroidetes and increased Firmicutes and Proteobacteria (Hildebrandt et al., 2009). The consumption of poly-unsaturated fatty acids increased bacteria, such as Bifidobacterium, Lachnospira, Roseburia and Lactobacillus, in humans (Watson et al., 2018). Of interest for the ageing population as they often show protein deficiency, the source of this nutrient also affects the microbiota composition (Zhu et al., 2015). Soybean and peanut proteins induced modulation of the abundance of beneficial bacteria in the gut; a diet enriched with 20 % peanut protein increased Bifidobacteria, and reduced Enterobacteria and Clostridium perfringens in rats (Peng et al., 2015). On the other hand, animal derived proteins induced a Bacteroides enterotype (Wu et al., 2011). Gut bacteria can convert L-carnitine and phosphatidylcholine, which are present in red meats, into trimethylamine N-oxide (TMAO), which is associated with the development of cardiovascular diseases, linking, here as well, the impact of diet on microbiota and the host physiology. Strikingly, a recent study showed that in older individuals, consumption of Mediterranean diet was associated with specific changes in microbiota composition and function; adherence to this diet was associated with a lower decline in microbiota diversity, an increase in taxa negatively associated with inflammation and positively associated with SCFA production (Ghosh et al., 2020).

In addition to diet composition, food supplements or additives also impact gut microbiota composition. In recent years, studies have investigated the effect of probiotics - ingested as food supplements - or fermented foods, which both have a high microbial load, on the survival of these microorganisms their residence time in the host’s digestive environment and their direct impact on the microbiota. Although fermented foods have shown to beneficially impact human health (Marco et al., 2017; Tamang et al., 2016), a detectable modification of the intestinal microbiota was not consistently observed in these studies, and it is therefore important to dissociate the direct effects of food microorganisms and associated bioactive compounds from those linked to the matrix itself. A recent study from Taylor et al. showed that, in stool samples from over 6000 individuals, there was a small significant change in beta diversity as well as differential taxa between people consuming fermented foods and non-consumers (Taylor et al., 2020). Finally, in one of the first reports on fermented foods effects on microbiota, McNulty et al. demonstrated the impact of these foods on the intestinal physiology of an individual without necessarily modification of the composition of their microbiota (McNulty et al., 2011). Even though microbial food ecosystems might have very little influence on the diversity, composition and stability of the gut microbiota, they are thought to impact the host physiology.

Whether food, via substrates or microorganisms, is able to modify the lung microbiota is not known so far. A main trend of changes observed in gut microbiota in elderly populations is a decreasing abundance of beneficial microbes, like *Lactobacillus* and *Bifidobacterium*. Therefore, we assume that a diet enriched with these microorganisms or promoting their growth should be beneficial to counter-balance the loss. A better knowledge of the evolution of lung microbiota with age would help to define nutritional enrichment by specific microbes to preserve the lung microbiota.

3.2.2. Impact of microbiota on cellular senescence

As food modulates microbiota composition and function as well as molecular ageing processes, it is believed that one of the possible mechanisms of action of diets on ageing processes is through their action on microbiota, particularly the gut microbiol ecosystem. This can occur through the metabolites they secrete or their interactions with the immune system and the epithelial barriers. Indeed, it has been shown that metabolites and secreted products from the microbiota are able to affect cellular senescence, either promoting or reducing it. In a healthy
context, senescence can be detrimental, whereas in a carcinogenic context, for example, the induction of senescence can eliminate cancerous cells. For example, colibactin, a genotoxin from *E. coli*, has been shown to induce senescence, thus promoting colon tumor growth (Dalmasso et al., 2014). Other metabolites such as Cdtb (Cytolethal distending toxin subunit B) of *Helicobacter hepaticus*, Trimethylamine-N-oxide or Urolithin A can also induce senescence, although mechanisms of action vary from one metabolite to another (Giménez-Bastida et al., 2020; Ke et al., 2018; Pére-Vedrenne et al., 2017). In the case of Urolithin A, it is of interest to note that the induction of senescence actually served to prevent irreversible, cell cycle progression of colon cancer cells. On the other hand, and of particular interest in the search for molecules promoting healthy ageing, certain bacterial metabolites can also reduce or prevent senescent process. This is the case of secreted products from *Lactobacillus fermentum*, for example, which protects the 3T3-L1 preadipocytes in vitro against oxidative stress-induced senescence by inhibiting the mTOR pathway (Kumar et al., 2019). Although the responsible molecules have not been identified in this case, this study provided a proof-of-concept that metabolites from probiotics may possess anti-ageing properties. Depending on the diet and type of food intake, gut microorganisms can also produce a family of metabolites termed short-chain fatty acids (SCFA). These are end products of bacterial fermentation that happens in the gut and play important roles at local and distant sites. In 2012, O’Callaghan et al. showed that a red meat rich diet was linked to a decreased telomere length in rat colonic cells and could be prevented by adding resistant starch to the diet. Interestingly, they found an association between the absolute telomere length and the caecal levels of two SCFAs, acetate and propionate (O’Callaghan et al., 2012).

It is now well established that the gut microbiome plays an important role in the development and maturation of the immune system throughout life. In healthy individuals, commensal bacteria rarely cross the physical barrier constituted by the epithelial cells and the mucus layer. However, when this happens, bacteria are rapidly killed by macrophages. Others can survive inside DCs but these cells only go as far as the mesenteric lymph nodes, restricting the bacterial challenge to the mucosal immune system (Macpherson and Uhr, 2004). As the epithelium becomes leaky with age, it is inferred that more commensals or bacterial components can cross that barrier and may induce aberrant immune responses (Man et al., 2014; Thevaranjan et al., 2017). The immune system may then react against native microflora as well as inappropriately control invading pathogens. Additionally, the decline in gut microbiota diversity, observed in older individuals, may also impact the immune system at the local and systemic levels. This could be due, at

![Fig. 3. Continuum and basis for the communication pathways between the gut and lung microbiota. The oral and nasal cavities are the major points of entry for microorganisms to colonise both the gastrointestinal and the respiratory tracts. In addition, transport of metabolites and immune cells through the blood and lymph circulatory systems allows for signal transduction between the two tissues.](image-url)
least partly, to the reduction in growth control of distinct groups of potentially pathogenic bacteria. Together, this may participate in the establishment of the low-grade inflammation observed in ageing individuals (Rehman, 2012), as well as the onset of age-related illnesses. 

Taken together, these studies show that diets modulate molecular mechanisms involved in ageing through their actions on gut microbiota. Thus, in older people, nutrition represents a means of action to maintain a balanced gut microbiota that will positively impact senescence and ageing, at the local and systemic levels.

4. The gut-lung axis and ageing lungs

In the literature, the first papers supporting the existence of an intestine-lung axis, trace back to the early 1990’s and referred to the occurrence of ARDS (Acute respiratory distress syndrome) following septic shock and translocation of bacterial products from the lumen of the intestine to the blood stream (Pugin and Chevrolet, 1991). It was actually mainly known as the gut-liver-lung axis as the ARDS was caused by degranulation of neutrophils that was triggered by inflammatory factors secreted by the liver (Pugin and Chevrolet, 1991). Using a bone marrow transplantation mouse model, Cooke et al. later proposed that controlling gut toxicity and specifically the translocation of lipopolysaccharide (LPS) across the intestinal epithelium could reduce idio-pathic pneumonia syndrome, demonstrating the existence of a gut-lung axis of inflammation (Cooke et al., 2000). It is now known that certain acute and chronic lung diseases are associated with dysbiotic microbial communities in the lung and gut, and with gut symptoms or disorders. This relationship is bi-directional and, although evidence for the lung-gut axis is not as abundant as data on the gut-lung axis, it is now well established that chronic and acute lung disease induce changes in the gut microbiology and physiology. One of the striking recent evidence supporting this is the presence of gastrointestinal symptoms in 10–18 % of patients infected by the SARS-CoV-2, according to the most recent meta-analyses (Trottein and Sokol, 2020), for which, although all age groups can contract the virus, older people (60+) are at increased risk of developing severe illness. Here, we present the physiological similarities between the two tissues, and the anatomical features enabling the gut-lung axis, and review the evidence of the reciprocal regulation of the microbial ecosystems and epithelial physiology between the airways and the gastrointestinal (GI) tract.

4.1. The anatomical continuum between the lungs and gut is more permissive to exchanges in the elderly

In the gut and lungs, the epithelium serves a crucial role of barrier that is at the same time, physical, chemical and physiological. Interestingly, the permeability of both the lung and gut epithelia is increased in aged individuals or ageing animal models (Cesar Machado and da Silva, 2016; Parrish, 2017; Tankersley et al., 2003), suggesting an impaired barrier function of these tissues with old age. These structures are in permanent contact with exogenous particles and microorganisms with a potential for pathogenicity and by regulating their permeability through their tight junctions; they allow selective transfer of materials across this physical barrier. They also take part in the innate immune response to pathogens, acting as a chemical barrier, by secreting soluble factors that will either have antimicrobial activity (direct response) or signal to the immune system their presence, and thus trigger the appropriate innate and adaptive immune responses. Both epithelial structures are also able to tightly regulate ion and fluid transport via the expression of many ion channels and transporters common to both organs, which are of particular importance in the regulation of the composition and pH of the luminal environment in which the microbiota live. These barriers become ‘leakier’ with age, but up to now there is no evidence this is a cause or consequence of microbiota dysbiosis. However, it is plausible that an impaired epithelial barrier would allow for less stringent regulation of the trans-epithelial transport of microbes and microbial metabolites, and therefore an enhanced and unfiltered communication along the gut-lung axis that would lead to a loss in compartmentalisation of the microbiota.

Moreover, microbiota from the gut, the nose and throat, have recently been shown to develop in a coordinated way during the first year of life (Grier et al., 2018). Both the GI and respiratory tracts share a common entry point for microorganisms – the oral cavity. In this organ, the microbiota has been shown to share significant overlaps with both the gut and lung ecosystems (Bassis et al., 2015; Segata et al., 2012), and it is able to modulate inflammation in bronchial cells in vitro (Mathieu et al., 2020). A study from the Human Microbiome Project revealed a 45 % overlap between the microbiota from the oral cavity and stool samples (Segata et al., 2012). Interestingly, Bassis et al. demonstrated that, using redundancy analysis of the microbiota from the mouth, nose and broncho-alveolar lavage (BALs), the microbial community from the BALs were closer to that of the mouth instead of that found in the nose, although the indices of intra-subject similarity ranged from dissimilar to highly dissimilar. When looking at bacterial Operational Taxonomic Units (OTUs), the bacterial communities of the lungs showed a significant overlap with the ones from the mouth, but they differed considerably from those found in the nose (Bassis et al., 2015). Therefore, this establishes an anatomical continuum for microorganisms from the mouth to colonize both the respiratory and GI tracts (Fig. 3). Microorganisms from the mouth migrate to the GI tract by swallowing, whereas they colonize the lungs through micro-aspirations and inhalation of micro-aerosols. The elimination of microorganisms from the lungs occurs via the mucociliary escalator, in which the coordinated movement of the cilia together with the secretion of mucus, ion and water, allows to move the mucus up towards the pharynx, where it will be swallowed or expectorated. By contrast, microbes present in the stomach may move back to the mouth via the oesophagus in cases of gastroesophageal reflux and be inhaled in the lungs. This is supported by the fact that the composition of the lung microbiome more closely resembles that of the oropharynx than the nasopharynx (Bassis et al., 2015; Dickson and Huffnagle, 2015). Additionally, a study by Rosen et al. showed that the concentration of some bacteria in the lung was correlated with full-column non-acid reflux burden in patients receiving acid-suppression therapy, supporting the fact that gastric microbiota can alter lung microbiota (Duvallet et al., 2019; Rosen et al., 2014). The prevalence of gastroesophageal reflux disease increases with age (Poh et al., 2010; Zhu et al., 1993), suggesting that transfer of microbiota from the stomach to the lungs might happen more easily in older individuals, providing here as well, an enhanced and unchecked communication pathway between the gut and the lung. Moreover, some studies have shown that the coordinated response to certain stresses or pathogens in the lungs and the gut are mediated through the modulation of the immune system and the transport, in the blood, of bacterial metabolites (Fig. 3).

4.2. From the lungs to the gut – impact of lung infections on gut health

Although it is difficult to establish a causal link between certain lung diseases and a dysbiotic gut microbiota in humans, animal models have strongly contributed to this field in recent years. The pioneering work from Sze et al. demonstrated that, in mice, acute lung injury induced by LPS caused an increase in bacterial load in the blood and caecum, whereas lung total 16S was slightly reduced in BALs and changes in abundance of certain bacterial species occurred (Sze et al., 2014). Another model of lung injury in mice, induced by cigarette smoke, further detailed the impact of acute exposure to stress on gut inflammation, and it identified the Th17-dependent pathway as a main player in the communication between the two tissues (Kim et al., 2019). In this study, mice were exposed to cigarette smoke and then to an intestinal inflammatory challenge (2 % DSS in drinking water for 6 days). DSS-induced weight loss was more pronounced in mice exposed to cigarette smoke, and this was accompanied by increased histological
| Study | Animal / Microbiota Analysis method | Infectious agent | Effect on gut microbiota | Mode of Action and consequences |
|-------|-------------------------------------|-----------------|--------------------------|---------------------------------|
| Viruses | | | | |
| Wang et al., 2014 | Mouse / Real-time PCR and selective culture | Influenza A/PR/8/34 (PR8), 0.1 HA of PR8, intranasally | No change in number of total bacteria | Lung-derived CD4+ T cells -> IFN-γ CCL25-CCR9 axis recruitment of CCR9+ CD4+ cells to the intestine -> gut microbiota dysbiosis |
| Qin et al., 2015 | Human / Illumina TruSeq | H7N9 | No change in number of total bacteria | N/A |
| Yu et al., 2015 | Mouse / Bacterial colony plate counts | Influenza A/FM1/1/47 20% Lethal Dose 50 intranasally | No change in number of total bacteria | N/A |
| Deriu et al., 2016 | Mouse / MiSeq Illumina | Influenza A / Puerto Rico/8/34 (PR8) – 200 PFU – intra-tracheal | No change in number of total bacteria | N/A |
| Bartley et al., 2017 | Mouse / MiSeq illumina | Influenza virus A/PR/8/34 (PR8), 400 EID50 intranasally | No change in number of total bacteria | N/A |
| Groves et al., 2018 | Mouse / MiSeq illumina | RSV-A2, 2 × 10^5 PFU/mL | No change in number of total bacteria | N/A |
| Yildiz et al., 2018 | Mouse / MiSeq illumina | Influenza A/Viet Nam/1203/2004, 4 × 10^4 PFU/mL | No change in number of total bacteria | N/A |
| Sencio et al., 2020 | Mouse (C57BL/6 J) / MiSeq illumina | Influenza H3N2 IAV Scotland/20/1974, 30 pfu, intranasally | No change in number of total bacteria | N/A |
| Bacteria | Mycobacterium tuberculosis | | | |
| Winglee et al., 2014 | Mouse (Balb/c) /454 FLX pyro-sequencing | Mycobacterium tuberculosis CDC1551 or H37Rv, aerosol (Middlebrook inhalation exposure system) | No change in number of total bacteria | N/A |
| Luo et al., 2017 | Human (adults) / MiSeq illumina | Mycobacterium tuberculosis | No change in number of total bacteria | N/A |
| Hu et al., 2019a | Human (adults) / MiSeq 2500 illumina | Mycobacterium tuberculosis | No change in number of total bacteria | N/A |

(continued on next page)
Table 2 (continued)

| Study | Animal / Microbiota Analysis method | Infectious agent | Effect on gut microbiota | Mode of Action and consequences |
|-------|------------------------------------|-----------------|--------------------------|---------------------------------|
| Hu et al., 2019b | Human (adults) / HiSeq 2500 Illumina | Mycobacterium tuberculosis | No significant difference | N/A |
| Huang et al., 2019 | Human (adults) / MiSeq Illumina | Mycobacterium tuberculosis | ↗ Bacteroidetes | Correlation between gut F/B ratio and blood IL-1β |
| Li et al., 2019 | Human (children) / MiSeq Illumina | Mycobacterium tuberculosis | ↗ Rikenellaceae, Bifidobacteriaceae, Lachnospiraceae, Roseburia, Faecalibacterium, Bacteroides, Clostridiales, Enterococcus, Prevotella | N/A |
| Namasivayam et al., 2018 | Rhesus macaques / Illumina NextSeq (V4 region) | Mycobacterium tuberculosis Erdman strain, <10 CFU, intra bronchial instillation | Minor changes | N/A |
| Streptococcus pneumoniae | Dabrowski et al., 2019 | Mouse (BALB/c) / MiSeq Illumina Streptococcus pneumoniae, NCTC 7978, 10^5 cfu | ↗ Lachnospiraceae, Ruminococcaceae | N/A |
| Fungi | Samuelson et al., 2016 | Mouse (C57BL/6 j) / MiSeq Illumina Pneumocystis murina (2 × 10^6 cysts/mL, intratracheal) | ↗ α-diversity | N/A |

Dive into lung microbiota, however possible to cough smoke-induced changes in the lung microbial community that drive the local and systemic immune responses.

Of interest, especially in elderly people, is the impact of respiratory infections on gut microbiota and physiological homeostasis. As previously mentioned, older people are at higher risk of complications when infected by certain respiratory viruses or bacteria (see chapter 2). To date, no study has specifically reported the effect of respiratory bacterial or viral infections on the gut microbiota in older human populations. However, studies in younger human populations and in mouse models have provided accumulating evidence supporting a central role for acute infections in modulating gut microbiota and impacting its homeostasis (Table 2).

Of note, respiratory pathogens, however diverse they are, trigger common shifts in microbiota composition; species from the Firmicutes phylum and Clostridiales order, including Lachnospiraceae, Faecalibacterium and Ruminococcus, are generally decreased as are Bifidobacteria from the Actinobacteria phylum. By contrast, Proteobacteria, especially *E. coli* species are found increased in the gut of individuals or animals infected with respiratory pathogens. As studies are sparse for certain types of pathogens such as fungi or certain bacteria commonly responsible for pneumonia in elderly people, it is, at the time of writing, impossible to identify specific patterns associated with specific types of pathogens.

Most studies that have searched for gut colonization of the respiratory pathogen have not found any evidence that this occurs, suggesting that there exist other lines of communication responsible for the dysbiosis observed in the gut. Mechanisms of action involved in transducing the signal of infection from the lungs to the GI tract are not yet fully understood, although certain pathways have been identified. For instance, Wang et al. showed that after Influenza A virus (IAV) infection, lung-derived CD4+ T cells activate the CCL25—CCR9 axis to induce the recruitment of CCR9+CD4+ T cells to the intestine and thus inducing gut microbiota dysbiosis. Likewise, a recent study by Liu et al. showed that mast cells might also be key players in transducing the signal of infection from the lungs to the gut (Liu et al., 2019).

4.3. From the gut to the lungs—Impact of gut microbiota and food intake/diet on lung health

As previously described, respiratory infections can impact the composition and diversity of gut microbiota either by modulating local immune populations that are then recruited to the gut, or by inducing anorexia, thus decreasing food intake and nutrient availability. Interestingly, these changes in microbiota feed back to the respiratory tract and increase the susceptibility to secondary infections, as in the case of Influenza virus infections (Sencio et al., 2020). There are now multiple reports supporting the role of intestinal microbiota in the maintenance of healthy lungs, as well as its responses to respiratory infections and vaccines (Dumas et al., 2018; Hanada et al., 2018). Many studies have used oral antibiotics administration in order to investigate the role of gut microbiota in other tissue responses to various stressors (e.g., infection, inflammation). However, the impact of such treatment on distal microbiota such as the pulmonary microbiota has rarely been investigated and thus requires further exploration. For example, early studies demonstrated that antibiotics treatment increased mortality of animals that were infected with IAV (Abt et al., 2012; Ichinohe et al., 2011) or *S. pneumoniae* (Schuitj et al., 2016). Although the effect of oral antibiotics on lung microbiota cannot be excluded, several studies have reported different means of communication between the gut and the lungs. This communication along this gut-lung axis can be mediated by (i) the immune system, (ii) transfer of microbes, or (iii) microbial and host metabolites in the blood from one tissue to the other. Since the gut microbiota plays a major role in shaping the immune system, it affects both local and systemic (in the lungs) responses to pathogens.

### 4.3.1. Communication via the immune system

Depleting gut microbiota with antibiotics modulated the degree of the macrophage response to respiratory IAV infection by decreasing the expression of macrophage-associated antiviral response genes in these circulating leukocytes, particularly genes related to IFN-dependent responses (Abt et al., 2012). Schuitj et al. also reported that alveolar
macrophages and whole-blood neutrophils displayed a decreased phagocytic activity against *S. pneumoniae*, and a decreased inflammatory profile in response to stimulation with TLR ligands (Schuijt et al., 2016). Interestingly, in the latter study, faecal transfer of a microbiota from healthy animals restored pulmonary bacterial clearance and certain cytokines levels in the lungs (Schuijt et al., 2016). Another study reported the pivotal role of Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-17A in the bacterial clearance of *S. pneumoniae* and *Klebsiella pneumoniae*. Both cytokine levels were impacted by oral antibiotics administration and neutralising antibodies increased bacterial burden in non-antibiotic-treated mice. Moreover, by orally or intra-nasally administering a consortium of bacteria that were strong Nod2 activators, it was shown that the restitution of either microbiota could rescue defects in pulmonary clearance of *S. pneumoniae* or *K. pneumonia* (Brown et al., 2017). In the case of viral infections with IAV, Ichinohe et al. demonstrated that antibiotics treatment altered B cells, CD4+ and CD8+ T cells, as well as DC homeostasis; mediastinal lymph nodes DC numbers were reduced and showed an impaired presentation of viral antigen peptide, making them unable to activate antigen specific CD8+ T cells (Ichinohe et al., 2011). Finally, Gauguet et al. showed that gut microbiota also impacts responses to pulmonary infections by modulating the Th17 cell-mediated immunity. Particularly, they found that the presence of the commensal segmented filamentous bacteria (SFB) in murine GI tract protected against Methicillin-resistant *Klebsiella pneumoniae* (Vareille-Delarbre et al., 2019). Results from randomised control trials and meta-analyses generally show improvement of lung health following probiotics supplementation, whether it impact the incidence of certain infections, the duration, or the severity of the disease (de Vrée et al., 2006; Hao et al., 2015; Wang et al., 2016).

5. Discussion

As described in this review, recent studies have provided evidence for the modulation of respiratory health by diets and/or shifts in microbiota composition and function (Sencio et al., 2020; Trompette et al., 2018, 2014; Vaughan et al., 2019). These studies have mainly been carried out on animal models at a young or adult age. The ageing process is influenced by both intrinsic and external factors. In addition to replicative senescence, events along people’s lifespan might have long-lasting impacts on their own physiology, as well as on their microbiota. Repetitive courses of antibiotics, for example, disrupt the gut microbial ecosystem, and we can assume that it is also the case for the lung microbiota. Considering the physiological characteristics of the elderly population, it is now important to investigate the interactions between diet, gut and lung microbiota, and lung health and disease. Particularly, fiber-rich diet has been associated with lower risk of developing COPD (Vaughan et al., 2019), improved response to viral infection (Trompette et al., 2018), and decreased severity of allergic airway disease (Trompette et al., 2014). It has been shown that probiotics can impact the course of respiratory diseases. Using a mouse model and the probiotic *Lactobacillus plantarum* CIRM653, Vareille-Delarbre reported a reduced response to intra nasal infection with *K. pneumonia* (Vareille-Delarbre et al., 2019). Results from randomised control trials and meta-analyses generally show improvement of lung health following probiotics supplementation, whether it impact the incidence of certain infections, the duration, or the severity of the disease.
Malnutrition

Gut dysbiosis

Immunodeficiency

Respiratory tract infections

Lung dysbiosis

Urinary tract infections

Sarcopenia

Falls

Bedridden

Pressure ulcers

Death

Reversibility

Adequate personalized nutrition

Total or partial irreversibility

Fig. 4. The slippery slope of malnutrition in the elderly. Malnutrition in the elderly leads to a sequence of reversible and irreversible pathophysiological changes leading to the degradation of the general state of the individual. One of the early signs of a degrading health is lung infection. We propose that targeting malnutrition, and more specifically gut microbiota, using probiotics containing foods, would help reverse this chain of events, thus preventing further health degradation.

6. Conclusions

Older age is associated with dysbiotic gut and lung microbiota along with a loss of resilience and compartmentalisation of microbial species in both tissues. In this review article, we propose the existence of an enhanced bidirectional communication between the gut and the lung, which could link the nutritional status to the susceptibility to respiratory diseases in older individuals. Collectively, the studies presented here highlight a central role for the gut-lung axis and the corresponding local microbiota communities in the maintenance of healthy lungs in older individuals.

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Declaration of Competing Interest

None of the authors of this paper have a financial or personal relationship with people or organizations that could inappropriately influence or bias the content of the paper.

CRediT authorship contribution statement

Vinciane Saint-Criq: Conceptualization, Writing - original draft, Writing - review & editing. Geanncarlo Lugo-Villarino: Writing - original draft, Writing - review & editing, Funding acquisition. Muriel Thomas: Conceptualization, Writing - review & editing, Funding acquisition.

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