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Aging-related alterations are a growing health concern

The global population is aging, and the World Health Organization (WHO) projects that the number of individuals aged 60 and older will double by 2050, while the number of individuals aged 80 and over will triple between 2020 and 2050. The increasing age of the global population is associated with significant consequences and costs for both societal and health infrastructure. Aging is associated with a host of health complications, including cancer and metabolic, cardiovascular, and neurodegenerative disorders (Deleidi et al., 2015; Franceschi et al., 2018; Goronzy & Weyand, 2012), yet not all individuals age equally, leading to the hypothesis that environmental and genetic factors conspire to promote healthy or unhealthy aging. Unraveling the qualities that promote healthy over unhealthy aging represents an important research question, which may translate into significant improvements in the quality of life for the global aging population and the rates of multifactorial age-associated comorbidities.

While the biomedical research enterprise focuses on understanding mechanisms to enhance healthy aging and longevity, there are coincident societal implications. Aged individuals can provide valuable societal contributions through their accumulated knowledge and generational insights, yet this wisdom is commonly overlooked in Western societies, resulting in increasing isolation of elders. Ageism has been recognized as a global challenge by WHO with an estimated 6.3 million cases of depression thought to be attributable to ageism. Further, ageism is associated with worsened physical and mental health, increased loneliness and isolation, financial insecurity, decreased quality of life, and premature death. A shift in these views and the perception of the role of the elderly in society will be necessary to ensure that the idea of “healthy aging” holistically considers quality of life and continued societal integration and inclusion, as well as disease-free lifespan.

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Common age-associated comorbidities are intimately tied to immune dysregulation. In aged individuals (generally > 65 years old for humans, > 20 months old for C57BL/6 mice), the immune system undergoes characteristic changes. First is the development of inflammaging, a state of chronic, systemic, sterile, low-level inflammation (Franceschi et al., 2000) that is associated with increased susceptibility to the development of metabolic, cardiovascular, and neurodegenerative disorders. Paradoxically, a concomitant process known as immunosenescence, which is characterized by dampened innate and adaptive immune responses to antigen challenge, underlies age-associated deficits in vaccine efficacy and response to infection. Age-related immunosenescence may also contribute to cancer risk as a consequence of suboptimal immunosurveillance.

Age-related alterations of the adaptive immune system include decreased B cell diversity, accumulation of age-associated B cells, and decreased antibody responses following vaccination; thymic involution, resulting in reduced rates of lymphopoiesis, fewer naïve T cells, and a less diverse T cell repertoire; and elevated numbers of hyporesponsive T cells expressing the inhibitory receptors Tim-3 and PD-1 (Agrawal et al., 2007; Appay & Sauce, 2014; Channappanavar et al., 2009; Ciabattini et al., 2018; Decman et al., 2012; Dunn-Walters, 2016; Frasca & Blomberg, 2009; Gibson et al., 2009; Gustafson et al., 2020; Lee et al., 2016; Ma et al., 2019; Pang et al., 2011; Rossi et al., 2005; Shimada et al., 2009; Thomas et al., 2020). Aging is also associated with profound functional changes in innate immune cells, including altered dendritic cell function, decreased phagocyte antimicrobial activity, reduced chemokine/cytokine production in response to damage-associated molecular pattern (DAMP)/microbe-associated molecular pattern (MAMP) stimuli, and downstream consequences in adaptive immune priming and function (Boehmer et al., 2005; Liang et al., 2009; Renshaw et al., 2002; Shaik-Dastagirisah et al., 2010; Shaw et al., 2013; Toapanta & Ross, 2009). For the purposes of this review, we have compiled a list of key characteristics of immunosenescence and inflammaging that are common in both mice and humans in Figure 1.

In recent years, multiple studies have begun to untangle the profound impact of the microbiota on host physiology, including the immune system. In humans (Odamaki et al., 2016; Ragonnaud & Biragyn, 2021; Xu et al., 2019), mice (Boehme et al., 2021; Fransen et al., 2017; Langille et al., 2014; Thevarajan et al., 2017), and flies (Broderick et al., 2014; Clark et al., 2015; Shukla et al., 2021), age-related shifts in the composition of the microbiota have been associated with immune consequences and complications. The conservation of these phenotypes has led to the proposal that the modifiable nature of the microbiota may be exploited to limit detrimental consequences of immunosenescence or inflammaging (Biagi et al., 2016; Bosco & Noti, 2021; Ragonnaud & Biragyn, 2021; Xu et al., 2019).

The gut microbiota of otherwise healthy people over 65 years of age often significantly differs compared with younger adults, and reduced α-diversity is a common feature (Bosco & Noti, 2021; Collino et al., 2013; Luan et al., 2020; Wu et al., 2019). These shifts in microbial community composition have been associated with frailty, altered immune signaling, and modified intestinal barrier integrity (Bosco & Noti, 2021; Claesson et al., 2012; Jackson et al., 2016; Magrone & Jirillo, 2013; Ragonnaud & Biragyn, 2021). Notably, centenarians (99–104 years old) and semi-supercentenarian (105–109 years old) exhibit unique hallmark changes to the microbiota, such as increased α-diversity, an association that suggests an intimate link between improved longevity and the microbiota (Biagi et al., 2016; Wilmanski et al., 2021).

Intestinal epithelial cells (IECs) are a diverse population of epithelial cells that form a continuous barrier separating the external environment (the intestinal lumen) from the underlying tissue. As such, they serve as a critical interface between the microbiota and the rest of the host immune system. However, we have limited

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**FIGURE 1** Hallmarks of inflammaging and immunosenescence in both humans and mice.
understanding of how age impacts the function of the multiple lineages of IECs that form the interface between our immune system and the microbe-rich intestinal lumen. In this review, we will provide an overview of age-related changes to the microbiota, IECs, and the immune system and propose that altered IEC function with age is central to the dysregulation of this tripartite interaction in aging individuals.

# 2 | AGE-RELATED ALTERATIONS TO THE MICROBIOTA AND ITS METABOLITES

## 2.1 | Age-associated shifts in microbial composition

The intestinal microbiome is a highly diverse community of microbes and eukaryotes, including bacteria, archaea, viruses, fungi, protists, and sometimes helminths that exist within a host (Belkaid & Hand, 2014; Filyk & Osborne, 2016). While in this review we will focus on bacterial components of the microbiota, the potential impacts of other members of the gut microbiome are often understudied, yet important, contributors to health outcomes. The community composition of the microbiota is impacted by a plethora of individual and environmental factors including geography, immunological exposure, infection history, medical history (type of birth, antibiotic use, etc), age, sex, and genetics.

Interestingly, successful aging and centenarian status is associated with a unique microbiome compared to adult controls. Unlike standard elderly populations, which generally exhibit dysbiosis, decreased microbial diversity, and increased representation of proteolytic bacteria (Woodmansey, 2007), individuals with improved longevity (>80 years) tend to harbor a microbiome characterized by depletion of core bacteria and increased α-diversity (Biagi et al., 2016; Wilmanski et al., 2021). For example, Akkermansia, Bifidobacterium, Alistipes, and Christensenellaceae (Biagi et al., 2016; Drago et al., 2012; Ragonnaud & Biragyn, 2021; Tuikhar et al., 2019) are enriched in centenarian and semi-supercentenarian humans relative to both younger adults and elderly individuals, suggesting that these microbial community members may be uniquely associated with successful aging. Akkermansia, in particular, has been linked to the production of mucin and maintenance of intestinal barrier integrity in aged murine models (Bodogai et al., 2018), as well improved longevity and healthspan following oral gavage in short-lived progeroid mice (Bárcena et al., 2019) and increased production of antiaging-associated polyamines and short-chain fatty acids (SCFAs) (Grajeda-Iglesias et al., 2021). Additionally, Christensenellaceae has been identified as one of the most heritable members of the microbial community, suggesting that there may be a genetic component to the acquisition of a successful aging/centenarian microbiota (Goodrich et al., 2014). This is further supported by the finding that siblings of centenarians have a life-long mortality advantage, though this study did not examine microbiome composition (Perls et al., 2002).

## 2.2 | Microbiota-derived metabolites in aging

Going beyond the structural organization of microbial communities, understanding the functional effects of microbial-derived metabolites is critical for enhanced understanding how host-microbiota interactions influence host health. In addition to the increased translocation of bacterial products seen in aged mice that could contribute to inflammaging, continually emerging evidence that bacterial-derived metabolites directly influence host cell function (including IECs and immune cells) suggests that age-associated immune dysregulation and associated comorbidities may be influenced by these molecules (Parker et al., 2022; Thevarajan et al., 2017). As an example, microbiota-derived SCFAs exert wide-ranging effects on the intestinal environment, including promoting intestinal barrier integrity and mucus production, regulating and supporting commensal microbes, and mediating immune tolerance in the gut, including T regulatory cell (Treg) homeostasis (Córreia-Oliveira et al., 2016; Smith et al., 2013). Despite evidence that SCFAs decline in the standard aged individual due to a shift from saccharolytic fermentation to more proteolytic, pro-inflammatory activities (Salazar et al., 2019), centenarian microbiomes have been noted to have a high capacity for central metabolism, including glycolysis and production of SCFAs (Wu et al., 2019).

Increased representation of proteolytic bacteria is a common feature in aging microbiomes, which could be predictive of elevated levels of the tryptophan-derived metabolite indole. Counterintuitively, indole levels have been reported to decrease with age in mouse and human fecal samples and mouse serum (Ruiz-Ruíz et al., 2020; Wu et al., 2021). Instead, in both aged mice and nonagenarians, kynurenine, an alternative tryptophan-derived product is elevated, and increased levels of kynurenine predicted mortality in nonagenarians, suggesting that diversion of tryptophan from indole toward kynurenine may negatively impact healthspan in aged individuals (Pertovaara et al., 2006; Wu et al., 2021). Evidence that commensal microbiota-derived indoles can increase healthspan in multiple organisms including Caenorhabditis elegans, Drosophila melanogaster, and mice (Sonowal et al., 2017) suggests that dietary supplementation with indole or alternative promotion of indole-producing bacteria in the microbiota may result in improved health outcomes for aged individuals. Indeed, indole-3-carbinol supplementation has been found to improve Clostridium difficile outcomes in mice (Julliard et al., 2017), and colonization of young and aged mice with indole secreting bacteria can promote epithelial cell proliferation (Powell et al., 2020), supporting a critical role for indole in the modulation of aged-associated changes to mucosal immunity and IEC renewal. Locally, metabolites impact IECs, which also undergo a variety of age-related changes. Whether these IEC changes are age-intrinsic and contribute to selecting an altered microbiota or are driven by an altered microbiome and microbial metabolites with age remains unknown, as does the relative importance of IEC function in age-related immune dysregulation.

Metabolites are promising candidates for the translation of intestinal signals and regulation of distal cellular function, as well as...
control of persistent, low-grade inflammation. Notably, the bio-
synthetic pathways of secondary bile acids, which have potent an-
timicrobial activity against Gram-positive pathogens, are enriched
in the centenarian microbiome (Sato et al., 2021). Secondary bile
acids represent an intriguing area of potential study for successful
versus unsuccessful aging as they have notable and predominantly
anti-inflammatory, enhanced barrier integrity, and pro-wound repair
effects on both IEC and immune cell populations (Sun et al., 2021).
However, given the multitude of factors at play in the development
and progression of the aged gut microbial community, there is likely
not one “panacea” gut microbial composition, but rather a balance
of diversity and evenness of microbial members and their metabo-
lites that supports healthy aging and immune homeostasis (Rampelli
et al., 2016).

2.3 | Microbiota, metabolites, and age-associated immune effects

Supporting the hypothesis that the microbiota is a key driver of
inflammaging and immune dysregulation, GF mice have a longer
lifespan than their conventional (CNV) counterparts. In contrast to
age-matched CNV mice, GF mice exhibited no detectable increase
in circulating IL-6 (a hallmark of inflammaging) and maintained in-
testinal barrier integrity as well as macrophage antimicrobial ac-
tivity (Thevarajan et al., 2017). Further, microbial transfer via
co-housing with aged mice conferred age-related inflammatory
phenotypes (including increased levels of circulating TNFα and in-
testinal permeability) to young and old GF recipients (Thevarajan
et al., 2017). Notably, these phenotypes were not replicated by
co-housing with young mice, suggesting that the age of the mi-
crobiota (not just microbial exposure) matters (Figure 2). An inde-
pendent study using fecal microbiota transplant (FMT) of young vs
aged donors into young GF recipients demonstrated that an “aged”
gut microbiota was uniquely capable of eliciting small intestinal
inflammation (Figure 2), elevated levels of circulating microbiota-
derived inflammatory components, and systemic increases in T
cell activation (Fransen et al., 2017). Notably, in a reciprocal ex-
periment, FMT from young donors to aged recipients antagonized
certain age-related immune alterations in the mesenteric lymph
nodes, including accumulation of migratory CD103+ DCs and re-
cently activated CD8+ T cells (Boehme et al., 2021). For the pur-
poses of experimental replication, it is important to note that in this
particular study, young and aged mice were acquired from different
commercial vendors and recipient mice retained an intact micro-
cbiota prior to FMT (Boehme et al., 2021).

Whether an aged microbiota directly contributes to impaired
protective immunity, or whether microbiome manipulation can
restore efficacy in aged mice, remains minimally examined. How-
ever, in humans, there is an association between increased
age and more severe clinical outcomes following C. difficile infec-
tion (Henrich et al., 2009; Pépin et al., 2005). Further, in a study
examining C. difficile in young and aged mice, microbiota exchange
resulted in a significantly improved early immune response and
survival in aged mice, providing support for the modulation of the
aged microbiome as a method of modifying protective immunity,
although the requisite pretreatment with antibiotics in order to
establish productive C. difficile infection in immunocompetent
mice slightly confounds the interpretation of this study (Shin
et al., 2018).

Emerging data indicate that an aged microbiota can influ-
ence immune cells at distal sites, including CNS-resident microglia
(Boehme et al., 2021; D’Amato et al., 2020; Golomb et al., 2020).
The observation that microglia in GF mice have a less activated phe-
notype than conventionally housed mice harboring a complex mi-
crobiota, and that a “normal” activation state could be restored by
SCFA supplementation (Erny et al., 2015), was critical to develop-
ing a framework for investigation of gut–brain communication. The
microbiota-dependent effects on activation, morphology, and func-
tion of microglia have been associated with cognitive and behavioral

![Image of a figure illustrating the impact of the age of the microbiota on inflammaging outcomes. Transfer of an aged microbiota is sufficient to elicit aspects of an inflammaging phenotype in young mice, including increases in circulating inflammatory cytokines and impaired phagocytosis. Conversely, aged germ-free (GF) mice are resistant to inflammaging, and transfer of young microbiomes can reverse some aspects of immune homeostasis in conventionally raised aged mice.](image-url)
effects, and their inflammatory and debris-clearing functions are being explored as contributors to age-related neurodegeneration (Lee et al., 2020; Mossad & Blank, 2021).

Collectively, these studies in mouse models and humans suggest that aging has the potential to drive significant changes to the intestinal microbiota and its associated metabolites, as well as localized intestinal and systemic immune responses. However, the relative contribution of environmental influences vs cell-intrinsic functional changes in the development of age-associated dysbiosis, immunosenescence, and inflamming remains incompletely understood. Given that aged GF mice are protected against age-associated inflammation (Thevaranjan et al., 2017), and an aged FMT is sufficient to confer inflamming (Fransen et al., 2017; Thevaranjan et al., 2017), which can potentially be reversed by young FMT (Boehme et al., 2021; Figure 2), at least some of these changes appear to be microbiota-influenced. Mechanistic understanding of how the microbiota influences immune homeostasis and function throughout the aging process is critical. In addition to direct host-microbe interactions, including those caused by increased translocation of bacteria and bacterial products through the gut mucosa with age, accumulating data indicate that differences in the intestinal microbiome correlate with healthy vs unhealthy aging (O'Toole & Jeffery, 2015; Parker et al., 2022; Ragonnaud & Biragyn, 2021; Thevaranjan et al., 2017).

The microbiota and microbiota-derived metabolites impact IEC activity and composition, which assist in relaying aberrations in intestinal homeostasis to the broader immune system (Ornelas et al., 2022; Peterson & Artis, 2014). The microbiota, its metabolites, and IECs undergo a host of changes during the aging process. The interplay between these factors throughout aging and their impact on the progression of inflamming and immunosenescence remains an understudied and important area of inquiry.

3 | INTESTINAL EPITHELIAL CELL POPULATIONS DURING THE AGING PROCESS

The intestinal epithelium is populated by a diverse group of differentiated IECs derived from intestinal epithelial stem cell (IESC) precursors, which serve a variety of distinct functions to maintain intestinal homeostasis, including communication with the gut microbial community. These cells include absorptive (colonocytes in the large intestine and enterocytes in the small intestine) and secretory (goblet cells, Paneth cells, enteroendocrine cells, M cells, and tuft cells) cell types (Clevers, 2013), which function as critical conveyers of environmental and microbiota signals to the host immune system (Figure 3).
Lgr5+ iESCs in intestinal crypts are the progenitors of all IEC subtypes (Barker et al., 2007). Both human and murine IECs express a variety of toll-like receptors (TLRs), including TLR1, TLR2, TLR4, TLR5, and TLR9 (Abreu, 2010). T helper cytokines have a dramatic impact on IEC function and rejuvenation. Tregs produce IL-10, which promotes iESC replenishment of the intestinal epithelium, while Th1-derived interferon (IFN)-γ drives expression of MHCII on iESCs (Biton et al., 2018), allowing them to function as unconventional antigen-presenting cells (APCs). Intestinal microbial populations, IECs, and immune signaling undergo dramatic changes during the aging process (Bosco & Noti, 2021; Müller et al., 2019; Nicoletti, 2015; Walrath et al., 2021); however, the implications of these changes on the complex interplay between these systems remain minimally understood.

Here, we review available literature on epithelial barrier function and IEC subtypes in the context of aging, highlighting areas where these relationships remain unclear, and in other cases suggesting hypotheses to link IECs to microbiota and/or immune function. This topic was also recently reviewed in the broader context of the interplay of these factors on other organs (Walrath et al., 2021).

### 3.1 Age-associated alterations to intestinal barrier function

The mucus layer is located between the microbiota and IECs and is composed of highly glycosylated mucins. This layer provides a physical, dividing interface and protection against digestive enzymes and pathogenic microbes in addition to acting as a nutritional source for anaerobic members of the microbiota (Ali et al., 2020). Goblet cells are primarily responsible for the secretion and renewal of the mucus layer through the production of Muc2, a highly O-glycosylated protein. Defective mucus production is associated with the development of chronic inflammation as seen in spontaneous colitis (Heazlewood et al., 2008; Turner, 2009). During the aging process, the gut mucus layer can go through dramatic alterations, including a six-fold reduction in the thickness of the colonic mucus layer in old vs young littermate mice that leads to more frequent direct IEC–microbiota interactions (Sovran et al., 2019). Interestingly, male mice are more susceptible to age-associated decreases in colonic mucus thickness than female mice (Elderman et al., 2017). Studies employing aged mice have documented microbiota-dependent defects in intestinal barrier integrity that in conventionally housed mice with complete microbiomes were associated with altered β-diversity and increased bacterial product translocation relative to young controls (Binyamin et al., 2020; Boehme et al., 2021; Conley et al., 2016; Parker et al., 2022; Sovran et al., 2019; Thevaranjan et al., 2017).

Supplementation with both *Lactobacillus plantarum* WCFS1 (van Beek et al., 2016) and *Akkermansia muciniphila* (van der Lugt et al., 2019) has been suggested as potential probiotic strains to protect against age-related decline of the mucus barrier and was found to protect mucus barrier integrity in the *Ercc1−/−* murine model of accelerated aging.

IECs themselves provide a second layer of physical separation between the microbiota and luminal contents and the surrounding tissues. This barrier effect is mediated by tight junction proteins between IECs such as occludins (Furuse et al., 1993), Claudins (Furuse, Fujita, et al., 1998; Furuse, Sasaki, et al., 1998), and zonula occludens (ZO-1, ZO-2) (Stevenson et al., 1986; Umeda et al., 2006). In colonic tissue from old baboons, tight junction protein expression is reduced, resulting in impaired barrier integrity and increased permeability of colonic biopsies in addition to elevated production of inflammatory cytokines (Tran & Greenwood-Van Meerveld, 2013). Gut microbial composition has been shown to correlate with circulating inflammatory cytokine levels and health in elderly nursing home patients (Claesson et al., 2012), rats (Li et al., 2020), and mice (Conley et al., 2016). However, there is conflicting evidence in humans as to whether aging results in increased gut permeability (Man et al., 2015; Wilms et al., 2020), despite the association of aging with increased levels of serum zonulin (Qi et al., 2017), a known regulator of intestinal permeability (Sturgeon & Fasano, 2016). While the impact of age on human intestinal barrier integrity remains less clear, altered epithelial barrier integrity allowing translocation of commensal microbes, microbial debris, and/or luminal metabolites represents a promising explanation for the aberrant inflamming seen with advancing age (Akdis, 2021).

### 3.2 Intestinal epithelial stem cells

Lgr5+ iESCs in the intestinal crypts are the progenitors of all IEC subtypes (Barker et al., 2007), which may act as unconventional MHCII-expressing APCs under inflammatory conditions and contribute to epithelial-cell remodeling after the resolution of an infection (Biton et al., 2018). These cells asymmetrically divide as regulated by Notch signaling and give rise to two different daughter cells, a self-replacing stem cell and a differentiating cell (Srinivasan et al., 2016). The differentiating daughter cell initially becomes a transit-amplifying progenitor and undergoes another 4–5 rounds of division before differentiating into a mature IEC subtype. As these cells mature, absorptive IECs (colonocytes, enterocytes) go through programmed cell death and are sloughed off, allowing for renewal of the intestinal epithelium every 3–5 days (Cheng & Leblond, 1974). Appropriate regulation of iESC proliferation and IEC renewal is a critical aspect of intestinal homeostasis.

In aged individuals, iESCs become dysfunctional, resulting in a diminished capacity to regenerate the intestinal epithelium and maintain intestinal homeostasis. In alignment with these observations, iESCs and crypt cultures from aged mice exhibit reduced expansion and fewer, less complex enteroids devoid of differentiated cell types with reduced expression of stem cell markers (Olfm4, Bmi1, and Hopx) and cell-type specific markers Alpi (enterocytes), Defa24 (Paneth), and Chga (enteroendocrine cells), but not Atoh1 (secretory lineage) (Cui et al., 2019; Moorefield et al., 2017). IEC organoids from aged mice exhibit epigenetic silencing of the stem cell marker Lgr5, resulting in a reduction of Wnt signaling and cell proliferation (Uchida et al., 2018). Aged iESCs also show a reduction in Notch1 expression and a corresponding increase in Atoh1.
expression (Nalapareddy et al., 2017), an important component in the balance of iESC activity regulated by Wnt and Notch signaling (Tian et al., 2015). Notably, restoration of Wnt signaling can rescue the proliferative defects characteristic of aged iESCs (Nalapareddy et al., 2017). Collectively, these studies suggest an overall reduction in the capacity of aged iESCs to regenerate the intestinal epithelium, resulting in a diminished maintenance of intestinal integrity and homeostasis (Figure 4). As these experiments were performed with cells isolated from conventionally housed mice, it remains unknown whether this is an age-intrinsic effect, or if an aging microbiota may contribute to functional impairments.

### 3.3 Enterocytes

Enterocytes are the most abundant IEC in the intestine and have a characteristic microvilli brush border on their apical surface. Given their abundance, enterocytes are critical for maintaining epithelial barrier integrity. Enterocytes are critical for the absorption and export of luminal nutrients and undergo age-related changes in nutrient absorption, consistent with the known changes in metabolic pathways during the aging process (Barzilai et al., 2012; Yoshimoto et al., 2021). Enterocytes from elderly, otherwise healthy, people demonstrate increased rates of both apoptosis and proliferation, which may lead to reduced enterocyte maturity and absorptive efficacy (Ciccocioppo et al., 2002). Consistent with these observations, aged mice have cleaved caspase-3 positive cells in their intestinal crypts and villi, suggesting increased rates of apoptosis (Moorefield et al., 2017). Further, enterocytes of aged rats expressed less enterocyte fatty acid–binding protein and had reduced intestinal lipid uptake (Woudstra et al., 2004), supporting age-related alterations in nutrient absorption. Collectively, these data suggest that changes in IEC nutrient absorption may contribute to the alterations in microbiota composition, microbiota-derived metabolites, and downstream immune signaling seen in aging populations.

While the primary function of these absorptive cells is to absorb and export luminal nutrients, enterocytes also produce anti-microbial proteins (AMPs), including β-defensin and the secreted C-type lectin regenerating islet-derived protein IIIγ (REGIIIγ). REGIIIγ, which is derived from both enterocytes and Paneth cells, is essential for enforcing the so-called “microbial firewall” (Hooper & Macpherson, 2010), as evidenced by the increased microbial colonization of the gut epithelium and corresponding increase in local Immunoglobulin A (IgA) and IFNγ in REGIIIγ−/− mice (Vaishnava et al., 2011). The epithelial-derived alarmin cytokine IL-33 is a critical primer for Th2 and Treg cell differentiation (Duan et al., 2012), but is also essential for optimal REGIIIγ expression. In the absence of IL-33, REGIIIγ expression is reduced, resulting in overgrowth of the colonic microbiota with an altered community profile (Xiao et al., 2019). Given the importance of REGIIIγ for the maintenance of intestinal epithelium integrity, REGIIIγ and IL-33 may represent interesting targets to further investigate in the context of aging. Consistent with this, REGIIIγ is elevated in the ileum of aged mice (Tremblay et al., 2017), though there has been little study of the human homolog REG3A in the intestinal epithelium. It is tempting to speculate that shifts in the microbial community, diminished mucus thickness, and the increased frequency of microbe–epithelial contact that are associated with aging may result in dynamic regulation of intestinal REGIIIγ expression.

### 3.4 Goblet cells

Goblet cells comprise 10%–15% of the intestinal epithelium (17% of epithelial cells in the colon, and 5% of epithelial cells in the small intestine (Nystrom et al., 2021), making them the most abundant secretory IEC. A central function of goblet cells is the production and secretion of the highly O-glycosylated protein Muc2, the primary component of the mucus layer. While goblet cell production of mucins is a key function, goblet cell-derived trefoil factor 3 (TFF3) and resistin-like molecule-β (RELMβ) also contribute to intestinal barrier integrity. TFF3 promotes mucus cross-linking and viscosity, as well as IEC resistance to apoptosis, and migration during wound repair (Dignass et al., 1994; Taupin et al., 2000; Thim et al., 2002). RELMβ promotes secretion of Muc2 (Krimi et al., 2008), regulates macrophage and CD4+ T cell responses in response to helmhit infection (Nair et al., 2008), and promotes CD4+ T cell differentiation during the aging process. Aging results in silencing of the stem cell marker Lgr5, resulting in a reduction in Wnt signaling and IESC regenerative capacity. Notch1-mediated inhibition of Atoh1 regulates the differentiation of secretory IECs and maintains balanced differentiation of IEC subtypes in healthy human adults. Decreased expression of Notch1 with age results in a corresponding increase of Atoh1 and preferential skewing toward secretory IEC fate.
T cell recruitment and mediation of IEC hyperplasia during pathogenic intestinal bacterial infection (Bergström et al., 2015).

GF mice have dramatically reduced levels of Muc2 compared with conventional mice, resulting in a thin mucus layer (Bergström et al., 2012) reminiscent of the mucus barrier reduction seen in aged mice (Sovran et al., 2019). When exposed to a conventional microbiota, GF mice produce significantly more TFF3 and RELMβ, resulting in a thickened mucus barrier (He et al., 2003). These observations are consistent with the effect of age-related dysbiosis on mucus integrity and suggest that a healthy, “young” gut microbiota contributes to immune homeostasis through maintenance of the mucus barrier.

Despite a skewing of iESCs toward the secretory lineage with aging (Nalapareddy et al., 2017), literature findings on goblet cells in the aged epithelium are mixed, with conflicting reports of both increased and decreased goblet cell numbers in the small intestine during murine aging (Nalapareddy et al., 2017; Powell et al., 2020; Sovran et al., 2019; Tremblay et al., 2017). Interestingly, one study found that not only are goblet cells present in higher amounts in the villi of aged mice, but they contain larger mucin granules that stain more intensely with the mucin stain Alcian Blue, suggestive of impaired mucin secretion by aged goblet cells (Tremblay et al., 2017). Examination of goblet cells in the colon of aged mice found that while goblet cell number was not affected, aged goblet cells exhibited higher levels of caspase-3 expression and increased apoptosis (Sovran et al., 2019). While the differential findings in the literature make accurate interpretation of these studies challenging, collectively these findings suggest that while goblet cell numbers may not be affected by age, changes in goblet cell functionality may contribute to compromised barrier integrity.

In addition to altered goblet cell functionality, aged mice also exhibit changes to the intestinal microbiota (Elderman et al., 2017). Colonization of geriatric mice with indole-secreting bacteria has been shown to increase IEC proliferation and promote goblet cell differentiation (Powell et al., 2020). Given that GF mice also show significant defects in mucus thickness (Bergström et al., 2012), these findings suggest a strong link between goblet cell function/mucus production with the microbiota and age, which likely influences immune homeostasis.

3.5 | Paneth cells
Paneth cells are a specialized subset of secretory IECs found in small intestinal crypts of Lieberkühn, with approximately 5–15 Paneth cells per crypt (Bry et al., 1994). These cells are packed with antimicrobial peptides and dense granule proteins, including defensins, cathelicidins, and lysozyme that can migrate to the mucus layer, embedding antimicrobial activity into the physical protective barrier (Meyer-Hoffert et al., 2008; Vaishnava et al., 2008). Paneth cells contribute to homeostasis at the host-microbiota interface via TLR-dependent recognition of microbe-associated molecular patterns (MAMPs) expressed by the gut commensal microbiota, activation of MyD88, and secretion of AMPs that impact microbial community composition and limit bacterial permeation into tissues (Vaishnava et al., 2008). In particular, an elegant study using mice that either expressed human α-defensin gene (hDEFA5) or lacked α-defensin function through genetic ablation of the α-defensin processing enzyme matrix metalloproteinase 7 (MMP7) demonstrated that Paneth-cell-derived α-defensin directly shapes the microbiota. hDEFA5-expressing mice exhibited reduced Segmented Filamentous Bacteria (SFB) with a population shift toward Bacteroides, while MMP7−/− mice showed an increase in Firmicutes, with a reciprocal decrease in Bacteroides, supporting a direct role for Paneth-cell-derived α-defensin in shaping the microbiota (Salzman et al., 2010). All experimental litters in this study were bred and maintained in the same SPF animal facility, suggesting that differences from WT controls were due to the experimental parameters and not institutional variability.

In aged mice, expression of the Paneth-cell-derived AMPs lysozyme (Sovran et al., 2019) and α-defensin (Tremblay et al., 2017) is reduced compared with young littermate controls, which was associated with compromised barrier integrity. Conflicting data between these two studies regarding the impact of age on the expression of the AMP angiogenin 4 (Ang4) suggest that this particular AMP may be more significantly impacted by facility variations in the microbiota than by age (Sovran et al., 2019; Tremblay et al., 2017). Overall, studies of the age-associated changes to Paneth cells remain minimal and the potential for these changes to impact the microbiota composition, resistance to intestinal bacterial colonization and translocation, and inflammingers merits further investigation.

3.6 | Enteroendocrine cells
Enteroendocrine cells (EECs) make up ~1% of the gut epithelium and span the entire gastrointestinal tract. EEC sensing of luminal nutrients elicits secretion of peptide hormones to mediate digestion (Sternini et al., 2008), immunity (Li et al., 2011; Zhang et al., 2011, 2014), and neuronal signaling (Rhee et al., 2009). As with other IECs, EECs develop from Lgr5+ iESC precursors, and their differentiation is facilitated by coordinated expression of the transcription factors Atoh1, neurogenin3, and neurogenic differentiation 1 (NEUROD1). EECs can be specifically identified by the expression of the surface marker Claudin-4 (Nagatake et al., 2014), which is present on all EEC subtypes. Until recently, EEC subtypes were thought to be characterized by secretion of unique hallmark peptide hormones (Worthington et al., 2018), though more recent work using transgenic mouse models suggests a more flexible and less terminally differentiated EEC secretome, with co-secretion of a given peptide hormone being most closely linked to the tissue environment (Adriaenssens et al., 2015; Egerod et al., 2012; Grunddal et al., 2016; Habib et al., 2018; Svendsen et al., 2015). EECs and their associated peptide hormones, which may exert a variety of effects on immune, neuronal, and metabolic activity, were recently and thoroughly reviewed by Worthington et al. (Worthington et al., 2018).

Aged mice exhibit increased numbers and activity of K cells, an EEC subtype that produces glucose-dependent insulintropic polypeptide/gastric inhibitory polypeptide (GIP), which functions
in a positive feedback loop: K-cell-derived GIP secretion is upregulated by and promotes the accumulation of fat. K cell hyperplasia-associated GIP hypersecretion promotes the build up of fat and insulin resistance in aged mice, which was ameliorated by ablation of the GIP receptor (Ikeguchi et al., 2018) or GIP itself in aged mice (Kanemaru et al., 2020). Consistent with this, older humans also exhibit increased circulating levels of GIP following glucose consumption (de Jesús Garduno-Garcia et al., 2018), suggesting that increased GIP is conserved across species and that the amelioration of age-associated fat and inflammation buildup seen in mice following GIP manipulation may be reproducible in humans. Older humans also have increased numbers of enterochromaffin cells (Yu et al., 2016), which secrete the hallmark hormone serotonin. Altered levels of and signaling by serotonin play a role in a variety of neurodegenerative disorders including Parkinson’s disease (Fox et al., 2009; Politis & Niccolini, 2015), multiple sclerosis (Malinova et al., 2018; San Hernandez et al., 2020), and Alzheimer’s disease (Yu et al., 2016), which secrete the hallmark hormone serotonin.

Mouse studies support an age-associated decline of IgA in the intestinal lumen (Koga et al., 2000), coincident with a reduction in mature M cells. Notably, this attrition of mature M cells can be reversed via exposure of aged mice to a young mouse microbiota, suggesting that the age-related loss of mature M cells is linked to the microbiota (Donaldson et al., 2020). Somewhat counterintuitively, but consistent with an elevated ratio of memory: naive B cells in older individuals (Agarwal & Busse, 2010), increased levels of serum IgA are associated with older age in humans (Arranz et al., 1992; Khan et al., 2021). This conflicting finding between murine and human systems may be due to inherent mouse vs human differences, or aging may be associated with local IgA reductions in the intestinal lumen, but not systemic serum changes in IgA. While there is some conflicting evidence between mouse and human systems that needs to be untangled, age-associated changes in the persistence and maturation of M cells may have a considerable impact on the regulation of intestinal homeostasis and immune-mediated containment of luminal contents and the microbiota.

3.8 | Tuft cells

Tuft cells are rare, secretory epithelial cells that can be identified by their unique expression of doublecortin and calcium/calmodulin-dependent protein kinase-like-1 (DCLK1, also known as DCAMKL-1; Gerbe et al., 2009) and the calcium-activated ion transient channel receptor potential cation channel subfamily M member 5 (TRPM5). Although tuft cell chemosensation has been associated with protective immunity in the respiratory tract, their function in the intestine was more mysterious until a series of papers in 2016 demonstrated their vital role in activating type 2 immune responses to helminth and protozoa (Gerbe et al., 2016; Howitt et al., 2016; Schneider, 2021; von Moltke et al., 2016). Since then, these chemosensory cells have been hypothesized to act as immune sentinels, which has been confirmed by recent demonstrations that tuft cells can “sense” metabolites produced by bacterial and protozoal members of the microbiota and helminths through a succinate receptor (SUCNR1) (Banerjee et al., 2020; Nadjsombati et al., 2018) and Tas2r bitter-taste receptors (Luo et al., 2019). The presence of tuft cells in GF mice indicates that their development is not microbiota-dependent (McKinley et al., 2017).

Another function of DCLK1+ tuft cells is regulating IEC survival and self-renewal responses following radiation-induced DNA damage, as evidenced by increased apoptosis and hypoplasia in tuft-cell-deficient mice (Chandrakasan et al., 2016). DNA damage accumulates in human hematopoietic stem cells (HSCs) during aging (Rübe et al., 2011), thus while tuft cell function in aging remains understudied, we propose that diminished tuft cells may factor into the loss of IEC maintenance and proliferative capacity during the aging process. Further, considering the importance of tuft cells for epithelial renewal following radiation-induced DNA damage in the context
of thymic tuft cells, which play a role in shaping thymocyte development (Miller et al., 2018), there may be interesting implications for the role tuft cells play in both stunted rejuvenation of the intestinal epithelium and the thymic involution individuals undergo during the aging process.

Overall, IECs are critical for barrier function and maintaining immune homeostasis in the intestine. This is already well demonstrated in young individuals with intestinal inflammation, such as IBD patients who present with microbial dysbiosis, IEC dysregulation, and defective barrier integrity (Martini et al., 2017; Nishida et al., 2018). During the aging process, IEC populations, the microbiota they interface with, and the systemic host immune state undergo dramatic changes. Better understanding of the interplay between these populations during the aging process and inflammaging represents a critical area of research to better understand potential factors impacting age-associated comorbidities.

4 | AGE-RELATED IMMUNE ALTERATIONS AND THE MICROBIOTA

An intact microbiota supports the generation of optimal protective immune responses to multiple infections in mice (Hagan et al., 2019; Ichinohe et al., 2011; Lynn et al., 2021). This finding has also been validated in healthy humans: following vaccination or infection with H1N1 influenza, antibiotic-treated individuals with low preexisting antibody titers exhibit dampened induction of antigen-specific IgG1 and IgA antibody responses, suggesting that priming of a novel immune response is compromised (Hagan et al., 2019). Collectively, these data suggest that antibiotic-induced dysbiosis and impaired generation of appropriate adaptive immune responses are conserved across species. In the context of age-related dysbiosis, this suggests that modulation of the aged microbiota may represent an appealing avenue to enhance protective immunity and vaccination responses in elderly individuals (Lynn et al., 2021; Lynn & Pulendran, 2018).

PPs represent a key location at which signals from the intestinal lumen and IECs are translated into an immune response via the production of cytokines and antibodies. The organized lymphoid architecture of PPs is central to T-cell-dependent IgA class-switch recombination, as PPs are the site of GC reactions that support B cell receptor somatic hypermutation and affinity maturation of IgA class-switched B cells. In contrast to the constitutive formation of GCs in the PPs in response to M-cell-derived microorganisms and luminal antigens in healthy adult mice, aged mice have defective GC reactions in PPs and have reduced activation and numbers of conventional CD11c+ DCs in PPs (Kato et al., 2003; Reboldi & Cyster, 2016; Stebegg et al., 2019). Consistent with this, aged mice exhibit immunosenescence via reduced antigen-specific T cell proliferation, effector cytokines, and antibody production at both systemic (spleen) and mucosal (PP) sites compared with young controls (Koga et al., 2000) as well as diminished oral tolerance as a consequence of PP dysfunction (Kato et al., 2003). FMT from young mice into older recipients can restore defective GC reactions in PPs, although the restorative effect did not extend to peripheral lymph nodes, suggesting a localized effect (Stebegg et al., 2019). Collectively, these findings suggest that some of the disruption in protective and tolerant mucosal immune responses associated with age may be due to altered PP function and that these defects are intimately tied to the aging microbiota.

In addition to adaptive immune alterations, increased age is associated with dramatic changes to the innate immune response and altered activity of HSCs, neutrophils, monocytes, macrophages, natural killer (NK) cells, and myeloid-derived plasmacytoid dendritic cells in both human and mouse models. While the majority of these cell populations exhibit age-related functional changes, the bulk numbers of innate cell populations remain largely unchanged in aged individuals (Shaw et al., 2013).

Aged mice and humans exhibit an increased propensity for HSC skewing toward myeloid lineage differentiation over lymphopoiesis (Cho et al., 2008; Pang et al., 2011; Rossi et al., 2005), which is consistent with the reduction in naïve T cell numbers and T cell receptor diversity seen in older individuals (Appay & Sauce, 2014). Providing evidence that the microbiota may contribute to this characteristic skewing of hematopoiesis, HSC isolated from aged conventional mice demonstrates the typical elevation in myeloid: lymphoid progeny, while the developmental potential of HSC isolated from aged GF mice was similar to that of young, conventional mice. Data from IL-1Rα-deficient mice suggest a potential mechanistic link. In the absence of IL-1Rα, mice acquire a dysbiotic microbiome that is associated with Th17 cell expansion in the small intestinal lamina propria. This phenotype was microbiota-dependent and transferable via FMT, demonstrating that the microbiota of il1ra−/− mice is both necessary and sufficient to promote intestinal Th17 differentiation (Rogier et al., 2017). Interestingly, aged specific-pathogen free (SPF) mice produce elevated levels of IL-1α/β that could be diminished via antibiotic-mediated depletion of the microbiota (Kovtonyuk et al., 2021). Further, genetic loss or pharmacologic blockade of IL-1 signaling protects HSCs from developing age-associated inflammatory signatures and restores the unbiased lymphoid-myeloid differentiation seen in young HSCs (Kovtonyuk et al., 2021). Collectively, these data suggest that changes in the aged microbiota are detected in the bone marrow and impact HSC function with downstream effects on immune homeostasis.

Neutrophils are rapid, front-line responders of the innate immune response. Aging results in altered neutrophil bone marrow egress, migration, and chemotaxis (Martin et al., 2003; Niwa et al., 1989; Nomellini et al., 2012), as well as reduced phagocytic and bactericidal activity (Wenisch et al., 2000). Further, elderly individuals also exhibit higher rates of spontaneous neutrophil reactive oxygen species (ROS) production (Ogawa et al., 2008), which may contribute to the inflamming process (Ligiuri et al., 2018). The microbiota is a major mediator of neutrophil aging, and antibiotic-mediated depletion of the microbiota in aged mice diminishes the number of circulating neutrophils and neutrophil-attributed inflammation (Zhang et al., 2015).
Overall, aged macrophages are less responsive to infection and exhibit reduced cytokine production (Renshaw et al., 2002; Shai-Dasthagirisheb et al., 2010), phagocytosis, and TLR expression/signaling (Boehmer et al., 2005; Liang et al., 2009; Renshaw et al., 2002), as well as increased expression of markers of senescence (Hall et al., 2016). Age-related microbial dysbiosis does not result in differential expression of maturation markers on macrophages (CD11b, Ly6C, F4/80, and Ly6G); however, aged macrophages are significantly less capable of conducting bacterial killing compared with young macrophages and aged GF mouse-derived macrophages better maintain their antimicrobial activity compared with their conventional counterparts (Thevaranjan et al., 2017). Monocytes are macrophage precursors that also undergo age-associated functional alterations, including reduced efferocytosis (de Maeyer et al., 2020), phagocytosis (Hearps et al., 2012), type I IFN production (Molony et al., 2017), and TLR signaling (Nyugen et al., 2010; van Duin et al., 2007). Strikingly, age-related microbial dysbiosis, and more specifically, age-related reduction in the commensal bacterium *Akkermansia muciniphila*, which metabolizes fibers into SCFAs such as acetate, propionate, and butyrate, results in not only impaired barrier integrity and leakiness, leading to increased bacterial products in the circulation, but a corresponding increase in the activation of CCR2+ inflammatory monocytes (Bodogai et al., 2018).

Notably, despite increased skewing of HSCs toward the myeloid lineage, the number of circulating myeloid DCs progressively declines with age (Della Bella et al., 2007; Orsini et al., 2012). Aged DCs have a reduced capacity to macrophagocytose and endocytose antigens (Agrawal et al., 2007), initiate T cell activation (Moretto et al., 2008), and migrate in response to the chemokines CCL19 and CXCL12 (Agrawal et al., 2007). These phenotypes are reminiscent of the reduced numbers of intestinal DCs seen in GF mice (Chung et al., 2012; Walton et al., 2006), suggesting that the microbiota influences DC hematopoiesis, migration, or tissue residency, although the specific impact of the aged microbiome on DC function requires further examination.

This constellation of age-associated immune changes, especially when considered in the context of IECs and the microbiota, provides a complex picture of potential aberrations, which may result in age-associated comorbidities. Centenarians represent a unique subset of aged individuals who, while still undergoing substantial changes to both immune and microbial populations, exhibit improved longevity and quality of life while appearing to avoid the worst of inflammaging.

### 4.1 Inflammaging in centenarians

Aging does not occur equally across a population and untangling the unique attributes of successful agers has the potential to open the door to novel therapeutic strategies and interventions. Compared with seniors who exhibit a pro-inflammatory inflamming phenotype, centenarians, despite showing elevated levels of certain inflammatory parameters, also exhibit an antagonistic anti-inflammatory immune response that is associated with longevity, referred to as anti-inflammaging (Biagi et al., 2010). Consistent with this, a lower inflammation score (which considered circulating IL-6, TNF-α, and C reactive protein) (Giovannini et al., 2011) has been established as a strong predictor of all-cause mortality (Giovannini et al., 2011; Marcos-Pérez et al., 2018) and is associated with the longevity phenotype seen in centenarians (Arai et al., 2015). On the contrary, elevated levels of circulating IL-6 (Biagi et al., 2010), IL-22 (Basile et al., 2012), IL-15 (Gangemi et al., 2005), and IL-18 (Gangemi et al., 2003) have been detected in centenarians, which may contribute to improved infectious immunity and survival. Despite conflicting evidence on the IL-6 levels in centenarians, suggesting that this inflammatory marker may vary based on the given population studied, a reduction in circulating TNFα, a known risk factor for frailty (Bruunsgaard et al., 2003; Van Epps et al., 2016) relative to other seniors, is a common theme among centenarians (Arai et al., 2015; Biagi et al., 2010). Considered together, these observations suggest a balancing of pro- and anti-inflammatory immunity in centenarians, which contributes to successful aging.

The separate observation of a highly diverse microbiota in centenarian “super-agers” has yet to be mechanistically linked to these immune phenotypes but may be due to altered metabolite production. Diet and exercise, among other lifestyle factors, have a significant impact on successful aging and the composition of the microbiota of both young and elderly individuals (Claesson et al., 2012; David et al., 2014; Gopinath et al., 2018; Ramos et al., 2022; Sepp et al., 2022). However, the critical components for successful aging and the acquisition of healthy centenarian status remain elusive, as the markers of successful aging are complicated and multifactorial, with genetic, environmental, and immune factors all contributing to a state of homeostasis and improved quality of life (Motta et al., 2007). How IECs differ between centenarians and aged individuals who are younger but frailer remains understudied but may provide further clues to improved longevity.

### 5 Conclusions and Implications

The complex interplay between the microbiota, IECs, and the broader immune system during the aging process represents an area of increasingly important study given the rising age of the global population and the resultant increases in common comorbidities, including cancer, metabolic, inflammatory, and neurodegenerative conditions.

IECs occupy a unique position as an interface between the microbiota and the immune system. We suggest that accumulating dysfunction of IECs with age likely contributes to the characteristic changes in microbial ecology, potentially creating novel nutritional niches as a result of altered enterocyte absorption or secretory cell function. A thinner mucosal barrier or reduced intestinal barrier integrity facilitates enhanced translocation of whole microbes, MAMPs, or metabolites into the circulation and/or other tissues, thereby contributing to inflamming and/or immunosenescence. Thus, further studies that examine and quantify the phenotype and
function of IECs in aged populations, long-lived healthy centenarians, and those living with age-related inflammatory conditions represent critical future research. Further investigation in this field may illuminate new therapeutic strategies, such as dietary interventions or supplementation with particular microbial community members, which could be used to improve both quality and expectancy of life for the aging global population.

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LSH wrote the manuscript and made figures with support and guidance from LCO.

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CONFLICT OF INTEREST
The authors have no conflicts to declare.

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