# Dysregulation of leukocyte trafficking in ageing: Causal factors and possible corrective therapies

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## Abstract

Ageing is a universal biological phenomenon that is accompanied by the development of chronic, low-grade inflammation and remodelling of the immune system resulting in compromised immune function. In this review, we explore how the trafficking of innate and adaptive immune cells under homeostatic and inflammatory conditions is dysregulated in ageing. We particularly highlight the age-related changes in the expression of adhesion molecules and chemokine receptor/ligands, and the accumulation of senescent cells that drive modulated leukocyte trafficking. These age-related changes to leukocyte trafficking are multifactorial and specific to leukocyte subset, tissue, type of vascular bed, and inflammatory status. However, dysregulated leukocyte trafficking ultimately affects immune responses in older adults. We therefore go on to discuss approved drugs, including anti-integrins, anti-chemokines and statins, as well as novel therapeutics that may be used to target dysregulated leukocyte trafficking in ageing, improve immune responses and delay the onset of age-related diseases.

## Graphical Abstract



**Key words:** Leukocyte, trafficking, ageing, senescence, inflammageing, therapies

## 1. Introduction

 Leukocyte trafficking is essential for efficient life-long immunity. Leukocytes must be able to relocate to sites of infection or injury within tissues in order to facilitate the clearance of pathogens and damaged cells, instigate tissue repair processes and promote the resolution of inflammation to reinstate tissue homeostasis [1]. As we age, the protective function of the immune system is compromised (immunosenescence) with increased susceptibility to infections, autoimmunity and cancer, and reduced responses to vaccination [2]. This is accompanied by constitutive, chronic inflammation (inflammageing) that contributes to the development of many age-related diseases [3]. The effect of advancing age on the trafficking and recruitment of leukocytes to peripheral tissues has yet to be fully elucidated. In this review, we explore what is known of the age-related changes in adhesion molecule and chemokine receptor expression, and the relation with immunosenescence that contribute to dysregulated leukocyte trafficking in advanced age (**Figure 1**). We specifically focus on studies demonstrating changes in the trafficking of leukocytes in the context of ageing. To this end, we have not included some major studies describing the mechanisms of immune ageing or the establishment of age-related inflammatory diseases as this is beyond the scope of the review and has been reviewed elsewhere [4-6].

## 1.1 Leukocyte recruitment in acute inflammation and homeostasis

 During acute inflammation, leukocytes are trafficked from the circulation into tissue (extravasation) to clear inflammatory stimuli. Endothelial cells upregulate the expression of adhesion molecules in response to locally generated pro-inflammatory mediators, such as tumour necrosis factor-alpha (TNFα) and interferon-gamma (IFNγ) [7]. Circulating leukocytes are captured by cytokine-activated endothelium through selectin-ligand interactions, which mediate leukocyte rolling [8, 9]. Chemokines on the endothelial surface interact with G-protein-coupled receptors on leukocytes to induce integrin activation and initiate firm adhesion [9-11]. Integrins interact with adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), and junctional adhesion molecules expressed on endothelial cells to mediate the firm adhesion of leukocytes to the vasculature [1, 12]. Adhered leukocytes migrate along the endothelial monolayer to identify permissible sites that enable transendothelial migration and entry into tissue. Here, leukocytes may migrate in a random fashion (chemokinesis) in the absence of chemoattractants, or if a strong chemoattractant gradient is available, leukocytes will move in a directional manner (chemotaxis) towards the area with the highest concentration of chemoattractants [13]. In the context of inflammation, leukocytes utilise a chemokine gradient to migrate towards the source of infection/injury. The leukocyte adhesion cascade has been reviewed in depth elsewhere [1, 14, 15].

 For successful recruitment and entry into inflamed tissue, leukocytes must be able to negotiate the endothelial barrier using an arsenal of molecules, including cell adhesion molecules, chemokine receptors and lipid mediators, which differ depending on the inflammatory stimulus, leukocyte subset and vascular bed involved in the migration process. Importantly, adhesion molecules involved in leukocyte trafficking also influence leukocyte effector functions, such as the involvement of integrin signalling in T-cell activation, differentiation and proliferation [16]. Any changes in expression or functionality of these molecules will disrupt the leukocyte trafficking process and affect immune responses.

 Although heavily associated with inflammatory responses, the trafficking of leukocytes into and out of tissues is an essential part of steady state homeostasis to provide ongoing immune surveillance [15]. Homeostatic leukocyte trafficking occurs in a time-dependent manner, with peak leukocyte extravasation from blood into tissues occurring in the day for humans and in the night for mice [17, 18]. The synchronization of homeostatic leukocyte trafficking with the circadian rhythm is partly due to the oscillating expression of adhesion molecules e.g. ICAM-1 and VCAM-1 on the surface of endothelial cells and the expression of chemokine receptors e.g. CXCR4 and integrin subunits e.g. CD11a on leukocytes; with peak expression on both cell types occurring at night in mice, promoting the extravasation of leukocytes from circulation [19].

 Leukocytes are not only trafficked between the circulatory system and peripheral tissues, but also within the lymphatic network [20, 21]. Lymphatic vessels facilitate the trafficking of antigen-loaded antigen presenting cells (APC) to draining lymph nodes (dLN) in order to initiate adaptive immune responses during acute inflammation, and also the trafficking of leukocytes capable of providing immunoregulation and immune surveillance during homeostasis [20]. APC enter the lymphatic system from tissue by migrating through interstitial matrix, peri-lymphatic basement membrane and crossing the external adhesion molecule-coated surface of afferent lymphatic capillaries in a process termed intravasation [20, 22]. Once within the lymphatic network, APC traffic into dLN using the lymph circulation. Lymphocytes, on the other hand, enter dLN from high endothelial venules and eventually exit the lymphatic network through extravasation within efferent lymphatic vessels [21].

## 1.2 Trafficking of innate immune cells in ageing

 Intrinsic cellular deficiencies caused by ageing modulate the homeostatic trafficking of innate immune cells. Single-cell RNA sequencing has revealed age-related changes to murine tissue-resident leukocyte population sizes under homeostatic conditions in a tissue-specific manner [23]. There was an increased relative abundance of granulocytes and decreased abundance of monocytes in the bone marrow (BM) of aged C57BL/6 mice (>18 months) compared to younger mice (<3 months), whilst the relative abundance of macrophages in the kidney increased with age [23]. It is not clear whether these changes in leukocyte population numbers are due to age-related changes in homeostatic leukocyte trafficking, or due to additional factors that may change with age such as leukocyte retention within tissue, proliferation/survival rates, and leukocyte differentiation. More studies in this area are needed to elucidate whether differences in leukocyte numbers within tissue are due to age-related defects in leukocyte trafficking and, if so, determine the mechanisms underpinning the differential recruitment of leukocytes to tissues in homeostasis, and whether the same effects are seen in humans.

### 1.2.1 Dendritic cells

 The trafficking of innate immune cells under inflammatory conditions is also affected by advancing age [24, 25]. In a murine model of respiratory infection, young (<2 months) and aged C57BL/6 mice (22 months) were inoculated with either influenza A, a severe acute respiratory syndrome coronavirus, a respiratory syncytial virus, or a mouse hepatitis strain 1 virus [24]. The migration of respiratory dendritic cells (DC) to lung dLN 18 h post-infection was impaired in aged mice compared to younger mice, and was attributed to an age-related increase in local levels of prostaglandin D2 (PGD2). Impaired respiratory DC migration was accompanied with poor T-cell responses in infected aged mice. Interestingly, blocking PGD2 function rescued respiratory DC migration to dLN in aged animals and correlated with increased surface expression of the homing chemokine receptor 7 (CCR7) on respiratory DC in the lungs and dLN. Age-related changes to local microenvironmental factors, such as PGD2, may therefore influence leukocyte migration during inflammation through regulating the expression of chemokine receptors on leukocytes. Indeed, PGD2 signals are necessary for the transmigration of neutrophils across an endothelial monolayer *in vitro* [26].

 To assess DC migration and function in ageing, terminally mature DC-like cells were generated from the BM of young (<6 months old) and aged C57BL/6 mice (>18 months old) using granulocyte-macrophage colony-stimulating factor and interleukin 4 (IL-4) [27]. After 5 days, DC were isolated and stimulated with lipopolysaccharide (LPS) for 24 h to generate terminally mature DC. Ageing impaired the ability of terminally mature DC to migrate towards CCL21 *in vitro*, and towards popliteal dLN *in vivo*. The impaired migratory ability of aged terminally mature DC was not attributed to age-related changes to the local microenvironment, as the adoptive transfer of aged terminally mature DC into young mice did not improve DC homing to dLN. Additionally, expression of CCR7 on terminally mature DC did not differ between young and aged mice. Instead, the impaired migratory capacity of aged terminally mature DC was attributed to defective intracellular signalling pathways following CCR7 stimulation. Western blot analysis revealed lower levels of tyrosine phosphorylation of intracellular proteins in aged terminally mature DC post-stimulation with CCL21, a CCR7 ligand, compared to young terminally mature DC. However, the level of tyrosine phosphorylation was only measured on two unidentified proteins, and the differences between the relative expressions of phosphorylated tyrosine proteins in young and aged terminally mature DC did not reach statistical significance. These studies require further evaluation and validation in order to determine whether aged terminally mature DC do indeed exhibit dysfunctional intracellular signalling in response to chemoattractant stimulation.

 In humans, similar findings regarding the age-associated impairment of DC migration were observed under inflammatory conditions, albeit in *ex vivo* studies. LPS-stimulated monocyte-derived DC (MDDC) isolated from older adults (>65 years old) exhibited impaired migration towardsCCL19 *in vitro* compared to young MDDC (<35 years old) [28]. Again, this was not due to differential expression of surface CCR7. Instead, the reduced chemotactic responses of aged MDDC was attributed to defective phosphoinositide 3-kinase (PI3K)-AKT signalling, a signalling pathway involved in regulating cell migration, as aged MDDC displayed defective phosphorylation of AKT and increased expression of a PI3K negative regulator compared to young MDDC. This was demonstrated through treating young MDDC with a specific PI3K inhibitor, which impaired their ability to migrate towards CCL19 *in vitro.* However, the effect of treating aged MDDC with a PI3K inhibitor was not explored in this study. As research in this area is currently limited, it is unclear to what extent the PI3K-AKT pathway plays in the age-related impairment of MDDC chemotactic responses.

### 1.2.2 Monocytes

The ageing process also modulates the trafficking of monocytes in humans. Intradermal injection of harmless substances such as air or saline resulted in the recruitment of CCR2+ monocytes to the skin in older adults (>65 years old), but not younger adults (<40 years old) (study not yet peer-reviewed, published in BioRXiv preprint bioarchive) [29]. Inappropriate monocyte recruitment was thought to be a consequence of CCL2 secretion by senescent fibroblasts in the skin. Recruited monocytes inhibited resident memory T-cell proliferation through secretion of PGE2, which impaired T-cell responses against recall antigens such as those derived from the varicella zoster virus (VZV). Importantly, treatment with a p38-MAPK inhibitor, Losmapimod, reduced CCL2 levels, monocyte recruitment to the skin of older adults, and boosted immunity against VZV. However, Losmapimod does not specifically target CCL2 production, but has broad anti-inflammatory effects including reducing the production of TNFα, IL-6 and IL-8 by LPS-stimulated PBMC *ex vivo* [30]. Elucidating the mechanisms driving inappropriate monocyte recruitment to the skin of older adults in response harmless substances, and whether this does specifically rely on CCL2 production, therefore requires further work.

### 1.2.3 Neutrophils

Neutrophils are also affected by the ageing process as their chemotaxis (directional migratory speed), but not chemokinesis (overall migratory speed), is impaired in humans [31-33]. Neutrophils isolated from healthy older adults (>65 years old) displayed reduced chemotaxis towards several chemoattractants, including CXCL8, N-formylmethionyl-leucyl-phenylalanine (fMLP) and CXCL1, *in vitro* compared to neutrophils isolated from younger individuals (<35 years old) [33]. Importantly, the age-related impairment of neutrophil chemotaxis appeared independent of age-related changes to the microenvironment, as the pre-treatment of neutrophils derived from young donors with serum derived from older donors did not modulate neutrophil chemotaxis. The age-related modulation of neutrophil migration was instead attributed to defective intracellular signalling, as neutrophils derived from older individuals exhibited constitutive PI3K signalling before and after stimulation with chemoattractants. Importantly, inhibition of PI3K signalling improved the accuracy of neutrophil migration towards chemoattractants [33].

In mice, both the chemokinesis and chemotaxis of neutrophils is modulated with age. Neutrophils isolated from aged BALB/c mice (>18 months) exhibited increased chemokinetic responses in the absence of chemoattractants, but impaired chemotactic responses in the presence of CXCL1 *ex vivo* compared to neutrophils isolated from younger mice [34]. In a burn injury model, neutrophilia occurred in the lungs of aged mice compared to younger mice (<6 months) 24 h after injury [34]. Surprisingly, neutrophils isolated from aged, burn-injured mice exhibited reduced expression of CXCR2, despite previous reports stating that CXCR2-CXCL1 directed chemotactic responses are necessary for neutrophil recruitment to the lung during burn-injury [35]. Instead, the age-related neutrophilia in the lung following burn injury was attributed to increased ICAM-1 expression on aged lung vasculature and the hyperchemokinesis of aged neutrophils, facilitating neutrophil retention in the lung [34]. Furthermore, a murine-model of peritoneal *Candida albicans* infection resulted in significantly more neutrophils and macrophages trafficking into the peritoneum of aged C57BL/6 mice (>18 months) compared to younger mice (<3 months) [36]. Although the reason for differential recruitment of neutrophils and macrophages to the peritoneum of young and aged mice was not clear, a significant population of peritoneal macrophages displayed impaired fungicidal activity in aged animals, diminishing the capacity of aged mice to clear the infection.

Dysregulated neutrophil recruitment in ageing also appears to be tissue-specific. Indeed, neutrophil infiltration into cutaneous wounds infected with *Staphylococcus aureus* was lower in aged BALB/c mice (>18 months) compared to younger mice (<4 months), despite similar levels of local CXCL1 and CXCL2 [37]. Impaired neutrophil migration was attributed to reduced ICAM-1 expression in the wounds of aged mice. Finally, aged mice (>22 months) infected with *S. Typhimurium* exhibited reduced neutrophil trafficking to secondary lymphoid tissues such as the spleen and mesenteric LN compared to young mice (<6 months) [38]. This lack of neutrophil recruitment resulted in increased levels of bacterial colonisation of multiple organs in aged mice, including the spleen, ileum, colon, Peyer’s patches and liver [38].

Together, these studies suggest that age-related changes in neutrophil, monocyte, macrophage and DC chemotactic responses are therefore dependent upon tissue type as well as the nature of the inflammatory signals. Ultimately, these studies emphasize age-related changes in innate cell migratory capacity, which affects development of appropriate immune responses (**Table 1**). However, only a handful of studies have investigated the effect of ageing on homeostatic leukocyte trafficking to identify pathways intrinsically affected by the ageing process, and so more studies in this area are required.

## 1.3 Trafficking of adaptive immune cells in ageing

The ageing process also affects the trafficking of adaptive immune cells in both humans and mice (**Table 1**). The number of T-cells residing in the brains of unchallenged aged mice (>18 months) was 3-fold higher than in younger mice (<3 months), and correlated with increased levels of CCL5, CCL11, CXCL9, and CXCL10 in aged brains which may have facilitated increased T-cell recruitment [39]. Single-cell RNA sequencing has revealed age-related changes in the abundance of B- and T-cells in various murine tissues under homeostatic conditions, albeit in a tissue-specific manner [23, 40]. The proportion of B-cells in the spleen and anterior tibialis muscles of aged C57BL/6 mice (>18 months) is reduced compared to younger mice (<3 months), whilst the proportion of T-cells in the thymus, spleen and mammary glands are also decreased [23]. In another study, single-cell RNA sequencing revealed increased B- and T-cell infiltration of the gonadal adipose tissue in aged mice (24 months) compared to young mice (3 months), along with increased levels of VCAM-1 in the serum, kidney and heart of aged animals [40].

### 1.3.1 T-cells: mouse studies

In mice, induction of subcutaneous West Nile virus (WNV) infection led to reduced trafficking of T-cells, natural killer cells (NK), macrophages and DC to the popliteal dLN of aged mice (>18 months) compared to younger mice (<4 months) [41]. Aged mice also exhibited poor anti-viral immunity, as aged animals presented with an increased viral burden in the blood, spleen, and brain. Impaired naïve CD4+ T-cell trafficking into the spleen and dLN of WNV-infected aged mice was partly attributed to intrinsic cellular defects, as the adoptive transfer of naïve CD4+ T-cells derived from aged mice into a young recipient experiencing WNV infection did not improve T-cell trafficking to youthful levels. However, defective naïve CD4+ T-cell trafficking in WNV-infected aged mice was also partly attributed to age-related changes in the microenvironment, as both young and aged naïve CD4+ T-cells displayed lower levels of migration into spleen and dLN when adoptively transferred into infected, aged recipients. Indeed, aged mice had significantly lower levels of CCL21, a chemoattractant for naïve T-cells, in dLN after 2 days of infection. Intravital two-photon microscopy revealed that leukocyte capture and rolling along HEV is unaffected by age, however, aged naïve CD4+ T-cells extravasated less efficiently into dLN [41]. Importantly, defective naïve CD4+ T-cell trafficking had profound effects on the development of anti-viral humoral responses, including formation of germinal centres, in aged mice leading to uncontrolled viral burdens and increased mortality rates.

### 1.3.2 T-cells: human studies

In a human model of delayed-type hypersensitivity, bacterial (tuberculosis), fungal (*C. albicans*) and viral (VZV) recall antigens were administered into the skin of younger adults (<40 years old) and older adults (>70 years old) to assess T-cell recruitment [42]. Older adults exhibited impaired cutaneous immune responses to recall antigens, which was attributed to reduced T-cell infiltration into the skin post-antigen administration. Importantly, this modulated T-cell trafficking in older adults was not due to reduced surface expression of chemokine receptors, CXCR4, or ICAM-1-binding integrins, or cutaneous lymphocyte associated antigen and integrin subunit CD11a. However, T-cells isolated from the blood of older individuals (>65 years old) are reported to express higher levels of CD11a mRNA compared to T-cells isolated from the cord blood of newborns, due to age-related changes in DNA methylation patterns [43]. Reduced T-cell trafficking into the skin of older adults was attributed to reduced expression of E-selectin, VCAM-1 and ICAM-1 on skin endothelial cells in response to recall antigen administration [44].

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| --- | --- | --- |
| **Innate immune cells** |  |  |
|  | Effect of ageing on cell recruitment and migration | Potential mechanisms | Ref. |
| DC | DC recruitment to lung-dLN post-burn injury in miceDelayed DC recruitment to the lungs of influenza A-infected miceCCL21-directed chemotaxis *in vitro*, popliteal dLN-homing *in vivo*CCL19-directed chemotaxis *in vitro*\* | PGD2 levels leading to CCR7-expression on DCDelayed local IL-8 productionDefective signal transduction pathwaysDefective PI3K-AKT signalling | 24252728 |
| Neutrophils | fMLP-directed chemotaxis *in vitro*\*fMLP- and PAF-directed chemotaxis *in vitro*\*fMLP-, CXCL8-, and CXCL1-directed chemotaxis *in vitro*\*Chemokinesis and CXCL1-directed chemotaxis *in vitro*, neutrophil recruitment to the lung post-burn injury in miceNeutrophil recruitment to peritoneum during *C. albicans* infectionNeutrophil infiltration into wounds infected with *S. aureus*Neutrophil trafficking to spleen and mesenteric LN during *S. Typhimurium* infection | Defective intracellular calcium signallingNo mechanisms described Defective PI3K-signallingICAM-1 expression in lung and neutrophil chemokinesisNo mechanisms described ICAM-1 expression in woundsNo mechanisms described  | 31323334363738 |
| Monocytes | Inappropriate recruitment to the skin in response to harmless substances\* | CCL2 secretion by senescent fibroblasts in skin | 29 |
| **Adaptive immune cells** |
| T-cells | Delayed recruitment to the lungs of influenza A-infected miceT-cell recruitment to popliteal LN during West Nile virus infection in miceT-cell recruitment to the skin in response to recall antigens\* | Delayed local IL-8 and MIP-1β productionCCL2 production, ability of old T-cells to extravasate E-selectin, ICAM-1 and VCAM-1 expression on endothelial cells in skin | 254142 |
| B-cells | Retention within marginal zones of spleens | CXCR5 expression on B-cells | 160 |

**Table 1**: A summary of human and mouse studies discussed in this review assessing age-related changes to the trafficking of innate and adaptive immune cells. \*Human studies.

## 1.4 Expression of adhesion molecules in ageing

Several studies have investigated the effect of ageing on endothelial expression of adhesion molecules and found their expression to be increased on the aged vasculature under homeostatic conditions [44, 45-49]. In rats, ageing is associated with enhanced leukocyte rolling, adhesion and transmigration across the mesenteric microcirculation, as well as increased expression of endothelial ICAM-1, P-selectin and VCAM-1 [44, 45]. Ageing is also associated with increased expression of ICAM-1 and VCAM-1 in the brains of humans and mice, respectively, and may contribute to the development of neuroinflammation with age [46, 47]. Importantly, the age-related increase of VCAM-1 on brain endothelial cells in aged mice (>18 months) was due to age-related soluble factors, as aged blood delivered to younger mice (<12 months) through heterochronic paraboisis resulted in increased levels of VCAM-1 expression in young brains [47].

### 1.4.1 Junctional adhesion molecules

Vascular endothelial (VE)-cadherin is a classical cadherin expressed on endothelial cells and is involved in regulating vascular permeability [50]. Ageing is associated with increased internalisation and degradation of arterial VE-cadherin in aged F344 rats (>24 months) compared to younger rats (<4 months) [51]. Increased arterial VE-cadherin degradation disrupts endothelial barrier integrity and contributes to the observed age-associated increase in vascular permeability in aged rats [52, 53]. The enhanced expression of adhesion molecules and reduction in junctional protein such as VE-cadherin in aged tissue under homeostatic conditions may be due to age-related changes of the inflammatory status of the tissue, therefore modulating homeostatic leukocyte trafficking and vascular permeability, which promotes leukocyte recruitment to and retention within tissue.

### 1.4.2 Microenvironmental factors

Age-related changes in the local inflammatory environment, including pro-inflammatory cytokine generation, nitric oxide (NO) availability, and increased oxidative stress, also modify leukocyte trafficking. In a murine model of endotoxic stress, enhanced ICAM-1 gene induction was observed in the hearts aged mice (24 months) compared to younger mice (4 months) following intraperitoneal LPS-administration [54]. Increased ICAM-1 mRNA expression in the aged heart was partly due to the age-related exacerbation of endotoxin-induced pro-inflammatory cytokines in plasma, such as TNFα and IFNγ [55]. In a study focusing on the effect of ageing on the development of atherosclerosis, increased VCAM-1 expression was observed in the aortic arch of aged LDLR-/- C57BL/6 mice (>20 months) compared to younger LDLR-/- mice (<4 months) [56]. Increased cardiac VCAM-1 expression was thought to be a consequence of either age-related endothelial cell dysfunction, driven by reduced NO availability, or due to increased oxidative stress with age. Interestingly, antioxidants are able to inhibit VCAM-1, but not ICAM-1, expression on TNFα-stimulated human umbilical vein endothelial cells (HUVEC) through inactivating NF-κB signalling and scavenging radicals involved in promoting VCAM-1 expression [57]. Although the expression of adhesion molecules is generally increased with ageing, this highly depends on the tissue-type and the nature of the inflammatory stimulus. For instance, the expression of ICAM-1 is decreased in the wounds of aged mice experiencing *Staphylococcus aureus* infection compared to younger mice, however, it is increased in the lungs of aged mice post-burn injury [34, 37].

### 1.4.3 Soluble adhesion molecule expression

Soluble adhesion molecules (sAM) in serum and plasma are suggested to be the result of endothelium shedding or endothelial damage. Plasma levels of soluble ICAM-1 and VCAM-1, but not E-selectin, were significantly higher in older Caucasian individuals [58]. Conversely, age is positively correlated with soluble VCAM-1 expression, but not soluble ICAM-1 or E-selectin, in healthy older adults [47, 59-61]. In contrast, Nash *et al.* reported a significant decrease in soluble E-selectin, ICAM-1 and VCAM-1 with age through comparing juvenile (<16 years old) and adult (21-47 years old) serum [62, 63]. However, an older study did not find a difference in serum levels of VCAM-1 of 155 healthy adults aged between 20 and 65 years old [64]. Whether advancing age has a direct impact on circulating sAM levels, and whether this affects leukocyte trafficking, therefore remains unclear and may depend on the heterogeneity of the population considered.

### 1.4.4 Endothelial-activating cytokines in age-related diseases

The circulating levels of TNFα and IL-6 increase with age, and their biological functions have been implicated in the pathogenesis of many inflammatory diseases such as rheumatoid arthritis (RA) and Crohn’s disease (CD) [65-68]. TNFα is a potent activator of endothelial cells by inducing the expression of ICAM-1, VCAM-1, E- and P-selectin on endothelial cells *in vitro* and *in vivo*, and promotes the recruitment and migration of neutrophils, monocytes and lymphocytes [69-74]. IL-6, a pleiotropic cytokine, can also induce the upregulation of ICAM-1, VCAM-1, and E-selectin on endothelial cells *in vitro*, and promotes the adhesion of lymphocytes, but not polymorphonuclear cells, to the endothelium *in vitro* [75, 76]. Additionally, IL-6 deficient mice exhibit defective leukocyte recruitment to air pouches in response to various stimuli, including IL-1β and carrageenan, compared to wild type mice [77]. IL-1 and IL-17 have been linked to the pathology of several autoimmune diseases, which are increasingly prevalent amongst older adults [78-82]. IL-1 is one of the key drivers of IL-17−producing Th17 cell differentiation, a T-cell subset involved in the pathogenesis of RA, systemic lupus and psoriasis [79, 83, 84]. Importantly, IL-17 is able to directly modify surface expression of VCAM-1, as well as transcript levels of ICAM-1 and platelet and endothelial cell adhesion molecule 1, on endothelial cells *in vitro* [85, 86]. The interplay between pro-inflammatory cytokines, such as TNFα, IL-1, IL-6 and IL-17, contribute to the chronic inflammation that underlies several age-related diseases partly through their endothelial activating properties and subsequent impact on leukocyte trafficking. Importantly, blocking the functions of pro-inflammatory cytokines through the use of biologics (e.g. anti-TNF and anti-IL-17, IL-1 and IL-6 receptor antagonists) are major tools in the treatment of many inflammatory diseases [87-90].

### 1.4.5 Adhesion molecule expression on leukocytes

Ageing is also associated with modified adhesion molecule expression on leukocytes. In mice, the expression of the integrins lymphocyte function-associated antigen 1 (LFA-1) and very late antigen 4 (VLA-4) is increased on circulating CD8+ T-cells derived from aged mice (>18 months) compared to younger mice (<3 months) [39]. This increase in integrin expression permitted higher incidence of CD8+ T-cell recruitment to peripheral tissues such as the brain [39]. In a murine model of mousepox, reduced migration of aged NK-cells to dLN occurred, therefore hindering the control of viral spread in aged animals [91]. Reduced migration of aged NK-cell to dLN was attributed to reduced surface expression of L-selectin, which facilitates lymphocyte homing to secondary lymphoid tissue. Ageing therefore profoundly affects the expression of integrins and selectins on lymphocytes, modulating their trafficking under inflammatory and homeostatic conditions. However, there is a clear lack of understanding on whether ageing is able to influence the capacity of integrins to change their affinity in response to activating chemokine receptor signalling.

## 1.5 Expression of chemokine receptors in ageing

Many studies have shown that advancing age affects the surface expression of chemokine receptors on T-cells. However, it is important to note that the pattern of chemokine receptors expressed on a given T-cell is unique to a particular T-cell subset, and so any age-related changes observed in overall chemokine receptor expression within pools of T-cells may just reflect age-related changes in the proportion of T-cell subsets. CD4+ T-cells from aged mice (>20 months) exhibit higher levels of gene and protein expression of CCR1, 2, 4, 5, 6, 8 and CXCR2-5, and lower levels of CCR7 and 9 compared to their younger counterparts (<4 months), as determined by Western blot analysis [92]. However, it is not clear whether these differences arise from age-related changes in the number of CD4+ T-cells expressing a particular chemokine receptor, or whether age affects chemokine receptor expression on a cell by cell basis in similarly sized populations of CD4+ T-cells. Importantly, differential chemokine receptor expression is functionally relevant, as CD4+ T-cells isolated from aged mice demonstrated increased chemotactic responses to CXCL12 and CCL3 *in vitro* compared to those isolated from younger mice [92]. In humans, circulating CD4+ T-cells isolated from older donors (>65 years old) exhibited enhanced chemotactic responses to CXCL12 compared to T-cells derived from younger donors (<30 years old), facilitated by increased surface expression of CXCR4 [93, 94]. Increased CXCR4 expression was attributed to differential ubiquitination patterns, and thus reduced degradation of the chemokine receptor in aged CD4+ T-cells.

Changes in the expression of chemokine receptors on both innate and adaptive immune cells have been reported with ageing [24, 27, 28, 34]. However, whether age-related changes to chemokine receptor expression on specific leukocyte subsets is context-dependent is unclear, as the expression of CCR7 on DC has been reported to decrease with age in mice infected with respiratory viruses [24], but is reportedly unchanged in older mice under homeostatic conditions [27]. Despite many insights showing the functional relevance of age-related changes in surface chemokine receptor expression on leukocyte migration, additional research is required to establish the molecular events that contribute to the age-related modulation of surface receptors and how this affects leukocyte migration under homeostatic and inflammatory conditions *in vivo*.



**Figure 1: Age-related changes modulating leukocyte trafficking.** The trafficking of leukocytes, such as monocytes, neutrophils and lymphocytes, into and out of tissues is modulated with ageing under homeostatic and inflammatory conditions. Direct consequences of ageing, depicted by bold black arrows (🡹/🡻), on leukocyte trafficking include: changes to the expression of adhesion molecules on the endothelium, changes to the expression of adhesion molecules and chemokine receptors on circulating leukocytes, reduced expression of junctional molecules between endothelial cells, and increased production of lipid mediators and chemokines within tissue. Together, these changes facilitate and drive leukocyte trafficking from the circulation into peripheral tissues. The indirect consequences of ageing which influence leukocyte trafficking are mediated through an accumulation of senescent cells within tissue and their downstream effects are depicted by bold blue arrows (🡹/🡻). The age-related dysregulation of leukocyte trafficking is therefore multifactorial and a direct, as well as indirect, consequence of ageing.

## 1.6 Immunosenescence, inflammageing and leukocyte trafficking

Cellular senescence is one of the major hallmarks of the ageing process [5]. Senescent cells are quiescent but metabolically highly active, secreting an influential mix of pro-inflammatory cytokines, matrix metallopeptidases and growth factors termed the senescence associated secretory phenotype (SASP), which contributes to the development of inflammageing [5, 95, 96]. TNFα and IL-6, two of the most extensively studied cytokines released as part of the SASP, are, as previously mentioned, increased in the serum of older adults and are able to modulate the expression of adhesion molecules on endothelial cells [65, 66, 69-71, 75]. Secretion of TNFα by senescent cells can induce senescence in neighbouring cells, therefore propagating a positive feedback loop of cellular senescence induction [97]. SASP-derived cytokines, such as TNFα and IL-6, therefore modulate leukocyte trafficking by increasing expression of adhesion molecules on endothelial cells and induce senescence in bystander cells (**Figure 2**). Importantly, those cytokines are able to act locally as well as systemically [98].

### 1.6.1 Chemokines

Chemokines are also part of the SASP, attracting leukocytes to peripheral tissues [5]. Senescent human fibroblasts secrete high levels of CCL5 and CXCL12, which promote the recruitment of both innate and adaptive leukocytes, to facilitate the removal of senescent cells [99-102]. In human primary biliary cirrhosis (PBC), infiltration of CCR2- and CX3CR1-positive mononuclear cells into the bile duct, which drives PBC pathology, was linked to the production of CCL2 and CX3CL1 by senescent biliary epithelial cells *in vivo* [103]. However, this study utilised immunohistochemistry techniques to investigate the presence of CCR2- and CX3CR1-positive cells in PBC liver sections, without determining the presence of senescent biliary epithelial cells, or confirming whether they were indeed the source of CCL2 and CX3CL1 production *in vivo*. Instead, the authors extrapolated back to a previous study, where they observed CCL2 and CX3CL1 production by senescent biliary epithelial cells *in vitro* [104]. Whether the generation of SASP-derived chemokines play a role in PBC requires robust investigation. In a murine model of liver carcinoma, senescent tumour cells secreted high levels of macrophage (colony-stimulating factor 1, CCL2), neutrophil (CXCL1) and NK-cell (IL-15) chemoattractants, which promoted their recruitment and subsequent antitumour immunity [105]. Importantly, autocrine or paracrine stimulation of CXCR2 by chemokines such as CXCL8 and CXCL1 that are secreted as part of the SASP reinforces replicative and oncogene-induced senescence in senescent primary human fibroblasts [106]. Chemoattractant secretion by senescent cells under homeostatic and inflammatory conditions therefore influences leukocyte trafficking, although whether this is beneficial or detrimental appears to be context-dependent.

### 1.6.2 Senescent T- and B-cells

Lymphocytes also undergo cellular senescence and the number of senescent T- and B-cells increases with age [96, 107]. In humans, an accumulation of pro-inflammatory replicatively-senescent IgD-CD27- B-cells is associated with ageing [107]. Senescent B-cells derived from older individuals express modulated levels of chemokine receptors, such as increased CCR7 and CCR6, decreased CXCR3, and more adhesion molecules, such as L-selectin, compared to younger individuals, modifying their migratory behaviour [108]. Senescent CD28-CD8+ T-cells exhibit modified gene expression of chemokines and their receptors compared to non-senescent T-cells, including increased transcription of CCL4 and CX3CR1 and reduced transcription of CCR6 and CCR7 [109]. Indeed, CD27-CD8+ effector memory CD45RA re-expressing (EMRA) T-cells, which exhibit traits of senescence such as defective proliferation and loss of CD27 expression, displayimpaired chemotaxis towards autologous serum *in vitro* compared to CD27-CD4+ EMRA T-cells [110]. This impaired migratory behaviour was attributed to mitochondrial dysfunction, which hinders the ability of CD8+CD27- EMRA T-cells to generate ATP and meet the energy requirements necessary for migration. Older adults (>55 years old) with type 2 diabetes mellitus (T2DM) had increased numbers of circulating CD4+ and CD8+ EMRA T-cells compared to healthy older adults, along with increased surface expression of CXCR2 and CX3CR1 [111]. However, both CD4+ and CD8+ EMRA T-cells derived from older adults with T2DM exhibited impaired chemotactic responses to autologous sera *in vitro* compared to healthy older adults. This is surprising, as CD4+ and CD8+ EMRA T-cells from individuals with T2DM had increased surface expression of chemokine receptors, and serum from older adults with T2DM had a higher concentration of chemokines than serum from healthy individuals [111]. ImpairedCD4+ and CD8+ EMRA T-cell migration was instead attributed to impaired glucose uptake, preventing these cells from meeting the energy requirements necessary for transendothelial migration [111]. Although senescent leukocytes accumulate with age, only a handful of studies have investigated their migratory capabilities. It is clear that increased chemokine receptor expression within senescent leukocyte subsets may not equate to increased chemotactic responses, as metabolic dysfunction plays a vital role in their migratory capabilities.

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**Figure 2: Cellular senescence drives modulated leukocyte trafficking in ageing.** Senescent cells accumulate within tissues in ageing, where they release pro-inflammatory mediators (senescence-associated secretory phenotype; SASP), such as TNFα, IL-6 and chemokines. SASP mediators TNFα and IL-6 can activate endothelial cells, upregulating endothelial expression of ICAM-1, VCAM-1, P- and E-selectins. Together, endothelial activation and chemokine production promote the recruitment of leukocytes, such as lymphocytes, neutrophils and macrophages to tissue. Importantly, TNFα can induce senescence in neighboring cells, therefore propagating a positive feedback look of cellular senescence.

## 1.7 Therapeutic targeting of leukocyte trafficking in ageing

Inflammation-driven diseases such as Alzheimer’s disease, T2DM and atherosclerosis are increasingly prevalent amongst older adults [112]. These chronic inflammatory diseases are primarily driven by age-related changes to the immune system. These changes range from increased production of pro-inflammatory cytokines, to changes in immune cell function, to the accumulation of senescent cells in tissues [113]. These age-related changes do not behave independently, but comprise intertwined mechanisms that ultimately drive the progression of both immunesenescence and inflammageing. It is therefore feasible that dysregulated leukocyte trafficking, as a consequence of immune ageing, could serve as a potential therapeutic target to attenuate the establishment of age-associated inflammatory disease in older adults. Here we review approved and novel therapeutics that target leukocyte trafficking processes [114-116].

### 1.7.1 Anti-integrin therapies

 Anti-integrin therapies target interactions between leukocytes and adhesion molecules, ultimately modulating leukocyte trafficking. Natalizumab, a humanised monoclonal antibody that inhibits VLA-4−VCAM-1 and LPAM-1−MadCAM-1 interactions, is an approved treatment for CD [117]. After 2 weeks of treatment, Natalizumab disrupted the extravasation of B-cells and T-cells from the circulation, and reduced CD activity [118]. However, treatment with Natalizumab had profound side effects on T-cells in the cerebrospinal fluid of young patients with multiple sclerosis, including restriction in the TCR repertoire and delaying the expansion of antigen-specific T-cells [119]. Importantly, long-term treatment of Natalizumab is associated with an increased risk of developing natalizumab-related progressive multifocal leukoencephalopathy (nrPML), a demyelinating disease of the central nervous system caused by the John Cunningham virus (JCV), particularly in older adults [120]. Natalizumab treatment is believed to increase the risk of nrPML through preventing JCV-specific T-cells trafficking into the brain, preventing lymphocyte retention in the BM (site of JCV latency) and by inducing expression of the Spi-B, the transcription factor that increases JCV transcription, in B-cells [121].

 Vedolizumab is a humanized monoclonal antibody directed against LPAM-1, blocking its interaction with MadCAM-1 on activated endothelial cells, and is an approved therapeutic for the treatment of inflammatory bowel diseases such as CD and ulcerative colitis [122]. In cotton-top tamarins with chronic colitis, Vedolizumab treatment disrupted the trafficking of T-cells, neutrophils and macrophages to mucosal sites and reduced the colonic inflammatory activity score [123]. Importantly, Vedolizumab treatment increased the rate of mucosal healing in older patients with CD and ulcerative colitis, with only a low incidence of mild side effects such as dyspnea, rashes and arthralgia [124]. Long-term treatment of older adults with Vedolizumab therefore appears to be effective and safe.

 Integrins have also been explored as therapeutic targets of dermatological inflammation, such as psoriasis, albeit not to the same extent as inflammatory bowel diseases [125, 126]. In a murine model of dinitrofluorobenzene (DNFB)-induced contact hypersensitivity, β7-/- mice exhibited blunted contact hypersensitivity responses and reduced cutaneous inflammation compared to wild type C57BL/6 mice, attributed to the impaired trafficking of sensitised β7-/- T-cells into the skin [126]. Importantly, the effects of β7 depletion on cutaneous inflammation during contact hypersensitivity were mimicked by the intraperitoneal administration of anti-LPAM into DNFB-sensitised C57BL/6 mice. There is obvious interest in the use of anti-integrin therapies in various inflammation-driven diseases, including inflammatory bowel diseases and psoriasis, however, whether anti-integrin therapies will play a role in regulating leukocyte trafficking in older adults and reduce the incidence of age-associated inflammatory diseases is currently unknown.

### 1.7.2 Anti-chemokine therapies

Anti-chemokine therapies target chemokine-chemokine receptor interactions to disrupt the trafficking of leukocytes in the context of inflammatory diseases [127, 128]. Such therapies include neutralizing antibodies and small molecule inhibitors, which target chemokine receptors. CCX282-B, a small molecule inhibitor of CCR9, has shown great promise in the context of CD treatment. In a preclinical study, CCX282-B was shown to prevent the development of spontaneous ileitis in TNFΔARE mice, and inhibit the CCR9-directed chemotaxis of human T-cells *in vitro* [129]. CCX282-B appeared effective at treating CD in a phase II clinical trial, as CD activity index was severely reduced in patients who received 500mg CCX282-B once daily for 12-weeks compared to the placebo group [130]. However, CCX282-B failed to show any therapeutic benefit in the context of CD in a phase III trial, although the reasons remain unclear [130]. The development of anti-chemokine therapies remains an attractive strategy to treat inflammatory diseases through disrupting leukocyte trafficking. However, the field has had very little success in this area, potentially due to the redundancy in the chemokine system.

### 1.7.3 Statins

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are used to treat a range of cardiovascular diseases through lowering circulating cholesterol levels and preventing atheroma [131]. However, statins also modulate the migration of leukocytes [132, 133]. Statins inhibited the secretion of CCL2 and CXCL8 and modulated the expression of ICAM-1, VCAM-1 and E-selectin on HUVEC *in vitro*. However, whether statins increase or decrease the expression of adhesion molecules on activated endothelial cells is dependent on the type of statin and inflammatory stimulus [132, 134-136]. Simvastatin treatment improved the chemotactic responses of neutrophils, isolated from healthy older adults (>60 years old) and older patients with mild-to-moderate community-acquired pneumonia, towards CXCL8 *in vitro*, by reducing the surface expression of LFA-1 [137]. With statins being more commonly prescribed to older adults for the prevention of cardiovascular disease in recent years [138], the impact of statins on inflammageing and the homeostatic trafficking of leukocytes requires further investigation.

### 1.7.4 Senolytics/Senostatics

Although therapeutics have not been developed to specifically target age-related changes to leukocyte trafficking in health and disease, novel therapeutics are currently being developed to target sources of inflammageing [139, 140]. Senolytics and senostatics are a novel line of therapeutics, which eliminate or suppress the SASP of senescent cells, respectively. Here, we focus on the use of senolytics/senostatics to limit age-associated changes to leukocyte migration as their role in treating age-associated diseases has been reviewed elsewhere [116]. Mammalian target of rapamycin (mTOR) is a key regulator of intracellular growth and nutrient-sensing pathways [141]. mTOR inhibitors such as rapamycin have long been associated with promoting longevity, and so interest in developing these inhibitors as anti-ageing drugs has grown [142-144]. Rapamycin is a macrolide that targets the mTOR complex, and is an approved immunosuppressant used to treat malignancy, transplant rejection and autoimmune diseases [145]. As SASP induction is partially regulated by mTOR signalling in humans, rapamycin can alleviate aspects of inflammageing through suppressing the secretion of pro-inflammatory mediators released as part of the SASP [146, 147]. Inhibiting the pro-inflammatory actions mediated by senescent cells could result in reduced leukocyte migration. In a murine model of experimental cerebral malaria, rapamycin treatment inhibited the trafficking of CD4+ and CD8+ T-cells into the brain, reduced brain haemorrhaging and enhanced survival rates of mice [148]. Reduced T-cell trafficking was a result of transcriptional changes in brain tissue, including repressed transcription of genes involved in leukocyte recruitment such as CCL7. Rapamycin treatment of BALB/c mice with dextran sodium sulfate-induced chronic colitis led to decreased trafficking of leukocytes into submucosal postcapillary venules, and reduced the histological inflammation score of the colon [149]. Furthermore, rapamycin inhibits the PI3K−mTOR-mediated upregulation of L-selectin and CCR7 expression on activated T-cells in C57BL/6 mice, redirecting T-cells from the circulation to secondary lymphoid organs such as LN and the spleen [150]. However, rapamycin treatment is associated with toxic side effects such as hyperglycaemia and immunosuppression in humans [151], and most who endeavour in this are focussed on novel rapamycin analogs/rapalogs.

Dasatinib and quercetin are novel senolytic agents that target senescent adipose cells and endothelial cells, respectively, through disrupting anti-apoptotic pathways [152]. In a phase 1 pilot study, co-administration of these senolytics promoted clearance of senescent cells in adipose tissue, and inhibited macrophage trafficking to adipose tissue in older adults with diabetic kidney disease [153]. Importantly, short-term intermittent treatment was sufficient to reduce adipose tissue inflammation, therefore limiting side effects. Infrequent treatment with senolytics may therefore offer a more plausible, yet effective, avenue to treat symptoms of inflammageing, including modified leukocyte trafficking, but also to suppress the establishment of age-associated disease.

### 1.7.5 Peptide inhibitor of transendothelial migration (PEPITEM)

PEPITEM is a small peptide secreted by B-cells, which imposes a tonic brake on T-cell trafficking across vascular endothelium during inflammation [154]. The pathway involves circulating adiponectin binding adiponectin receptors (AdipoRs) on peripheral blood B-cells, stimulating the secretion of PEPITEM. PEPITEM induces the release of sphingosine-1-phosphate (S1P) from vascular endothelia, which interacts with S1P receptors (S1PR) on recruited T-cells. S1P-S1PR interactions inhibit the activation of LFA-1, which results in the inhibition of T-cell transendothelial migration. The PEPITEM pathway is impaired in age-associated diseases such as RA, as the expression of AdipoR on circulating B-cells derived from RA patients is reduced in comparison to B-cells derived from healthy individuals [154]. Consequently, the ability of adiponectin to inhibit the transmigration of peripheral blood lymphocytes across TNFα/IFN-γ activated human dermal blood endothelial cells *in vitro* is lost in RA patients. Importantly, the expression of AdipoRs on peripheral blood B-cells is reduced in healthy older adults, which may contribute to dysregulated T-cell trafficking in ageing [154]. Restoration of the PEPITEM pathway in older adults through administration of PEPITEM may therefore offer a potential avenue to re-establish regulated T-cell trafficking in ageing.

Targeting the regulation of leukocyte trafficking rather than aspects of inflammageing in older adults is an appealing therapeutic strategy in the prevention of age-related inflammatory disease progression for two major reasons. Firstly, leukocyte trafficking-modifying treatments such as statins are already widely prescribed amongst older adults to prevent the incidence of cardiovascular disease without adverse reactions or long-term repercussions [138, 155]. On the other hand, treatments specifically aimed at alleviating aspects of inflammageing, such as senolytics, are only in their early developmental stages [156]. Secondly, the factors that drive inflammageing are broad and multi-factorial [139], and so targeting the trafficking of leukocytes offers a more specific therapeutic target. However, the use of approved drugs and novel therapeutics to modulate leukocyte trafficking in older adults is accompanied by ethical concerns. The question must be raised: is it ethical to medicate otherwise-healthy older adults in an attempt to prevent the development of age-related diseases, considering not all older adults go on to develop said diseases? Some individuals termed “centenarians” and “supercentenarians” experience “successful” ageing, a term that relates to the healthspan and lifespan of an organism, as they go on to live long lives with a low incidence of age-related disease [157]. To that end, should the preventative leukocyte trafficking-modifying treatments only be administered to older adults experiencing “unsuccessful” ageing? If so, how would we identify these individuals? Furthermore, the use of life-long treatments to modulate leukocyte trafficking could impede immunity in the context of infection, in a similar manner to immune-modulating biologics that are used to treat active inflammatory disease [158, 159]. The use of leukocyte trafficking-modifying therapeutics is also faced with medical challenges, including uncertainty over whether these therapeutics are effective at preventing inflammatory diseases in older adults, whether these therapeutics interact or interfere with any other medications that may be prescribed to older individuals, and how to determine an appropriate age to begin treatment. Nevertheless, the prospect of pre-emptively manipulating homeostatic leukocyte trafficking in an attempt to prevent, or at least delay, the onset of age-related diseases remains a promising concept. There is great need for studies aimed at investigating and deciphering the age-related changes to homeostatic leukocyte trafficking *in vivo*, and whether therapeutic intervention would be effective in the prevention of age-related diseases.

In this review, we have described the limited number of studies that have investigated age-related changes in the migratory capacity of innate and adaptive immune cells. However, the majority of these studies were focused on leukocyte trafficking under inflammatory conditions, and so the impact of ageing on homeostatic leukocyte trafficking has been largely overlooked. Furthermore, the extent to which indirect consequences of ageing, such as immunesenescence, drive age-related changes in leukocyte trafficking has not been addressed. Overall, little progress has been made to elucidate the underlying mechanisms driving changes in leukocyte trafficking in ageing, and to determine whether targeting dysregulated leukocyte trafficking has therapeutic potential in the prevention of inflammatory disease development in older adults.

# Contributions

 SJH wrote the first draft of the manuscript. MC and JML contributed to manuscript revision, read and approved the submitted version.

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# Conflict of interest

 The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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