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How Inflammation Blunts Innate Immunity in Aging

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Abstract

The collective loss of immune protection during aging leads to poor vaccine responses and an increased severity of infection for the elderly. Here, we review our current understanding of effects of aging on the cellular and molecular dysregulation of innate immune cells as well as the relevant tissue milieu which influences their functions. The innate immune system is composed of multiple cell types which provide distinct and essential roles in tissue surveillance and antigen presentation as well as early responses to infection or injury. Functional defects that arise during aging lead to a reduced dynamic range of responsiveness, altered cytokine dynamics, and impaired tissue repair. Heightened inflammation influences both the dysregulation of innate immune responses as well as surrounding tissue microenvironments which have a critical role in development of a functional immune response. In particular, age-related physical and inflammatory changes in the skin, lung, lymph nodes, and adipose tissue reflect disrupted architecture and spatial organization contributing to diminished immune responsiveness. Underlying mechanisms include altered transcriptional programming and dysregulation of critical innate immune signaling cascades. Further, we identify signaling functions of bioactive lipid mediators which address chronic inflammation and may contribute to the resolution of inflammation to improve innate immunity during aging.

Inflammation and Aging

Aging is the single greatest risk factor for developing chronic disease. Compared to younger adults, the elderly are at increased risk of infection and experience greater morbidity and mortality upon infection [1]. Similarly, the elderly also have poor vaccine responses, making them more susceptible to vaccine-preventable disease such as influenza or vari-

cella zoster (causative agent in chickenpox and shingles) viruses, even when they have been vaccinated [2]. Central to this susceptibility is the functional deterioration of systemic immunity, or "immune senescence." This term encompasses the collective loss of immune protection during aging and includes atrophy of the thymus leading to decreased naïve T cell output, an increased proportion of experienced lymphocytes contributing to adaptive immune memory but limiting responses to novel targets, an increased proportion of myeloid cells released from the bone marrow, and impaired functions of multiple existing immune cell types. Immune senescence is also characterized by functional dysregulation in immune cells at the cellular and molecular levels, ultimately leading to increased infection susceptibility and poor vaccination responses in the elderly as discussed in detail throughout this chapter.

Underlying many deficiencies in immunity is a chronic proinflammatory state. Many age-related diseases are driven by and promote increased inflammation, and elevated circulating inflammatory markers such as CRP, TNFα, and IL-6 correlate with age-related conditions including atherosclerosis [3] and frailty [4]. Importantly, even clinically healthy elderly individuals exhibit elevated inflammatory cytokines in serum [5]. While the precise source and cause of inflammation during aging is still unknown, this so-called "inflammaging" state contributes to the onset of multiple comorbidities in the elderly, including but not limited to Alzheimer's disease, cardiovascular disease, muscle wasting, and immune senescence [6], making older adults a uniquely challenging patient population. Here, we will focus on the impact of inflammation on dysregulation of innate immune responses and relevant tissue microenvironments that influence immune cellular function.

Critical Functions of Innate Immunity

The innate immune system is responsible for initial control of pathogens by directly eliminating infections, engaging nearby cells, and recruiting adaptive immune cells. In contrast to the adaptive immune system, which requires training and is exquisitely specific to particular pathogens, the innate immune system senses and responds to numerous infections directly. The innate immune system is composed of multiple cell types with distinct critical functions both in the circulation and following infiltration into tissues to provide early responses to infection or injury. Innate immune cells such as neutrophils and monocytes circulate throughout the body and are capable of rapidly infiltrating tissues; macrophages and dendritic cells (DCs) reside within tissue and have important roles in tissue surveillance and antigen presentation. Innate immune cells rely on a variety of pattern recognition receptors (PRRs) to sense tissue disturbance and also recognize pathogenic invasion. Membrane-associated Toll-like receptors (TLRs) on the cell surface and within endosomes sense diverse structural patterns associated with pathogens such as lipoproteins, lipopolysaccharide, flagellin, and nucleic acids. Numerous studies have reported diminished responsiveness to TLR ligands in innate immune cells from elderly donors as

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compared to younger donors and are discussed in more detail in the sections below. Nod-like receptors and retinoic acid-inducible gene-I (RIG-I)-like receptors are cytosolic sensors that respond to bacterial or viral molecular components to initiate inflammatory responses that limit pathogen spread. While aging affects each of these cell types and functional responses differently, some unifying mechanistic alterations offer insights to immune dysfunction in aging.

Neutrophils

Peripheral blood polymorphonuclear leukocytes (PMNs), the most abundant circulating white blood cells, account for 45–75% of circulating leukocytes. An estimated 10^{11} PMNs are released from the bone marrow daily to maintain a continuous supply of these crucial yet short-lived terminally differentiated cells. PMNs circulate throughout the body and therefore can potentially impact every tissue. They are rapid early responders to sites of infection or tissue injury and have high phagocytic and inflammatory capacity to limit pathogen spread. PMNs also contribute to chronic sterile inflammatory diseases such as gout in which they periodically accumulate and reactivate in afflicted joints causing debilitating pain in patients [7].

Despite their abundance and high inflammatory capacity, PMNs are less well characterized in the field of aging immunology. PMNs from older donors have lower TLR1 expression that correlates with reduced activation of TLR1-dependent IL-8, CD11b, and glucose uptake [8]. While PMNs from healthy elderly donors have reduced phagocytic (FITC-labeled E. coli) capacity and increased superoxide in response to fMLP and PMA [9, 10], generalization of these findings has been complicated by differences noted from different stimuli and experimental conditions [11]. PMNs from elderly individuals also show reduced actin polymerization [12, 13], suggesting impairments in chemotaxis. Indeed, in support of this possibility, PMNs isolated from aged mouse bone marrow exhibited reduced chemotaxis [14]. In the aged, poor chemotaxis is proposed to prolong PMN presence in tissue, causing collateral tissue damage [14, 15].

PMNs can undergo a novel form of cell death, NETosis, in which DNA content containing digestive and inflammatory enzymes is extruded from the cell. NETosis is a unique method to control pathogenic spread but is also recently implicated in sterile inflammation [16–18]. PMNs from old mice have impaired ability to undergo NETosis in response to in vivo cecal ligation and puncture-induced model of sepsis and also in vitro after stimulation with TLR2 ligands, suggesting a cell-intrinsic defect in signaling to induce NET formation and/or extrusion [19, 20]. In parallel with these impairments, however, human PMNs from healthy older donors maintain their ability to activate the NLRP3 inflammasome when stimulated in vitro [21]. Despite certain PMN functions being retained during aging, the accumulated defects that have been identified outnumber them, and these multiple defects in critical early responding cells allow more rapid pathogenic spread early after infection, putting the elderly host at increased susceptibility to infection and morbidity.

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Monocytes

Monocytes are a heterogeneous subset of circulating myeloid cells that can infiltrate tissues and differentiate into macrophages or DCs. Their normal functions include phagocytosis, antigen presentation, and cytokine production. Multiple subsets of monocytes can be found in human blood at different stages of differentiation and maturity that are distinguishable by CD14 and CD16 expression [22]. Monocytes from older subjects have reduced production of cytokines after TLR1/2 stimulation that was associated with reduced surface TLR1 expression [23]; a generalized alteration in TLR-induced CD80 and CD86 expression correlates with reduced responses to influenza vaccination [24]. Monocytes from older subjects also have significantly diminished IFN-α/β responses to RIG-I stimulation [25]. Interestingly, these same monocytes retain the ability to produce proinflammatory cytokines upon stimulation, suggesting that aging may lead to cell-intrinsic dysregulation specifically in the IFN arm of this response [25, 26]. As there is no evidence of altered basal IFN expression with age, impaired IFN induction is representative of a model of age-related reduced dynamic range distinct from that of TLR-mediated proinflammatory cytokine induction. However, a significantly higher percentage of unstimulated monocytes from older donors exhibited nuclear NF-κB (p65) translocation, i.e. a higher activation status at baseline, and these cells secreted significantly more TLR5-induced IL-8 compared to monocytes from younger individuals [27], representing a possible avenue for vaccine adjuvant design. The age-related defects in monocytes have not yet been reported in other innate immune cells and highlight that each cell subset accumulates its own functional defects ultimately culminating in impaired innate immune protection during aging.

Macrophages

Macrophages are versatile innate immune cells that are important for initiating proinflammatory immune responses in addition to roles in phagocytosis, resolution, and tissue repair after injury. In the steady-state, anti-inflammatory macrophages help maintain homeostatic conditions within the tissue and become activated in response to infection or injury. Activated macrophages can secrete a variety of cytokines (e.g., TNFα, IL-1β, NO) that prime the inflammatory immune response and chemokines (MIP-2, KC) that recruit additional immune cells. After pathogen clearance, anti-inflammatory macrophages help clear apoptotic and necrotic debris and secrete cytokines and growth factors that promote tissue repair and regeneration. Mouse studies have shown the large variety of functions carried out by macrophages reflects the existence of multiple subsets and lineages of macrophages, each occupying distinct niches within tissues. For example, resident macrophages have recently been reported to interact directly with the nervous system in the intestine [28] and adipose tissue [29, 30] to regulate tissue function. Taken together, these data indicate macrophages have a central role in maintaining tissue homeostasis and also orchestrating immune responses.

Despite this importance, relatively little is known about changes in tissue macrophage function during aging, largely due to their poor accessibility within tissues. Monocyte-derived macrophages from human elderly human blood donors show impaired DC-

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SIGN-induced reduction in the expression of TLR3 following infection with West Nile virus (WNV) in vitro [31]. This impairment via the signal transducer and activator of transcription 1 (STAT1)-mediated pathway may be relevant for elevated cytokine production contributing to permeability of the blood-brain barrier and increased severity of WNV infection in older individuals [31, 32]. Murine studies also support an age-related increase in influenza A virus (IAV) susceptibility that may contribute to impaired tissue repair and altered cytokine dynamics [33–35]. In aged mice, elicited peritoneal macrophages showed reduced phagocytosis of FITC-labeled *Escherichia coli* [36]. Importantly, this same study found in vitro differentiated bone marrow-derived macrophages from old mice did not have this defect, suggesting mechanisms beyond cell-intrinsic changes during aging. Notably, peritoneal macrophages transferred from adult into old mice lost their phagocytic capacity. This result emphasizes that the tissue environment is a critical determinant of macrophage function.

Dendritic Cells

DCs are key sources of inflammatory cytokines and costimulatory molecules that instruct the development of the adaptive antimicrobial immune response. Multiple classes of DCs exist, with the most common being myeloid DCs (mDCs) that activate naïve T cells, and plasmacytoid DCs (pDCs) which are major sources of IFNα following viral infection. DCs reside within lymph nodes or other tissues and survey the local microenvironment and then migrate to nearby lymph nodes that are being patrolled by adaptive immune cells. Recent studies using a unique resource of tissue acquisition from human organ donors have revealed that DC subset composition varies by tissue and age in humans, and these changes may impact site-specific immunity [37]. Both mDCs and pDCs from older donors show lower expression of TLRs globally and substantial decreases in cytokine production following TLR stimulation [38, 39]. Recent studies of DCs detected lower levels of RIG-I from older human subjects [40]. Similarly, pDCs and monocyte-derived DCs from healthy older subjects also secrete less IFN in response to IAV [41–43] and to WNV [38, 40]. DC production of type I IFN was significantly lower in older donors compared to younger donors, with diminished induction of late phase signaling responses, e.g. STAT1, IRF7, and IRF1, suggesting defective regulation of type I IFN induction [40]. IFN production by pDCs is decreased in older HSV-2-infected mice owing to impaired IRF7 upregulation upon viral infection, potentially further compromising antiviral immunity [44]. Multiple functional defects in these critical cells that bridge the innate and adaptive immune responses greatly contribute to impaired immune activation and responsiveness to infection in the elderly.

Inflammation and Innate Immunity

While most vaccine responses are assessed by generation of antigen-specific memory T cells and protective antibody titers, proper activation of the innate immune system is essential for orchestrating this process. Innate immune cells create local cytokine and che-

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mokine gradients to recruit cells to sites of damage or infection. They also carry antigen back to lymph nodes to initiate adaptive immune cell activation and expansion. During aging, many of these critical functions performed by innate immune cells become compromised, leading to poor overall immune protection and vaccine responsiveness. The chronically elevated basal levels of proinflammatory cytokines in the elderly lead to impaired responsiveness of innate immune cells by raising the threshold of activation, thereby compressing the dynamic range of responsiveness. Evidence from multiple studies in old mice illustrate the role of inflammatory cytokines in impaired innate immune function during aging. Splenic macrophages isolated from old IL-6-deficient mice have restored secretion of TNFα, IL-1β, and IL-12 after ex vivo stimulation with LPS [45]. Similarly, inflammatory monocytes were found to correlate with elevated serum TNFα and interfere with bacterial clearance from the lungs of old mice, but aged TNFα-deficient mice were able to effectively clear the infection [46]. Taken together, these data support a hypothesis that continuous bathing of innate immune cells in the inflammatory milieu of the aged individual reduces the abilities of these cells to sense and respond to signals such as tissue damage, infection, or vaccination.

Influence of Tissue Milieu on Innate Immune Cell Function

Much of what is known about innate immune cell functional changes during aging has been elucidated in vitro in cells isolated from peripheral blood and do not reflect tissue milieu. Mounting a functional immune response depends not only on intrinsic responses by innate immune cells, but also their ability to communicate with the neighboring cells around them. Animal models and studies of ex vivo human tissues have provided some insights into how the tissue microenvironment significantly shapes the function and identity of its resident immune cells [37, 47–49]. Rodent studies utilizing heterochronic parabiosis, the surgical joining of a young and old animal in which a shared circulatory system develops, have revealed environmental defects in the aged animal that can be improved by exposure to circulating factors from the young animal [50]. Similarly, adoptive cell transfers of adult or old cells into reciprocally aged hosts reveal that the aged environment impairs functional responses of innate immune cells [36, 51, 52]. Although these experimental techniques are limited to inbred animal models, innovative studies in lung transplant patients have recently been used to study tissue-resident T cells in humans [53]. In the following sections, we describe selected tissues that exhibit strong age-related alterations and discuss how these might impact innate immunity and vaccine efficacy.

Skin

The skin is the largest organ in the human body and represents one of the first physical barriers to protect against pathogens. Skin also contains a unique composition of innate immune cells, including macrophages, innate-like γδ T cells, as well as classical memory αβ T cells, and a specialized subset of DCs called Langerhans cells. While obvious physical appearance reflects important cellular and tissue organizational changes in aged skin, we

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lack a detailed understanding of how the immune system in skin changes with age. To address this gap, sophisticated methods have been developed by Dr. Arne Akbar and colleagues in which a suction blister is used to collect leukocytes and fluid from the skin after cutaneous antigen challenge. They found impaired memory T cell migration to the skin after challenge with fungal (*Candida albicans*), viral (varicella zoster virus, VZV), and mycobacterial (tuberculin PPD) antigen challenges. They further showed with the *C. albicans* model that impaired memory CD4 T cell homing to aged skin is due to reduced TNFα secretion from macrophages [54]. The reduced TNFα led to impaired endothelial activation of selectin molecules including E-selectin, VCAM-1, and ICAM-1. Ultimately, the lower adhesion molecule expression on the endothelium led to reduced memory CD4 T cell migration to the skin. Importantly, the defects in both the endothelium and macrophages could be restored in vitro, suggesting they reflect the influence of the tissue environment within the skin and may be reversible.

Skin biopsies from elderly individuals exhibit elevated p38 MAPK transcriptional signatures that correlated with impaired VZV skin response. Treating these subjects with an oral MAPK inhibitor prior to antigen challenge improves systemic inflammation and their VZV-specific recall response in the skin [55]. Similar depressed immune responses have been reported in a murine skin infection model of *Staphylococcus aureus* in which old mice have delayed bacterial clearance, delayed wound closure, and reduced neutrophil chemotaxis to the wound site [56]. This highlights the detrimental effects of elevated basal inflammation that compresses the dynamic range of innate immune activation in the elderly. Improving immunity in aging skin has potentially enormous clinical implications particularly as skin is a common vaccination site. Perhaps improving immune cell recruitment to and from the skin and draining lymph nodes represents a realistic approach towards achieving the goal of improved vaccine efficacy in the elderly.

Lung

Like the skin, the lung is another barrier tissue constantly exposed to environmental and microbial pathogens. Individuals aged 75–84 have nearly 20-times higher morbidity and mortality compared to younger adults after acute lung injury [57]. People over age 65 account for 70% of influenza- and pneumonia-related hospitalizations [58], and studies in mice show that aging increases susceptibility to secondary bacterial challenges after influenza infection [59]. Together, these studies highlight multiple defects in the aging lung, including local immune responsiveness and tissue maintenance and repair, which increases host vulnerability to lung damage and disease. Age-related changes in the lung milieu are significant given that even in young animals the lung environment strongly regulates the activation and function of resident immune cells [60]. In a prospective study of emergency room patients with burn inhalation injuries, older patients were at increased risk of death after burn injury and had higher concentrations of inflammatory cytokines in their serum and bronchoalveolar lavage fluid [61]. High vascularization within the lung makes it a unique site that can be rapidly infiltrated by circulating leukocytes. Increased neutrophil infiltration and activation is associated with excess immune

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pathology during infection in mouse and human studies [25, 62–66]. As described above, dysregulation of neutrophil responses and impaired chemotaxis could impair pathogen clearance and prolong detrimental inflammatory responses in the lungs of elderly individuals.

Lymph Node

Lymph nodes are the central hubs in which innate and adaptive immunity coordinate productive immune responses. They are highly organized structures strategically placed at intersections between draining lymphatics and the circulating blood vasculature. Upon encountering and processing pathogens in the periphery, innate immune cells such as DCs migrate to nearby lymph nodes. Migration of cells towards and within lymph nodes has been expertly reviewed previously [67]; resident innate immune cells, including macrophages, are poised to respond immediately in the case of pathogen entry, or relay immune information further into the lymph node. T cell and B cell zones in the inner cortex are spatially organized and surrounded by macrophages. Lymphocytes enter through high endothelial venules, guided by fibroblastic reticular cells. Here, they scan migratory DCs for cognate antigen. T and B cells that are continuously circulating and patrolling the body migrate through these lymph nodes and upon encountering a DC-presented cognate antigen, clonally expand and mount a massive and highly-specific adaptive immune response with the purpose of eradicating the microbial pathogen and generating long-lasting immunity. In order for this entire process to be successful, many coordinated events must be executed successfully.

Proper function of lymph nodes requires intense cross-talk between hematopoietic cells and the stroma. Accumulation of lipid droplets and increased fibrosis are common features of the disrupted lymph node architecture and disrupted spatial organization associated with aging [68, 69]. These structural changes not only impair physical communication between lymphocytes and the lymph node stroma, but also probably perturb the environment and disrupt normal homeostasis within the lymph node. Multiple studies have reported reduced lymphocyte cellularity of aged lymph nodes both during the basal state and during infection [52, 68, 70]. Disrupted organization of T cell and B cell zones in the aging lymph node further compounds the diminished immune response and may explain, in part, lower-magnitude T cell responses and lower antibody responses after infection or vaccination in the elderly.

Adipose Tissue

Although classically considered an energy storage organ, it is becoming increasingly clear that adipose tissue is also an immunologically responsive organ that contributes to systemic inflammation. Adipose tissue remodeling and redistribution into abdominal fat are common features of age-related adipose tissue dysfunction. Importantly, these physiological changes can occur independently of obesity. In addition to increased visceral adiposity, ectopic lipid accumulation in tissues, including bone marrow, the thymus, liver, and muscle increases during healthy aging and can upset normal tissue homeostasis [71].

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As adipose tissue inappropriately accumulates in tissues and lymphoid organs, it disrupts tissue architecture, function, and perhaps essential cell-cell communication. Adipose tissue secretes cytokine-like molecules, known as adipokines, such as leptin and adiponectin that modulate immune cell function. Besides these secreted factors, the adipose tissue itself contains a unique immune phenotype [72]. Under steady-state conditions, the adipose contains primarily anti-inflammatory macrophages, γδ T cells, and other innate immune cells with tissue maintenance and reparative properties. However, during aging, the composition of the adipose-resident immune populations become skewed and heavily enriched for proinflammatory macrophages, B cells, and memory T cells [73–75].

Mouse studies indicate that adipose-resident macrophages exhibit particularly intriguing changes during aging. Unlike obesity, in which proinflammatory macrophages increase numerically, aging is accompanied by an overall reduction in the proportion of macrophages in visceral adipose tissue, although the population still manifests a generally proinflammatory phenotype [73]. The macrophages that remain occupy several distinct niches, including crown-like structures surrounding dead or dying adipocytes, scattered in the parenchyma, and lining sympathetic nerves within the adipose tissue [29]. The "aged" macrophages gain a unique transcriptional profile that includes upregulation of enzymes monoamine oxidase A (*Maoa*) and catechol-*O*-methyltransferase (*Comt*) that degrade catecholamines, leading to impaired lipolysis during fasting. This phenotype may also be driven by chronic low-grade inflammation by macrophages, as NLRP3 inflammasome-deficient old mice are protected from lipolysis resistance. Notably, NLRP3-deficient mice are also protected from numerous age-related inflammatory diseases, including aspects of immunosenescence [76, 77], sarcopenia [78], and experimental lung fibrosis [79], highlighting its role as a potential driver of age-related inflammation. While human studies show transcriptional activation of inflammasome gene signatures during aging [78], more studies are needed to formally understand how these proinflammatory immune complexes promote immune senescence during aging.

Mechanisms of Dysfunction in Innate Immune Cells during Aging

For the numerous innate immune defects that develop with age, the impact of tissue milieu on innate immune cells may have particular relevance, but data from humans are limited, and additional novel approaches are desperately needed. Multiple mechanisms that cause cell-intrinsic defects have been identified in experiments using innate immune cells isolated from peripheral blood of elderly and adult donors. Notably, these mechanisms may occur simultaneously within particular cells, or across multiple populations, ultimately disarming the proper function of the aged innate immune system.

Altered Transcription after Stimulation

Transcriptional programming coordinates the proinflammatory programs needed for innate immune control of pathogens. PBMC from healthy aged participants had elevated

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baseline type 1 interferon gene signature compared to PBMC from younger adults, and levels could not be further induced by influenza vaccination [80]. Younger adult PBMC also showed increased oxidative phosphorylation and mitochondrial biogenesis programs that were absent in older adult PBMC, particularly in older adults that did not respond to vaccination. Circulating isolated monocyte subsets from elderly individuals showed altered transcriptional profiles in response to ex vivo TLR ligand stimulation including exaggerated superoxide and oxidative stress program signatures [81]. A large multicohort analysis showed that baseline gene expression predicts influenza vaccination response in young adults. Fifteen genes (upregulated: *RAB24*, *GRB2*, *DPP3*, *ACTB*, *MVP*, *DPP7*, *ARPC4*, *PLEKHB2*, *ARRB1*; down-regulated: *PTPN22*, *PURA*, *SP4*, *CASP6*, *NUDCD2*) were identified in young adults classified as "high responders" to influenza vaccination. These nine upregulated genes were not induced in older individuals, and no genes in older adults were differentially expressed in low and high responders, suggesting distinct responses lead to lower vaccine response in older individuals [82]. Hematopoietic stem cells (HSCs) from older individuals exhibit hypermethylation of the *IRF8* locus [83], and thus epigenetic regulatory mechanisms may link the well-known myeloid skewing of HSCs with impaired IFN induction with age [26]. These age-related impairments may contribute to impaired vaccine response and the increased susceptibility of older persons to IAV infection.

Impaired Mer Signaling

TAM receptors (Tyro3, Axl, and Mer) are a family of receptor tyrosine kinases that play critical roles in tissue homeostasis by recognizing and inducing phagocytosis of apoptotic cells. TAMs are also negative regulators of TLR-mediated immune responses that broadly inhibit both TLR and TLR-induced cytokine receptor cascades to limit inflammation [84]. The importance of TAMs in immune activation is illustrated by the observation that reduced levels of TAMs in humans and in a TAM-deficient mouse model are associated with susceptibility to autoimmune disease and higher or chronic inflammation [85–87]. Monocytes from older donors showed elevated expression of TAM receptors but impaired activation of the Mer pathway following binding of the ligand Protein S, leading to impaired signaling through AKT [88]. The elevated expression of TAM receptors in monocytes from older adults has important implications for dysregulation of immune responses in aging, in particular as the Mer pathway is critical for clearance of apoptotic cells that contribute to inflammation in aging [89, 90]. Defective TAM signaling in alveolar macrophages in old mice may also explain impaired phagocytic clearance of apoptotic PMNs and increased mortality during influenza infection [91]. Further, TAMs play a key role in mediating autophagy [84, 85], and the reduced efficiency of autophagy in aging has been shown to contribute to accumulation of damaged proteins in cells [92]. The importance of TAMs in aging may be especially significant in tissue, where levels of Mer are highest, and may present avenues for modulation of chronic tissue inflammation noted in aging.

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Reduced RIG-I Signaling

Innate immune cells rely on intracellular sensors known as PRRs to recognize pathogen-associated molecular patterns. One such PRR induced during viral infection by recognition of 5′-triphosphate (5′-ppp) is the RIG-I which induces type 1 IFN to control viral infections. Recent studies of DCs detected lower levels of RIG-I from older human subjects [40], and monocytes from older subjects have significantly diminished IFN-α/β responses to RIG-I stimulation [25]. Total human PBMCs exhibit impaired IFN responses to 5′-ppp RNA transfection relative to younger controls 6 h after stimulation, although in this complex cell population responses were comparable after 24 h [93]. Studies of potential mechanisms mediating these age-associated findings revealed that monocytes from older adults exhibit decreased expression of the adaptor protein TRAF3 as a consequence of its increased proteasomal degradation with age, thereby impairing the RIG-I primary signaling pathway for type I IFNs. Monocytes from older adults also fail to effectively upregulate the interferon regulatory transcription factor IRF8, compromising their ability to participate in IFN induction through secondary RIG-I signaling [26]. Such RIG-I signaling defects in multiple cell types could likely contribute to increased risk for infection and morbidity and mortality from viral infections in the context of aging. As the innate immune system helps instruct appropriate responses of the adaptive immune system, these innate signaling defects may also contribute to impaired adaptive immunity and vaccine efficacy during aging.

Energy Balance and Inflammation Regulation

Recent progress targeting metabolic programming suggests potential treatment strategies to enhance immune responses in older adults. While several non-pharmaceutical dietary interventions have demonstrated improved longevity in animal models, including calorie restriction, fasting-mimicking diet, and ketogenic diet, few have investigated their impact on immune function during aging [94–97], and this area presents opportunities for future investigation. Many lifespan-extending interventions induce a negative energy balance in which energy expenditure exceeds energy consumption [98–101]. In this adaptive starvation response, the body switches from glucose to lipid breakdown to support energetic requirements via production of short-chain fatty acids such as ketone bodies. Accordingly, ketogenic diets comprised almost entirely of fat and protein actually promote fat break down and weight loss because of this adaptation to low-glucose availability. In addition to serving as an alternative fuel source, the most abundant ketone body, β-hydroxybutyrate, potently inhibits NLRP3 inflammasome activation in macrophages, monocytes, and neutrophils from adult and older humans and mice [21, 102] and extends lifespan in *Caenorhabditis elegans* [103]. Notably, two studies recently reported increased lifespan and improved cognition in old mice fed a ketogenic diet [95, 96]. This highlights the importance of whole-body metabolism in regulating age-related inflammation and presents a critical window for future exploration.

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Immune Cell Energy Metabolism

Metabolic programming in immune cells is a critical determinant of their downstream functions and mounting a robust immune response is energetically expensive. Increased glycolysis is generally associated with elevated proinflammatory activity, whereas fatty acid oxidation and oxidative phosphorylation is associated with quiescence and anti-inflammatory functions [104]. At the population level, a balance between these programs allows for proinflammatory immune-mediated pathogen clearance, while preserving tissue repair functions and long-lived immunity in the case of adaptive immune cells. In addition to the importance of overall metabolic programming, specific metabolites such as succinate, itaconate, and β-hydroxybutyrate regulate immune cell function [105, 106]. Therefore, targeting immune cell metabolism represents an attractive strategy for modulating immune responsiveness and vaccine efficacy. It should be noted that the simplified model presented here is derived from mostly in vitro studies and whether this programming balance occurs in vivo or is maintained during aging is not known. Future studies are needed to test whether basal metabolic programming and/or activation-induced metabolic upregulation in innate immune cells is retained during aging and what cues stimulate this reprogramming.

Bioactive Lipids

In addition to metabolic programming, dietary metabolites can have important cell signaling functions. While we have focused on innate immune activation defects that contribute to increased infection susceptibility in the elderly, an equally important aspect of the innate immune system is the resolution of inflammation. Key to resolution is a family of pro-resolution bioactive lipid mediators synthesized from omega-3 fatty acids, namely docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) – the resolvins, lipoxins, and maresins [107]. Aged mice exhibit delayed bacterial clearance and have reduced levels of these pro-resolving lipid metabolites [108]. Innate immune cells are capable of metabolizing DHA and EPA to generate these metabolites, and this improves efferocytosis in human monocytes [108]. Finally, MerTK-dependent ERK activation induces pro-resolving lipoxin LXA_4 production in human monocyte-derived macrophages [109]. Perhaps age-related changes in tissue milieu can be restored by improving inflammation resolution in the elderly. Future investigations in this domain are warranted to explore their potential for dampening chronic inflammation during aging to improve innate immunity.

Perspectives and Future Directions

The impact of chronic inflammation on innate immunity, both within immune cells and their tissue microenvironment, highlight a critical area for future investigation and potential novel therapeutic interventions. As we have described, multiple interconnected deficits arise during aging, both within innate immune cell subsets and the tissue milieu, to

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impair in vivo innate immunity in the elderly. With these complex layers of regulation, it remains challenging to fully define mechanisms of innate immune deficiencies. Collectively, these defects lead to poor priming of the adaptive immune system, culminating in poor immune protection and vaccination in the elderly. Given that in vitro stimulation of isolated circulating immune cells probably does not fully reflect their responsiveness within the tissue milieu, future studies will require appropriate in situ tissue studies and animal models. Along with development of new approaches to define age-related defects in innate immunity, a critical priority is novel therapeutic interventions targeting systemic inflammation to address immune dysfunction and enhance healthy life-span.

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