HHS Public Access

Author manuscript

Transl Med Aging. Author manuscript; available in PMC 2021 February 25.

Published in final edited form as:

Transl Med Aging. 2020 ; 4: 93–95. doi:10.1016/j.tma.2020.07.005.

Integration of immune-metabolic signals to preserve healthy aging

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Abstract

Inflammation is a broad term that refers to a collection of carefully balanced programs in the body. These pathways are essential for detecting invading microorganisms, controlling the spread of infection, and instructing appropriate immune responses to eliminate pathogens. During aging there is deterioration of important regulatory mechanisms, giving rise to persistent low-grade inflammation that drives chronic conditions such as metabolic dysregulation, immune senescence, and cognitive decline. Understanding this aspect of the pathobiology of aging is key to uncovering the source(s) and cause(s) of age-related inflammation that underlies disease.

Keywords

Aging; Immunometabolism; Immunology; Metabolism; Inflammation

Decades of research in numerous model organisms have consistently shown that metabolic signaling and nutrient sensing are intrinsically linked with longevity [1–3]. Through genetic, nutritional, and pharmaceutical approaches, overall slowing of metabolism, with specific dampening of anabolic processes and enhancement of fatty acid oxidation favors increased longevity and extension of healthspan. Although greatly oversimplified, this general paradigm also describes the regulation of inflammation in leukocytes: inflammatory cells tend to have preferential utilization of glycolytic metabolism, whereas anti-inflammatory cells prefer oxidative metabolism, and these fate decisions are coordinated by nutrient-sensing signaling pathways [4,5]. It is therefore no coincidence that lifespan-extending manipulations, which target the same pathways required for immune activation, are often associated with reduced inflammation. In addition, individual metabolites can act like cytokines, capable of regulating immune cell function. These findings highlight a unique interconnectedness between metabolism, inflammation, and aging.

Metabolism has emerged as a key regulator of immune cell function. However, most of what we understand about this relationship is in the context of immune activation during infection. Although anti-microbial protection defines the classical role of the immune system, it is becoming increasingly clear that immune cells also participate in organ

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Declaration of competing interest

The author declares no conflict of interest.

maintenance and tissue repair. Each organ contains its own resident immune compartment, tailored to the unique needs of that tissue. Tissue-resident immune cells perform a surprising variety of homeostatic functions in all tissues that are required for survival. For example, type 2 innate lymphoid cells (ILC2s) and γδ T cells induce adaptive thermogenesis by promoting subcutaneous adipose tissue browning to maintain core body temperature during cold exposure [6–8]. Regulatory T cells (Tregs) in visceral adipose tissue are associated with glycemic control and metabolic health [9], whereas Tregs in the skin protect against fibrosis [10]. Notably, all of these homeostatic programs become impaired in the elderly. Studies in humans indicate that immune cells vary by tissue across lifespan, further supporting the likelihood of dynamic age-dependent regulation within these compartments [11,12]. In addition, tissue-resident immune cells are often seeded embryonically or early post-natal, and then maintained throughout life, making them uniquely susceptible to age-dependent dysregulation. Given that nearly every organ system functionally declines during aging, and that immune function wanes during aging, it seems highly likely that mechanisms of immune-mediated homeostasis might also be degraded during aging.

Immune cells, including those that are tissue-resident, are highly sensitive to the host's metabolic state. This has been well-studied in the context of obesity, in which adipose tissue macrophages, accounting for 40–60% of the resident immune compartment, obtain pro-inflammatory phenotypes, whereas anti-inflammatory cells such as Tregs, eosinophils, and ILC2 decline [9,13,14]. Due to some overlapping phenotypes, obesity has been used as an accelerated aging model. However, there are immunological distinctions between obesity and aging, so these comparisons must be made carefully [15]. Two cell types illustrating this dichotomy are macrophages and Tregs: both are important regulators of adipose tissue inflammation that exhibit opposite patterns in obesity versus aging [16,17]. Another relatively rare cell found to be sensitive to systemic metabolic perturbation are γδ T cells, which are considered more innate-like than conventional CD4 and CD8 αβ T cells due to their rapid cytokine production and T cell receptor-independent activation. Switching mice to a longevity-associated ketogenic diet [18,19], which is a very high-fat (90% of calories) low-carbohydrate (<1% of calories) diet that forces a metabolic switch favoring fatty acid oxidation by limiting glucose availability, activates a protective subset of γδ T cells in the lung and adipose tissue. These rare cells, representing less than ~3% of the resident immune compartments in their respective tissues, are required for protection against influenza virus A infection and obesity-driven metabolic disease in mice [20,21]. Moreover, mice deficient in any of the cell types described above exhibit profoundly altered susceptibility to metabolic inflammation. These data collectively indicate that both abundant and rare immune cell subsets are subject to regulation by systemic metabolism. Thus, targeting metabolism represents a viable strategy to improve immune-mediated homeostasis and alleviate inflammatory burden.

So how can we exploit the metabolic susceptibility of immune cells to improve age-related inflammation? We cannot assume by default that any lifespan-extending intervention also improves immune function. Lifespan studies in model organisms, particularly rodents, have the important caveat that they are performed in clean, specific pathogen-free environments that do not model the numerous daily microbial encounters faced by humans. Therefore, the impact of any intervention on the immune system must be deliberately tested. In calorie-

restricted healthy young adults, aspects of cell-mediated immunity are preserved [22], but whether this is true in elderly individuals, and if immune protection against acute or novel infection is maintained, remains unknown. In old mice, calorie restriction increases mortality after infection with influenza A virus and West Nile virus [23,24]. Another anti-aging intervention that has gained popularity during the last decade is rapamycin and other mechanistic target of rapamycin (mTOR) inhibitors, known as rapalogues. Rapamycin extends chronological lifespan [25] and delays age-related pathology in multiple organs [26]. However, rapamycin is a clinical immune suppressant due to the essential role of mTOR signaling in activation of anti-microbial immune responses. In young mice, rapamycin treatment promotes CD8 T cell memory formation at the cost of effector differentiation in response to infection [27], and this is associated with increased mortality after West Nile Virus infection [28]. Young mice vaccinated against influenza virus during rapamycin treatment were protected from lethal heterosubtypic secondary influenza infection, but whether rapamycin would have altered susceptibility to a lethal primary challenge was not tested [29]. Notably, the heterosubtypic protection conferred by rapamycin was due to cross-reactive antibodies as a result of reduced antibody class switching, a mechanism normally used by B cells to generate highly specific and protective antibodies. Old mice fed the lifespan-extending dose of rapamycin have impaired hematopoiesis [30], accelerated thymic involution, and reduced lymphocyte proliferation [24], all of which are characteristics of immune senescence. In elderly humans, influenza virus vaccination 2 weeks after withdrawing rapalogue treatment leads to modest increases in influenza antibody titers [31,32]. However, vaccination during simultaneous rapalogue treatment was not tested. Given that mTOR inhibition reduces lymphocyte proliferation in the periphery, increased antibodies after vaccination could be due to a proliferative rebound upon withdrawing the inhibitor, similar to what has been demonstrated during refeeding after periodic fasting-mimicking diet [33]. All together, these findings underscore the importance of purposefully testing the impact of any longevity intervention on the aging immune system. With the variety of compounds being tested by the National Institute on Aging's Interventions Testing Program, some of which have known anti-inflammatory and/or immune-modulatory properties (aspirin, hydrogen sulfide, ketone body inducers including medium chain triglycerides and 1,3-butanediol, and metformin), this area of research will be ripe for future investigations studying how they impact the aging immune system.

Efforts to better understand mechanisms of sterile inflammation and immune-mediated homeostasis must be increased to match the years we have invested in studying age-related defects in antimicrobial immunity. In fact, these areas of study are not mutually exclusive; non-lymphoid metabolic tissues, such as adipose tissue, can be a reservoir of pathogen-specific CD8 T cells, and lifelong murine cytomegalovirus infection in mice increases adipose tissue inflammation and glucose intolerance [34,35]. Given the growing importance of resident immune cells in physiological responses to systemic stress, being able to predict the behavior and fates of tissue-resident immune cell subsets during aging should be a top priority. Exceptional resources like the Tabula Muris provide unprecedented single-cell resolution of numerous mouse tissues across lifespan [36,37]. However, rare but important immune subsets, which might account for less than 0.1% of cells in a tissue, are not easily

analyzed within these databases. A similar resource is needed that contains exclusively resident immune cells across aging tissues. This would provide the data to model and predict the trajectories of aging tissue-resident immune compartments. Identifying molecular signatures of aged tissue-resident immunity is desperately needed for developing targeted therapeutic strategies while also identifying ideal time points for intervention. Many groups have previously identified unique age-dependent defects in cell functions and signaling, highlighting the importance of developing treatments that would not rely on defunct pathways. For example, if the protective functions of a given cell type become impaired during aging, expanding that dysfunctional cell will not provide the desired protection, and could even worsen inflammation or age-related disease. We also need a better understanding of the metabolic needs of different tissue-resident immune cells, and how these might change over time, to develop metabolic strategies to improve their functions and survival. Given that tissues age at different rates (for example, the thymus becomes dysfunctional far earlier in life than the brain), that tissue structural cells also have inducible immune and inflammatory pathways [38], and that each tissue has a unique resident immune compartment, it will also be critical to consider how the aging microenvironment shapes the identity and function of the resident immune cells.

In conclusion, tissue-resident immune cells are poised to integrate and respond to immune-metabolic signals, making them strong candidates for preserving and improving tissue function during aging. The maintenance and regulation of these essential cells deserves further attention.

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