Aging, nutrition and immunity – their relationship and interaction

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Abstract. Demographic shifts worldwide are resulting in ever-increasing numbers of the elderly in both developed and developing countries. With aging come changes in physical and physiological integrity that are accompanied by a gradual decline in immunocompetence, commonly termed ‘immunosenescence’. Indeed, there are marked differences between young and old subjects with respect to the proportions of naive and memory T cells and less marked differences in B cells and other immune cells. The number and proportion of late-stage memory T and B cells commonly increases, being particularly prominent in the CD8+ cytotoxic T cell pool. The accumulation of late-stage potentially “terminally” differentiated CD8+CD27\textsuperscript{−}CD28\textsuperscript{−}CD45RA+ cells is often considered a hallmark of immunosenescence. Malnutrition in old age can further add to the severity of this age-associated remodeling of the immune system. Age-associated obesity, in particular, is accompanied by greater chronic inflammation, as reflected in increased plasma concentrations of C-reactive protein (CRP), IL-6, TNF and other factors which may mark compromised immunity. These physiological and immunological changes accompanying aging, markedly affected by nutritional status, are likely to be different in different parts of the globe. Data suggest a gradual decline in both nutritional status and immune functions with aging, but the details of these processes, and potential differences in different societies are unclear. In the following review, we will discuss the hallmarks of age-associated immune system changes and consider how these might be affected by nutritional status.

Keywords: Aging, physical changes, nutrition, immunity, immunosenescence

List of Abbreviations

- APC: Antigen Presenting Cells
- BMI: Body Mass Index
- BMR: Basal Metabolic Rate
- CM: Central Memory
- CMV: Cytomegalovirus
- CR: Caloric Restriction
- CRP: C-reactive protein
- DTH: Delayed-Type Hypersensitivity
- EM: Effector Memory
- GM-CSF: Granulocyte colony-stimulating factor
- IL-1RI: Interleukin-1 receptor, type I
- IL-6: Interleukin-6
- LBM: Lean Body Mass
- IRP: Immune Risk Profile
- MCH: Major Histocompatibility Complex
- MH: Metabolically Healthy
- MUH: Metabolically Unhealthy
- NK: Natural Killer
- PCNA: Proliferating Cell Nuclear Antigen
- TLC: Total Lymphocyte Count
- TNF: Tumor Necrosis Factor
- WEIRD: White, Educated, Industrialized, Rich and Democratic

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1. Physical and physiological changes associated with the aging process

Demographic studies have indicated that the numbers of elderly individuals in both developed and developing countries is increasing, due predominately to major improvements in living conditions and better health-care facilities [1–3]. Indeed, worldwide, life expectancy has increased markedly during the last few decades [1], promoted further by recent improvements in nutrition, hygiene, antimicrobial therapy and vaccinations [4, 5]. A universal definition of “elderly” is hard to formulate, as it must rely on the conditions and circumstances that are different in different countries and societies. Nonetheless, most countries in the developed world have accepted the chronological age of 65 years as a definition of an “elderly” or “old” person [6], although it is noted that this cut-off derives from living conditions of over a century ago. Presently, a redefinition of elderly has been discussed in industrialized countries, where most studies indicate that a figure of ≥75 years [7] may be more appropriate, whilst in developing countries, it may still be appropriate to consider “elderly” as 65 years of age. Throughout the current review we will use this arbitrary cut-off of 65 years.

Changes in the immune system with aging have been studied extensively over the past few decades, although most studies report differences between young and old in cross-sectional studies in developed countries and attribute changes to age. The conclusion from the majority of these studies is that aging leads to marked changes in the composition, function and competence of the human immune system, commonly termed “immunosenescence” [8–10]. These changes in the immune system with age are in part thought to contribute to increased morbidity and mortality from infectious disease, e.g., respiratory tract pathogens [11, 12], gastrointestinal infections [13], and antigen-specific responses to orally administered vaccines are diminished [14]. Major age-related phenotypic and functional changes to the immune system manifest as significant alterations in the T-cell compartment of adaptive immunity [9], whilst smaller changes in B-cell function [15] and the innate immune system [16] are also apparent.

During normal aging, a decline in lean body mass (LBM) with a simultaneous increase in fat tissue usually occurs, leading to adverse changes in physiological functioning of the body due to large alterations in body composition. Increased fat infiltration into muscles with aging is associated with reduced muscle performance, a reduction in muscle strength, a sudden fall in basal metabolic rate (BMR) and a reduced ability to resist infections and a decline in immunity [17]. Changes in body weight are a sign of changes in LBM [18–21] and weight loss in the elderly is typically unintentional and is associated with increased risk of functional impairment [21], mortality [18, 22], and other related complications [23]. Perhaps rather surprisingly, the exact prevalence of weight loss among elderly adults is not well documented, and the literature on this topic is limited to a few small studies that utilize a variety of definitions for weight loss [24, 25]. For example, over a 3 year follow up, more than 15% of the Cardiovascular Health Study cohort experienced ≥5% weight loss while an additional 5% had weight loss of ≥10% [25]. In a separate study, one quarter of male Veterans living in Seattle experienced ≥4% weight loss over a 2 year period [26].

Gender differences in nutritional and health status of elderly have also been investigated extensively. Of particular note are studies reporting gender-associated differences in total body fat distribution and content; with women having higher levels of adiposity deposited in the subcutaneous compartment compared to men [27]. Particularly, after menopause the fat distribution in women shifts toward a more central/male-like pattern of fat distribution [28]. It has been previously shown that females between 12 and 80 years of age have a higher percentage of body fat as compared to males. This difference starts notably with puberty [29] and varies between 6–11% higher for every decade studied [30] with variations due to ethnicity, genetic, and environmental factors [31]. Sex hormones, including oestrogen, progesterone and androgen, have been reported primarily responsible for these differences [32–37]. Importantly, these sex differences in the distribution of BF are significantly associated with differential risks for various chronic and immune diseases [38].

With such marked physical and physiological changes with aging, the overall nutritional well-being of the individuals is compromised. Consequently a number of nutrient deficiencies emerge in old age including zinc [39], vitamins A, B6, folate and B12 [40, 41]. Data from the third National Health and Nutrition Examination Survey [42] in the USA as well as other studies [43–46] clearly demonstrate a linear decline in food intake starting from the age 20 to 80 years in both men and women, particularly a drastic
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decrease in caloric intake [47]. Average daily energy intake has been reported to decrease by about 30% between 20 and 80 years [47]. The loss of muscle mass with aging can further contribute to a loss of mobility [48], and decreased physical functioning and activity, which may lead to reduced energy requirement [49]. It is also noteworthy that the rate of the aging process may differ greatly between individuals, resulting in different subgroups within the elderly population (e.g., the healthy elderly versus the frail older group) [50], implying that nutrient requirements with aging are highly individualized.

2. Immunity and its modulation by age and diet

2.1. Composition of the immune system

2.1.1. Innate immunity

Innate immunity is comprised of five types of defensive barriers: anatomic, physiologic, endocytic, phagocytic, and inflammatory. Soluble factors such as lysozyme, which is a hydrolytic enzyme capable of cleaving the bacterial cell wall, or complement, also contribute to innate immunity [51–54]. The innate immune system is also composed of protective cells and molecules. Some examples are natural killer cells (NK cells), scavenging macrophages [52, 53] and the complement system [53, 54].

2.1.2. Adaptive immunity

The other main arm of immunity is termed adaptive because it generates highly antigen-specific memory after encountering target antigens which, unlike those triggering the innate system, are infinitely variable, usually derived from infectious agents. Adaptive immune cells are the thymus-dependent T cells and the antibody-producing B cells, produced in the bone marrow by continuous haematopoiesis, a process requiring stem cell renewal over the whole lifespan, which may be affected by age and extrinsic circumstances [51, 52].

2.2. Cells of the immune system

2.2.1. T and B cells

Most of the lymphocytes in the blood are T cells, making up 22–30% of total nucleated white cells (the majority of which are polymorphonuclear phagocytes, part of the innate immune system), whereas circulating B cells represent only 7–10% of white blood cells. T and B cell differentiation stages can be distinguished by their expression or lack of expression of certain cell surface molecules. For example, approximately 75% of circulating B cells in young people do not express a monomorphic costimulatory receptor called CD27, indicating that they have recently emerged from the bone marrow and have not yet encountered antigen in the periphery [52, 55]. While B cells mature in the bone marrow, T cell precursors migrate to and mature in a distinct organ, the thymus, where they go through further developmental stages, to produce mature naive CD4+ and CD8+ T cells (often called “helper” and “cytotoxic” T cells, respectively). CD4+ and CD8+ are cell surface co-receptors which assist in binding of the T cells to antigen-presenting cells (APC), required for their activation. After their “education” in the thymus, CD4+ T cells recognize peptide fragments of antigen only when presented in the context of class II self-major histocompatibility molecules (MHC class II) by the APC, usually dendritic cells (DC). In contrast, CD8+ T cells recognize shorter peptide fragments presented on MHC class I molecules. On completion of maturation, i.e., elimination of overly self-reactive cells and selection of cells recognizing self-plus-antigen complexes, these preprogrammed naive cells leave the thymus and migrate to the periphery. Clearly, the output of naive T cells depends on the integrity of the thymus, but this with changes adversely with age and poor nutrition. Naive T cells are long-lived cells and can circulate for years if not stimulated by their cognate antigen (processed and presented by APC, as mentioned above). They may, however, die before ultimately encountering their specific antigen, and this could happen in old age [56], leaving a “hole in the repertoire” should infection with the relevant specific pathogen occur in later life. Otherwise, upon antigen encounter, naive T cells become activated, proliferate and differentiate into memory and effector T cells to exert their anti-pathogen functions. CD8+ cytotoxic T cells mediate lytic reactivity once activated and can kill infected cells directly by production of cytotoxins such as perforins and granzymes [57]. Activated CD4+ T helper T cells supply cytokines to “help” B cell maturation and CD8 differentiation, and may also be cytotoxic themselves.

2.2.2. Sub-populations of T cells

CD4+ and CD8+ T cells are further divided and categorized into sub-populations based on the expression
of additional cell surface molecules indicative of differentiation stage. This division is useful when one is interested in studying various cell phenotypes associated with specific functional characteristics. However, it must be borne in mind that these represent a continuum of differentiation stages and are not discrete cell subsets.

There are at least two established models in use for identification of T lymphocyte differentiation stages. The first model utilizes the expression of the TNF-family costimulatory receptor CD27 in combination with the CD45RA isoform of the leukocyte common antigen (a phosphatase). This strategy identifies one population of antigen-inexperienced cells, the naïve cells (CD27+CD45RA+) and three memory populations designated central memory (CM; CD27+CD45RA−), effector memory (EM; CD27−CD45RA−), and the most differentiated ‘revertant’ memory cells, which have re-expressed the ‘naïve’ cell marker CD45RA (EMRA; CD27−CD45RA+) [58–60]. In a second model, instead of CD27, the immunoglobulin super-family co-stimulatory molecule CD28 or the chemokine/lymphoid homing receptor CCR7 are used in combination with CD45RA [59, 61, 62]. Identifying cells on the basis of this combination with the CD45RA isoform of the leukocyte common antigen (a phosphatase). This strategy identifies one population of antigen-inexperienced naive T-cells in the periphery after age-associated thymic involution [67]. A steady loss of naive T-cells throughout life is therefore the norm, as they differentiate into memory/effector T cells after antigen challenge. Because thymic output declines significantly with age due to thymic involution [68], there is a decline in the contribution of the thymus to naïve T-cell homeostasis over the life-span. This suggests that homeostasis of the naïve T-cell compartment in adults may rely mostly on peripheral T-cell proliferation and prolonged survival (longevity) of naïve T cells. This contributes to the age-related changes in the immune system, particularly in T cells, as discussed in detail in the next section.

2.2.3. Homeostasis of T cells

It has now been well established that the homeostasis of naïve T-cells remains relatively stable during life [66]. Production of large numbers of naïve T cells in early life is followed by their exposure to pathogens, clonal expansion, and differentiation, performance of their function, clonal contraction and death of the majority with retention of some as memory cells. In later life, the numbers of naïve T cells can only be increased by homeostatic proliferation of existing naïve T cells in the periphery after age-associated thymic involution [67]. A steady loss of naïve T cells throughout life is therefore the norm, as they differentiate into memory/effector T cells after antigen challenge. Because thymic output declines significantly with age due to thymic involution [68], there is a decline in the contribution of the thymus to naïve T-cell homeostasis over the life-span. This suggests that homeostasis of the naïve T-cell compartment in adults may rely mostly on peripheral T-cell proliferation and prolonged survival (longevity) of naïve T cells. This contributes to the age-related changes in the immune system, particularly in T cells, as discussed in detail in the next section.

2.3. Aging and immunity

Changes to the immune system with aging have been studied and reviewed extensively over the past few years [9, 11, 69, 70] as briefly summarized in Table 1. However, most of the previous studies mainly reported on the so-called WEIRD (white, educated, industrialized, rich and democratic) aged populations in the developed world. Hence, much of our knowledge of immunity and aging is derived from and may in some ways be limited to this minority of people worldwide.

Although many studies refer to age-associated changes, the majority is cross-sectional and can therefore actually only refer to differences between a current
Table 1
Selected Age-related changes in B and T cells and their activities

<table>
<thead>
<tr>
<th>Decrease</th>
<th>Increase</th>
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<tr>
<td>T cells</td>
<td>CD7</td>
</tr>
<tr>
<td>CD4+</td>
<td>CD8+</td>
</tr>
<tr>
<td>Thymic output</td>
<td>CD45RA+</td>
</tr>
<tr>
<td>B-cell-derived antibody affinity</td>
<td>Memory B cells</td>
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<tr>
<td>Lymphopoiesis (B and T cells)</td>
<td>CMV-specific CD8+ T cells</td>
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<tr>
<td>Naive B cells</td>
<td>CMV-specific CD4+ T cells</td>
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<tr>
<td>Generation of immature B cells</td>
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Young and old cohort. It is usually difficult to investigate the actual changes in immunity with age in humans in longitudinal studies due to time and resource constraints [71]. However, there is limited number of longitudinal studies on individuals over 85 years of age, the group of people deliberately focused on in the Swedish OCTO/NONA studies. Both OCTO (subjects selected for exceptionally good health) and NONA (free-living subjects but representative health status) identified a so-called “immune risk profile (IRP)” for 2, 4 and 6-year mortality at follow-up consisting of little or no thymic output and selective accumulations of CD8+CD27−CD4+CD45RA+ cells and decreased B and T cells [72]. However, nutritional variables were unfortunately not taken into account in these studies.

Marked differences have been observed between young and old subjects in the proportions of naive and memory T cells present in the peripheral blood. In newborns, the ratio of naive to memory T cells is quite high; in adults the ratio is reversed because most of the naive T cells have been exposed to antigen, and hence converted to memory cells, as mentioned above. As the thymus progressively involutes with age, fewer T cells are produced, and the naive T cell subpopulation is not replenished. Consequently, the stock of naive T cells becomes depleted and the aged immune system cannot respond as well as a young person to a new antigen [51]. It is important to note, however, that possessing fewer naive cells has not actually been shown to be deleterious in aged people. T cell homeostasis ensures that as naive cells are lost, there is a compensatory increase in the numbers of memory cells. Consequently, the number and proportion of memory T cells with a late-differentiated phenotype (e.g. CD27−CD28−CD45RA+) commonly increases [73–76]. These phenotypic changes are particularly prominent in the cytotoxic T cell pool.

The accumulation of CD8+CD27−CD4+CD45RA+ cells is considered a hallmark of immunosenescence [73–75], which implies that young individuals exhibit marked alterations in their T cell repertoire as compared to the elderly [77, 78]. As with the naive cell situation, however, this “remodeling” of immunity, or rather the relative proportions of T cell differentiation phenotypes, has never been shown to be causally related to mortality or any other deleterious clinical outcome, and should thus be considered a hallmark of aging but not necessarily “senescence” per se. It may be viewed as an adaptive change to the requirements of an elderly host, and has been termed “remodeling”.

However, as discussed above, it is clear that the involution of the thymus is an important feature of normal anatomical as well as physiological development but nonetheless has profound effects on aging of the immune system [79–81]. Thus, even the apparently normal shrinkage of the thymus may have an active role as a weakening source of naive T lymphocytes and the related thymic hormones [82]. Consequently, this process indirectly results in immunity being greatly dependent on the existing pool of memory T cells and the remaining naive cells depending on the individual’s “immunological history” of exposures [83].

We now know that young adults thymectomised in the first few years of life exhibit reduced numbers and proportions of naive T lymphocytes, and sometimes increased numbers of cytotoxic T cells in adulthood [84–86]. These immune profiles of the young after thymectomy are quite similar to those of far older adults, who also show little or no thymic output [84, 85]. The thymectomy study also highlighted an important contribution of the individual’s exposure to micro-organisms in determining their immune profile. Sauce et al. showed that infection with Cytomegalovirus (CMV) exhibited more severe alterations in the T cell repertoire compared to those who were free of CMV infection [84]. This combination of little or no thymic output and selective expansion/maintenance of cytotoxic T cell populations leads to a gradual “filling of the immunological space” with CD8+ T cells just as is the case with “normal” aging [87]. It is noteworthy that CMV infection was also part of the cluster of parameters making up the immune risk profile in the OCTO/NONA studies,
that in cross-sectional studies of CMV-negative people, no significant age-associated difference in proportions of naive T cells can be found [88].

Most immunosenescence research has focused on adaptive immunity as it was once postulated that innate immunity is better preserved with aging [89]. It is now appreciated, however, that age-related changes are visible in nearly all cells of the innate immune system as well. For example, aging is associated with decreased natural killer cell function and altered neutrophil migration [90, 91], which starts as early as adolescence [74, 92]. Immunosenescence, by definition, is reflective of the erosion occurring in immune competence over the course of life and is at its maximum in old age [9, 93, 94].

2.4. Nutrition and immunity in the elderly

2.4.1. Under-nutrition and its effects on the immune system

On the other hand, undernutrition also exerts a strong negative effect on immune responses in the elderly [reviewed in ref. 95]. Early work on nutrition and immune functions was primarily based on the findings from studies on nutritional deficiencies in young children from developing countries [96]. Much evidence today points to nutrition as an important determinant of immune functions across all age groups worldwide. Cell-mediated immunity is particularly sensitive to deficiencies in macronutrients [reviewed in ref. 97]. In the elderly, immunological dysfunctions may occur because of single nutrient deficiencies, such as of vitamin A, iron or zinc, or because of multiple nutrient deficiencies in conjunction with general malnutrition [47, 98–114] and protein-energy malnutrition [115, 116], many of which can be reversed by nutritional supplementation interventions [117, 118].

Nutrient deficiencies often result in an increased risk of developing infections [12, 13, 119, 120]. This relationship between nutrient deficiencies and infections has been better investigated in studies with the effect of multi-micronutrient supplementation on resistance to infection in the elderly subjects [113, 121]. While some have shown benefits of nutritional intervention in reducing the burden of infectious diseases in the elderly [e.g. 121, 122], others have shown no significant effects [e.g. 112]. A multi-center nutritional trial [123] demonstrated a slightly reduced risk of pressure ulcer infections in elderly patients who were given daily protein-calorie supplements. The study concluded that this energy protein intervention was associated with a decreased risk of pressure ulcer incidence. The study of institutionalized elderly persons that demonstrated clinical benefits [122] also suggests that trace minerals, in particular, may be the key nutritional factors for preventing infection in older adults. Other studies of zinc supplementation in older adults have demonstrated enhanced DTH responses and elevated lymphocyte numbers and function of natural killer cells [e.g. 39]. Some studies have examined the effects of vitamin C (ascorbic acid) supplementation as adjunctive therapy for respiratory tract infections. One such study [116] recruited hospitalized elderly patients with bronchitis or pneumonia to compare vitamin C (200 mg/day) with placebo. The addition of the deficient nutrients back to the diet can restore immune function and resistance to infection [117]. Taken altogether, states of malnutrition and infection can aggravate each other and lead to a vicious circle [100].

2.4.2. Over-nutrition and its effects on the immune system

Like undernutrition (or underweight), overweight and obesity are the other reciprocal forms of malnutrition at epidemic proportions globally [118]. The relationship between obesity and immunity is logically to be expected mainly on three lines of evidence. First, obesity is linked with a multiplied risk of virtually all types of cancers. Second, obesity has a close association with all chronic, systemic states of inflammation, which may contribute to the development of obesity-related co-morbidity. Third, a number of hormones (e.g. leptin and adiponectin), which have been shown to play an important role in regulating immune functions, are likely to be deregulated in obesity [124].

2.4.3. Obesity as chronic inflammation

Obesity in humans is associated with low-level inflammation [125]. The inflammatory response triggered by obesity involves a number of components of the classical inflammatory response to pathogens [126]. These include systemic increases in circulating inflammatory cytokines, adipokines and acute phase proteins, recruitment of leukocytes to inflamed tissues, activation of tissue leukocytes, and generation of reparative tissue responses. However, the nature of obesity-induced inflammation is unique in comparison to other inflammatory paradigms including infections,
autoimmune diseases, and the likes. Qualitatively, for example, in chronic obesity, a low-grade activation of the innate immune system is produced that affects steady-state measures of metabolic homeostasis over time. Obesity-associated inflammation is hence characterized by a low-level but chronic inflammatory state.

The association between obesity and the development of major complications in acute pancreatitis [127], fatty liver diseases [128], vascular inflammation and coronary heart disease [129], chronic obstructive pulmonary disease [130], risk of cerebral ischemia and brain injury [131], atherosclerotic vascular disease and myocardial infarction [132], and cancers [133] are strongly linked to chronic inflammation. In particular, insulin resistance, a direct or indirect result of obesity, is characterized by a chronic state of subclinical inflammation [134] and inactivation of a number of inflammatory mediators [135]. An elevated serum concentration of CRP [136], IL-6, IL-8 and TNF is observed in obese individuals with elevated insulin resistance [137]. In brief, obesity may affect immunity through the mediation of one or more of the aforementioned inflammatory states.

In addition to the findings that obesity leads to inflammation, there are also some recent data showing that the immune system can affect obesity in the same way as obesity can affect immunity. In particular, deficiency of several genes coding for innate immune factors (e.g., IL-6, GM-CSF, IL-1RI, and IL-18) has been shown to lead to mature-onset obesity in mice [138, 139]. Moreover, combined IL-6 and IL-1 deficiency causes early-onset obesity in mice [139]. Conversely, mice with enhanced IL-1 activity are lean and resistant to diet-induced obesity [140]. IL-6 has been shown to have obesity suppressing effects by increasing the size of the thymus [141]. It was, therefore, suggested that CR preserves immature T cell precursors in the thymus during aging to maintain higher concentrations of circulating T-helper and naive T cells. Using aged rats, CR has been shown to attenuate the age-associated increase in memory/naïve T cell ratios, attributable to a significant reduction in proinflammatory cytokines such as TNF and IL-6 [150]. A CR-associated increase in thymopoiesis and improvement in the TCR diversity with increased naive/memory T cell ratios in the periphery has also been demonstrated [151]. What is the underlying mechanism of CR-induced effects on the thymus? This remains unclear, but arguably, the neuroendocrine factors responsible for regulating energy balance in the body may be partly having significant effects on immune function during CR by causing an increase in a number of orexigenic factors, importantly, ghrelin [152] and possibly by reducing anorexigenic hormones, such as leptin [153].

2.4.4. Caloric restriction (CR), inflammation and immunity

The effects of obesity and its associated inflammatory state can be reversed through caloric restriction (CR); a state of chronic negative balance achieved in various experimental animals. CR has been successfully exploited for robust, nongenetic means of extending the mean and maximal lifespan in some experimental animals [144]. With a sufficiently large set of research data, mostly from studies with animal models, the CR has been suggested to have significant impact on various components of the immune system [145]. These include responses of T cells to mitogens, NK cell activity, CTL activity, and the ability of mononuclear cells to produce proinflammatory cytokines [145–147]. CR has been suggested to have positive effects on NK cells and CTL as reflected in the much reduced incidence of tumors in caloric restricted mice [148–150].

What is the possible mechanism by which CR may induce the aforementioned effects? An improvement in thymic cellularity has been suggested as a result of CR in old mice [150]. In that study the number of total thymocytes and double-positive T cells was doubled, interestingly, without significantly increasing the size of the thymus It was, therefore, suggested that CR preserves immature T cell precursors in the thymus during aging to maintain higher concentrations of circulating T-helper and naive T cells in peripheral blood. Using aged rats, CR has been shown to attenuate the age-associated increase in memory/naïve T cell ratios, attributable to a significant reduction in proinflammatory cytokines such as TNF and IL-6 [150]. A CR-associated increase in thymopoiesis and improvement in the TCR diversity with increased naive/memory T cell ratios in the periphery has also been demonstrated [151]. What is the underlying mechanism of CR-induced effects on the thymus? This remains unclear, but arguably, the neuroendocrine factors responsible for regulating energy balance in the body may be partly having significant effects on immune function during CR by causing an increase in a number of orexigenic factors, importantly, ghrelin [152] and possibly by reducing anorexigenic hormones, such as leptin [153].

2.4.5. Metabolic implications of obesity

It is noteworthy, however, that not all obese individuals may be similarly at risk for adverse inflammatory outcomes and immune compromise and that metabolically healthy (MH) obese individuals have a considerable edge over metabolically unhealthy (MUH) obese individuals. As an example, Lynch et al. reported significantly more CD8+ and NK cells in lean controls compared to obese individuals. The authors
2.4.6. Malnutrition and thymic involution

166], and on Zn [e.g. ref. 167] in relation to thymic
the impact of protein–energy malnutrition [e.g. ref.
has been conducted in both humans and animals on
[162–165]. A considerable amount of research work
thymic weight with symptoms of immunosuppression
amino acids, fatty acids, and zinc) results in decreased
specific deficiencies of some micronutrients (vitamin B6,
been suggested that general undernutrition with spe-
very sensitive one
malnutrition directly leads to thymic involution, truly
understood. Currently, it is well-established that
role of the thymus in lymphocyte development was
tions were made, however, over almost a century before
size and functions of the human thymus and malnutrition [16]. He described atrophy of the
thymus in malnourished patients and since then, the
term ‘nutritional thymectomy’ has been coined and is
in common usage today. By 1845, Simon had observed
that the thymus is ‘a barometer of malnutrition and
very sensitive one’ [161]. Interestingly, these observa-
tions were made, however, over almost a century before
the role of the thymus in lymphocyte development was
truly understood. Currently, it is well-established that
malnutrition directly leads to thymic involution, truly
making the thymus ‘a barometer of malnutrition and
a very sensitive one’ [161].

To link malnutrition with immune decline, it has
been suggested that general undernutrition with spe-
cific deficiencies of some micronutrients (vitamin B6,
amino acids, fatty acids, and zinc) results in decreased
thymic weight with symptoms of immunosuppression
[162–165]. A considerable amount of research work
has been conducted in both humans and animals on
the impact of protein–energy malnutrition [e.g. ref.
166], and on Zn [e.g. ref. 167] in relation to thymic
development. Much of this work has used the simple
outcome measure of thymic size, although some of the
studies, particularly those on humans, have looked at
cell-mediated immunity [168, 169].

On the other hand, nutritional deprivation has been
shown to have proportionately greater impact on the
size of thymus [170]. However, just as the size of thy-
mus has been suggested as ‘a crude index of function’,
T cell number and various tests of cell-mediated immu-
nity are also ‘crude measures of protection’ [161].
Circulating T-cell levels are homeostatically regulated
and hence often maintained or in most of the cases may
be even elevated in sick and malnourished individuals,
which may mask defective functions [168, 169] or a
‘critical hole’ in the T-cell repertoire caused by defec-
tive clonal selection in a malnourished thymus [161].
The observation that the thymus is always the organ
most vulnerable to nutritional stress also fits with the
observation that thymic atrophy represents an ordered
process controlled by the induction of apoptosis [171].

Malnutrition-associated thymic atrophy has been
reported to be largely due to changes in the lymph-
oid compartment. Thymocyte depletion appears
as an outcome of both acute and chronic experi-
mental protein malnutrition. The main phenotypic
feature of this depletion is the loss of immature
CD4+CD8+ cells, a finding consistently seen in mal-
nutrition secondary to diets deficient in protein, metal
elements (zinc, magnesium and iron) and vitamins
[172–174]. As recently demonstrated in rats exposed
to deficiencies of Mg or Zn, the consequent thymo-
cyte depletion actually reflects a massive apoptosis
of these cells in the organ [171, 174]. In addition
to the increase in thymocyte death in the thymus
of malnourished individuals, thymocyte proliferation
seems to be affected. Thus, the numbers of thymic
cells expressing the proliferating cell nuclear anti-
gen (PCNA) marker decreases in malnourished rats
[175]. This finding is further supported by data show-
ing that thymocytes from animals subjected to distinct
protocols of dietary restriction had low mitogen-
induced proliferative responses [172]. Thus, the overall
malnutrition-related thymocyte depletion seems to
result from enhanced thymocyte death plus decreased
thymocyte proliferation.

It would be important to know whether major
changes in the thymic lymphoid compartment are
also observed in humans suffering from malnutri-
tion. Consistent with this, severe thymic atrophy with
cortical thymocyte depletion is a common finding in necropsies of malnourished subjects [176]. In further support of this observation, thymic atrophy was also observed in malnourished children by the technique of echography [177]. Nevertheless, such alterations in the thymus seem to be reversible, at least in the experimental animals, if an appropriate diet is provided [178].

Like under-nutrition, over-nutrition which leads to obesity, has also been studied extensively with regard to thymic size and function. It has been suggested that obesity-induced accelerated thymic involution and restricted and limited T cell repertoire diversity represents a potent modifier of immunosenescence mechanisms that may further increase the risk and severity of infections in the "gerobese" (geriatric obese) population [179]. This situation is likely to leave the subject with potentially greater predisposition to emerging diseases. Although the true mechanistic pathway of obesity-induced thymic involution is still not known, some previous studies examining immune function in extreme monogenic rodent models of obesity have shown clear thymic involution [180] and significant defects in T-cell responsiveness [181]. Interestingly, despite massive replacement of thymic with adipose tissue, the aging thymus still retains limited capacity for generating naive T cells [182], suggesting that restoration of thymic function may be achievable, particularly by the mechanisms of caloric restriction in obesity [151].

3. Conclusions and outlook

Decline in immunity with aging is well-established and much of the evidence today supports the notion of an overall impairment of immune functions even with normal "healthy" aging. There is also strong evidence that malnutrition (both under- and over-nutrition) impairs elements of adaptive and innate immunity and that nutrition plays an important role in modulating immune functions. The relationship between malnutrition and infection is an intimate one, and it is often assumed that this is because of impaired immune function. There is good evidence of links, particularly between micronutrient deficiencies and immune impairment and obesity and a number of infections. Much of the evidence is suggestive that the size and function of the thymus is affected in the same way both by age and malnutrition; a fact further authenticating the importance of nutrition in the context of immune integrity.

Present day nutritional immunology research is mainly centered around studying the mechanisms underlying the modulation of immune responses by nutrients. Using many sophisticated tools, researchers of nutritional immunology try investigate the role of dietary components and their interactions with immunological parameters. The challenge remains to integrate nutritional immunity with age-associated changes to immune status, and to confirm that knowledge gained in one human population is comparable and informative for different populations. Further work is needed to elucidate the underlying mechanisms and how to perform adequate nutritional intervention for immunologic preservation. For this, larger studies on nutritional supplementation need to be launched and the observations of geriatricians integrated with nutritional immunology. There is still a need to study the effects of nutrients on different components of the immune system, because we know that immunity depends on multiple components that react differently to nutrients. Considering the complex nature of nutritional immunology, there is a need to dissect the networks of interactions that define the relationships between nutrition, immune function, infections and genetic background in age-associated changes of immune and inflammatory responses. Special emphasis must be given to find how to reverse and/or delay the onset of immunologic and age-related changes by appropriate dietary modifications and to determine the molecular mechanisms by which nutrients modulate immune cell functions. New methods have to be developed to use the immune response as a biologically meaningful index in determining specific dietary requirements.

The main focus of future nutritional immunology will include 1) studying cellular and molecular mechanisms of age and nutrition-induced changes in immune and inflammatory responses, 2) determination of the efficacy of food components (total calories, lipids, micronutrients such as vitamin E, zinc, flavonoids, and pre- and pro-biotics) on improving the immune function and/or dampening inflammatory responses using various techniques (cell culture, animal models and clinical trials), 3) determination of the efficacy of various food components in the prevention of infectious diseases in animal models, clinical trials and observational studies, 4) determination of the impact of reducing caloric intake on immune response of humans.
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