**Introduction**

Aging is a complex physiologic process that involves a number of biochemical reactions that lead to functional impairment and increased pathology. Aging is also associated with a decline in immune function, known as immunosenescence, that contributes to the increased susceptibility to infection, cancer, and autoimmune diseases observed in old organisms, including humans. Immunosenescence is reflected at the cellular, molecular, and genetic levels, with alterations of gene expression that may be due to a decreased capacity of the immune system to respond to antigenic stimulation, altered cytokine microenvironment, and impairment of both innate and adaptive immunity.

The immune system exhibits increased deterioration with age and undergoes significant age-related changes. In this context, recent advances have focused on natural killer (NK) and natural killer T (NKT) cells, which have been suggested as a bridge between the innate response and the adaptive system. NK and NKT cells with cytotoxic activity directly kill the target cells and play a pivotal role in providing signals to initiate the adaptive immune response. Age-related alterations of the cellular components of innate immunity might therefore be involved in the impairment of adaptive immunity observed in the elderly. Age is associated with an increased morbidity to virus infections as well as delay in the clearance of symptoms after infection, which may cause changes in the innate response to the production of and response to interferon (IFN) and cytotoxicity to NK cells. Speziali et al. reported that age-associated changes in CD16^+IFN-γ^+ NK cells may play a role in controlling (reducing) parasitic infection intensity in the elderly in Brazil. As for the other diseases like depressive symptoms, Tsuboi et al. showed that well-preserved NK cell cytotoxicity and increased NK numbers have a significant association with low depressive symptoms and more life satisfaction in elderly women.

More and more aging-related diseases are reported (Table 1), e.g., Parkinson’s disease, osteoporosis, cancers, and Alzheimer’s disease (AD). Among these, AD, with the contribution of immunologic factors in the etiopathogenesis, is increasingly noted. In order to clarify the altered lymphocyte distribution in AD, Richartz-Salzburger et al. investigated a sample
of 43 patients with AD and of 34 healthy age-matched controls for the distribution of the T, B, and NK cell subsets. The results demonstrated a significant decrease in numbers of T (CD3⁺ and CD8⁺) and B (CD19⁺) cells in AD, sustaining the hypothesis of a general decline of immune activity in AD. The number of NK (CD16⁺, CD56⁺) cells was not altered. However, other studies found decreased circulating concentrations of CD8⁺ lymphocytes and NK cell activity in AD patients. Thus, there is a putative association with premature immunosenescence and possible pathogenetic implications in AD.

In this review, we report on the role played by NK and NKT cells during aging and the changes that lead to healthy aging and longevity. Finally, potential therapeutic strategies and nutrients in regulating NK/NKT cells and aging are also discussed.

**NK/NKT Cells and Aging**

**NK cells**

NK cells, a kind of antigen-nonspecific lymphocytes, play an important role in anti-viral immunity. NK cells kill abnormal cells and orchestrate subsequent adaptive T and B lymphocyte immune responses. NK activation is controlled by a balance of signals from stimulatory receptors and major histocompatibility complex (MHC) class I-specific inhibitory receptors. When NK cells respond to virus-infected cells and cancer cells, they will express down-regulated MHC class I molecules and up-regulated NK stimulatory receptor signals. The most important MHC class I-specific receptors, CD94/NKG2 and KIR, are expressed by most NK cells and a minority of T cells. CD94/NKG2 receptors are heterodimers composed of an invariant CD94 chain that is paired with NKG2A, NKG2C, NKG2E, and possibly other NKG2 family members, and NKG2 members are either inhibitory (e.g., NKG2A) or stimulatory (e.g., NKG2C and NKG2E).

The most characteristic function of NK cells is non-MHC restricted killing of target cells, such as tumor, and thus NK cells are important for maintaining health. The influence of aging to NK cells attributed to various factors, such as decreased responsiveness to the positive modulation with interleukin (IL)-2, could explain the high frequency of cancer and infectious diseases with aging. Low NK activity was found to be a good predictor of morbidity; the diminution of NK activity with aging is a putative association with premature immunosenescence and possible pathogenetic implications in AD.

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**Table 1.** *Aging-related diseases*

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Etiology</th>
<th>Pathology</th>
<th>Semiology</th>
<th>Therapeutics</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Genetic defect, environmental factors, etc.</td>
<td>β-amyloid plaque formation results in loss of cellular connections with other neurons and provocation of neuronal death</td>
<td>Thinking, understanding and decision-making impairment, etc.</td>
<td>There are no known treatments or medications for curing this disease; estrogen replacement may slow the decline in memory</td>
<td>15-17</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Genetic defect, environmental factors, etc.</td>
<td>Cell degeneration and loss of pigmented neurons</td>
<td>Slowing of emotional and voluntary movements, muscular rigidity, postural abnormality, and tremors</td>
<td>There are no known treatments or medications for curing this disease; levodopa (L-DOPA) treatment may reduce the progression</td>
<td>11, 12</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Genetic defect, environmental factors, etc.</td>
<td>Thinning and weakening of bones, especially bones in the hip, spine, and wrist</td>
<td>Thinning and weakening of bones to the point where they break</td>
<td>Preventable with a diet rich in calcium and vitamin D, and weight-bearing exercise; hormone replacement therapy</td>
<td>13</td>
</tr>
<tr>
<td>Cancers</td>
<td>Genetic defect, carcinogenic factors, etc.</td>
<td>Uncontrolled cancer cell division and spread</td>
<td>Increased occurrence of many cancers with age, resulting in death and morbidity</td>
<td>Surgery, chemotherapy, radiotherapy, gene therapy, etc.</td>
<td>14</td>
</tr>
</tbody>
</table>
aging has been reported in both experimental animals and humans\textsuperscript{24}.

**NKT Cells**

NKT cells are a subset of regulatory lymphocytes that co-express cell surface receptors characteristic of both T lymphocytes (e.g., CD3, \(\alpha/\beta\) T-cell receptor [TCR]) and NK cells (e.g., CD56, NK1.1)\textsuperscript{25}. NKT (CD3\(^+\)CD56\(^+\)) cells have a very limited TCR repertoire, with a V\(\alpha 14\)–\(\alpha 28\) V\(\alpha\) chain and V\(\beta\) chains skewed to use of V\(\beta 8.2, V\beta 7,\) and V\(\beta 2\)\textsuperscript{15,25}. The activation of NKT cells is restricted to the MHC-like molecule CD1d. Although the natural ligand for the receptor is not known, the receptor can be detected by the binding of CD1d tetramers loaded with a synthetic glycolipid, \(\alpha\)-galactosylceramide (\(\alpha\)-Gal-Cer)\textsuperscript{26}. After engagement of the TCR with \(\alpha\)-Gal-Cer, the cells rapidly secrete large amounts of IL-4 and IFN-\(\gamma\), suggesting that these cells play an important role in regulating immune responses\textsuperscript{27}. The contribution of NKT cells to some microbial infections, such as *Listeria monocytogenes*, *Toxoplasma gondii* and *Cryptococcus neoformans*, which are controlled by cell-mediated immunity, has been reported\textsuperscript{28–30}. Blackstock et al.\textsuperscript{31} demonstrated that age-related resistance of C57BL/6 mice to *C. neoformans* is dependent on maturation of NKT cells. The possible role for NKT cells was determined by passive transfer of thymocytes from 10-week-old mice (containing mature NKT cells) or 2-week-old mice (containing immature NKT cells) to 6-week-old mice\textsuperscript{31}. Although the proportion of NKT cells was rather low, they were tightly associated with aging and other T cells. It has been shown that the ratio of CD4 to CD8 tends to decrease among NKT (i.e., NK1.1\(^+\)CD3\(^{int}\)) cells and T cells at all intraepithelial sites in the intestine with age\textsuperscript{32}.

**Aging**

The genetic theory of aging holds that several genes are involved in longevity\textsuperscript{33}. Up to 25\% of the variation in human life span is heritable\textsuperscript{34}. In the several models that are used to study aging, such as nematode worms (*Caenorhabditis elegans*), fruit flies (*Drosophila*) and mice, genetic mutations can increase the life span as much as sixfold, apparently by slowing the aging process\textsuperscript{35}. The exceptional longevity or life beyond the age of 90 years appears to have an even stronger genetic basis\textsuperscript{36}, which can explain why centenarians and near-centenarians tend to cluster in families.

Some “longevity genes” may be involved in prolonging the human life span, especially those related to the inflammatory status, in particular pro-inflammatory cytokines (IL-1, IL-6, and TNF-\(\alpha\)), anti-inflammatory cytokines (IL-10), and Hsp70\textsuperscript{37}. Some other genes linked to oxidative stress (PON1)\textsuperscript{38} or IGF1/insulin pathway\textsuperscript{37} seem related to the longevity, as well as the genes involved in the regulation of DNA repair, nuclear structure, and telomere length\textsuperscript{33}. However, the genes related to inflammation seem particularly relevant taking into account that the innate immunity is more involved during inflammation, and a chronic inflammatory status (called inflamm-aging) appears to be the major component of the most common age-related diseases, including cardiovascular diseases and infections\textsuperscript{37}.

During aging, T cells acquire expression of molecules usually associated with NK cells, including CD16, CD56, CD57, and CD94. T cells with NK-associated markers are found in much smaller numbers in young adults and are not identical to the regulatory NKT cells that express the highly restricted V\(\alpha 24\) TCR\textsuperscript{39}. Studies have shown that T cells with NK-associated markers from elderly subjects are hyporesponsive to antigen stimulation\textsuperscript{39}. An article reported that the number of extrathymic T cells surpasses thymus-derived T cells in various immune organs of mice with aging\textsuperscript{40}. Congenitally athymic nude mice carry only a small number of lymphocytes when young (i.e., up to 10 weeks) but acquire a considerable number of lymphocytes (i.e., extrathymic T cells) in the liver and at the intraepithelial site of the intestine when old\textsuperscript{41}. This is because of the phenomenon in which extrathymic T cells tend to increase as a function of age\textsuperscript{42}. Ishimoto et al.\textsuperscript{32} reported that in comparison with young mice (4 weeks of age), the number of total lymphocytes yielded by all tested organs was greater in adult (9 weeks) and old (40 weeks) mice. Their results showed that both the liver and intraepithelial sites in the intestine carry many extrathymic T cells, the distribution of lymphocyte subsets and their age-associated variation are site-specific\textsuperscript{32}. The major lymphocyte subset that expanded with age was IL-2 receptor (IL-2R) \(\beta\)\(^+\)CD3\(^{int}\) cells (50\% of them expressed NK1.1) in the liver, whereas it was CD3\(^+\)IL-2R\(\beta\)\(^−\)NK1.1\(^−\) cells at all intraepithelial sites in the intestine.

According to previous reports\textsuperscript{33}, certain age-related baseline differences in the composition of the peripheral lymphocyte pool were observed, including higher numbers of NK cells and lower numbers of B cells and CD45RA\(^+\)CD4\(^+\) T cells in the elderly. Sfikakis et al.\textsuperscript{44} investigated the potential role of the adult thymus in
T-cell homeostasis subsequent to lymphopenia, and they found that the adult patients \((n=21; \text{mean age, 30 years; range, 18–49})\) had higher baseline numbers of B and lower numbers of NK cells than elderly patients \((n=15; \text{mean age, 79 years; range 70–91})\), while total T-cell numbers did not differ. However in advanced age, although peripheral homeostatic pathways appear intact, regeneration of the naive repertoire is incomplete\(^44\).

The Correlation Between NK/NKT Cells and Aging

**The role of NK/NKT cells in aging**

The ability of NK cells to exert cytotoxic function is well preserved in our life until old age. High NK activity is a prerequisite of good health and longevity\(^45\). Low NK activity in the elderly may be associated with infectious diseases, such as influenza, the most important of all infectious diseases\(^46\). The role of NK cells as one of the immune mechanisms engaged in the protection and recovery from the infectious diseases as well as vaccine efficacy in older people have been linked to their health status\(^47\). Human NK cells recognize the influenza virus hemagglutinins which can enhance NK cytotoxic activity *in vitro*\(^48\). Even in volunteers injected with the inactivated influenza virus vaccine, an increase in NK cytotoxic activity has been reported after vaccination\(^49,50\).

T-cell functions and NK activity seem to be the immune responses most affected by aging. De la Fuente et al.\(^51\) have studied the changes of several immune functions with age in rats of both sexes. The results showed that an age-related decrease was found in lymphocyte chemotaxis, T lymphoproliferative response to the mitogen ConA, IL-2 release, and NK activity of cells from axillary nodes and spleen of male and female rats, as well as of females ovariectomized at 12 months of age have been studied. The data showed that a certain degree of immunosenescence takes place with age in rats, with males being less immunocompetent than intact age-matched females, but showing an immune response similar to that of ovariectomized animals\(^51\).

**Receptors of NK/NKT cells in aging**

Aging of the immune system is characterized by the contraction of the lymphocyte repertoire in the peripheral circulation. TCR repertoire contraction is a likely cause of the decline in immunity with chronologic age as evidenced by the increased morbidity and mortality to common and new infections, and the low rates of protective responses to vaccination in the elderly. *In vitro* studies have demonstrated that senescent (or pre-senescent) T cells and T cells of the aged express unusually high densities of the killer cell immunoglobulin-like receptors (KIRs), the most diverse NK receptors (NKR), on NK cells. NKR comprise a superfamily of C-type lectin and Ig-like receptors that trigger either an activating or inhibitory signal\(^52\). Several kinds of NKR that usually found on aging T cells and on T cells of the aged are CD16 (i.e., FcγRIII), CD56 (i.e., NCAM), CD94, CD161 (i.e., NKRPA1), NKG2D, and members of the KIR family\(^53\). CD16, CD56, and KIRs are Ig-like NKR, whereas CD94, NKG2D, and CD161 are C-type lectin NKR.

NK cells are essential for healthy aging, and their activation is controlled by MHC class I-specific CD94/ NKG2 receptors and KIRs. Lutz et al.\(^54\) reported that an age-related decrease was seen in CD94 and NKG2A expression and a reciprocal age-related increase in KIR expression. However, neither NK activation nor cytotoxic granule release was mediated by CD16 with age. NKG2A expression also declined with age on CD56+ T cells. The distinct roles of CD94/NKG2A and KIR receptors suggest that shifting MHC class I receptor expression patterns reflect age-related changes in NK cell and CD56+ T cell turnover and function *in vivo*\(^54\).

KIRs, which constitute the largest family of human NKR with multiple inhibitory and activating members, are commonly found on human NK cells, γδT cells, and CD8 T cells\(^55,56\). The inhibitory receptors bind classical human histocompatibility leukocyte antigen (HLA) class I molecules and mediate “missing self” recognition. The physiological ligands for the activating KIR are unknown. The KIR family displays a high degree of polymorphism; KIR haplotypes contain between five and 12 highly homologous KIR genes\(^57\), and up to nine alleles for individual KIR genes\(^58\). The literature shows that KIRs are associated with several diseases; KIR3DS1 and its proposed ligand HLA-Bw4 confer resistance to the development of full-onset AIDS in HIV-infected individuals\(^59\), and the KIR2DS2 gene is associated with various autoimmune conditions, such as psoriatic arthritis\(^60\), diabetes\(^61\), and vascular complications in rheumatoid arthritis\(^62\).

Aging is accompanied by deficits in both innate immunity (NK function) and adaptive immunity (T-cell function)\(^62\). Therefore, NKR induction on aging T cells
confers the advantage for the integration of innate antigen-nonspecific immunity and adaptive/acquired antigen-specific immunity. NKR expression on T cells can have profound impact on immunity. Abedin et al.63 showed that T cells are programmed to express NKRs/KIRs, and T-cell clonal lineages express a variety of NKRs toward the end stages of their replicative lifespan. NKRs/KIRs comprise a diverse superfamily of receptors whose induction in aging T cells is an adaptational diversification of the immune repertoire, and the functional diversity of these unusual NK-like T cells is central to the creative development of new strategies to enhance protective immunity in the aged53,63. As shown in Table 2, robust antigen-specific immune responses are attributed to a large pool of polyclonal (TCR-diverse) T cells. TCR diversity is shaped by selection and maturation processes in the thymus, the extent of diversity being largely determined at birth. With the postnatal involution of the thymus and a lifetime exposure to antigens, the naive compartment becomes restricted and the memory compartment expands. With advancing age, the T-cell repertoire becomes populated with highly oligoclonal, long-lived T cells, a majority of which have lost expression of CD28. Such CD28null T cells have limited or no proliferative capacity but are functionally active53. Despite identical TCRs, these T cells of the aged express a diversity of NKRs, exemplified by members of the KIR family55, indicating functional diverse subsets of cytotoxic KIR T cells (diverse subsets of T cells with different NKR/KIR adornment).

**Cytokines production**

NK and NKT cells play a role in directing the differentiation pathway (T helper 1 [Th1] vs. T helper 2 [Th2]) followed by CD4+ T cells after antigenic stimulation, thus establishing a link between the innate and adaptive immunity. It was thought that NK cells secreted IFN-γ and contributed to Th1 development, while NKT cells secreted IL-4 and contributed to Th2 development. However, later reports showed that NKT cells can secrete both IL-4 and IFN-γ and contribute to the development of the cell-mediated immune response31,64. van Bergen et al.55 reported that the KIR+ CD4 cells, in the absence of the Th2 marker CCR4, produced mainly IFN-γ and little IL-4, IL-10 or IL-17 upon TCR triggering. Moreover, the KIR-expressing CD4 T cells are predominantly HLA class II-restricted effector memory Th1 cells with significant expression of KIR55.

The literature indicates that T-cell functions are the most impaired with age, followed by NK cell activity65. Biologically, the age-related decrease of T-cell proliferation, IL-2 production, and cytotoxicity could be related to the low response of old animals to infections or malignant cells24,66–68. Mariani et al.69 showed that the ability of NK cells to synthesize chemotactic cytokines upon stimulation by IL-12/IL-2, or to express the corresponding chemokine receptors in healthy human with the age over 90 years are still maintained. However, most investigations found that functional competence of individual human NK cells declines with age32,70. NK cells of aged people exhibited a diminished production of IFN-γ and chemokines in response to IL-2 and IL-670. Albright et al.71 also found that severe impairment in the production of mRNA transcripts representing several cytokines in NK/lymphokine-activated killer cells of aged mouse.

Age-related changes in leukocyte subsets and impairment in lymphocyte functions, especially in

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**Table 2. Comparison of adaptational diversification of the immune repertoire (TCR-clonal NKR/KIR-diverse T cells) in different age groups**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adaptational diversification</th>
<th>Expression of surface molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Mostly naive, TCR-diverse</td>
<td>CD28: highly expressed</td>
</tr>
<tr>
<td></td>
<td>Polyclonal CD28*</td>
<td>KIR3DL2, KIR2DL4, CD16/CD56: not expressed</td>
</tr>
<tr>
<td></td>
<td>Highly proliferative</td>
<td>KIR-a/b/c, CD161, NKG2, KLRG1: not expressed</td>
</tr>
<tr>
<td>Young adult</td>
<td>Reduced naive CD28*</td>
<td>CD28: moderately expressed</td>
</tr>
<tr>
<td></td>
<td>Memory CD28null and CD28*</td>
<td>KIR3DL2, KIR2DL4, CD16/CD56: moderately expressed</td>
</tr>
<tr>
<td></td>
<td>Oligoclonal NKR/CD28null</td>
<td>KIR-a/b/c, CD161, NKG2, KLRG1: not expressed</td>
</tr>
<tr>
<td>Old adult</td>
<td>Limited naive</td>
<td>CD28: lowly expressed</td>
</tr>
<tr>
<td></td>
<td>Memory CD28null and CD28*</td>
<td>KIR3DL2, KIR2DL4, CD16/CD56: highly expressed</td>
</tr>
<tr>
<td></td>
<td>Clonal senescent NK-like CD28null</td>
<td>KIR-a/b/c, CD161, NKG2, KLRG1: highly expressed</td>
</tr>
</tbody>
</table>
T-cell activities, have been observed\textsuperscript{72}. In old age, a decrease in the lymphoproliferative capacity, IL-2 production, and NK activity has been found\textsuperscript{73}, while pro-inflammatory cytokines such as TNF-\textalpha increased\textsuperscript{74}. A study indicated that old mice (72 ± 2 weeks) showed a decrease in proliferation, NK activity, and IL-2 release, and increase in TNF-\textalpha; whereas in very old mice (128 ± 2 weeks), these functions were more similar to those in the adults (24 ± 2 weeks)\textsuperscript{75}.

Potential Strategies or Nutrients in Anti-aging by Regulating NK/NKT Cells

\textbf{Exercise}

It is well accepted that aging is characterized by a diminished ability to respond to stress\textsuperscript{76}. Proper exercises help to relax and eliminate stress-related physiologic and psychologic diseases. Consistent reports of the positive relationship between regular physical activity and immunosenescence have generated much excitement in the field of exercise immunology\textsuperscript{77}. Athletes have been found to have stronger immune function, including the cytotoxicity of NK cells and proliferative response of phytohemagglutinin-induced lymphocytes, as well as a lower prevalence and mortality from cancers\textsuperscript{78}. However, athletes are also at risk for what is known as the overtraining syndrome. Prolonged heavy exertion lasting beyond normal limits adversely affects immunity, leading to increased susceptibility to upper respiratory tract infections, gastroenteritis, leptospirosis, herpes simplex, and viral hepatitis\textsuperscript{79}. Woods et al.\textsuperscript{80} reported that 6 months of supervised exercise training can lead to nominal increases in some measures of immune function; NK cell cytolysis versus K562 cells tended to increase ($p < 0.1$) in the exercise group of previously sedentary elderly subjects. However, data from similar studies conducted failed to reach a statistical significance because of small sample sizes and short exercise periods. Therefore, larger samples sizes and longer intervention periods (i.e., 1 year) would be needed to demonstrate the statistical significance in NK response and aging, respectively. Moreover, studies free from limitations (larger sample size, true sedentary control group, controlled for seasonal variation, etc.) need to be carried out in order to definitively determine the effects of exercise training on immune measures among the elderly and younger people.

\textbf{Nutrients}

It has been reported that people consuming a Mediterranean diet, including micronutrients like vitamins, essential minerals and other compounds required in small amounts for normal metabolism, display a better health status with higher probability to escape some age-related diseases and to reach healthy longevity\textsuperscript{82}. The deficiency of macro- and micronutrients in aging is considered to be closely related to global impairments of immune functions, metabolic harmony, and antioxidant defence by external noxae with subsequent appearance of age-related diseases\textsuperscript{82}. Moreover, nutritional factors may play a pivotal role for healthy aging in which the combination of genetic factors is fundamental in order to better understand human longevity. Several potential nutrients are listed as follows.

1. \textbf{Melatonin}

Many hormones that are associated with maintenance of immune function also decline with advancing age and the interrelationship between the endocrine system and the immune system is considered to be of crucial importance in normal human physiology and in mediating age-associated degenerative diseases\textsuperscript{83}. The decline in the production of a number of hormones associated with aging, such as growth hormone, estrogen, and dehydroepiandrosterone, as well as of the pineal substance melatonin (N-acetyl-5-methoxytryptamine), has been proposed to play a significant role in contributing to immunosenescence\textsuperscript{83}. Melatonin has been demonstrated to bear a general immunoenhancing effect in many animal species as well as in humans\textsuperscript{84}. Melatonin has significant immunomodulatory roles in immunocompromised states; for example, Maestroni et al.\textsuperscript{85} first showed that inhibition of melatonin synthesis causes inhibition of cellular and humoral responses in mice. Melatonin is formed mainly in the pineal gland of most mammals\textsuperscript{86}; however, administration of exogenous melatonin is also important in both innate and cellular immunity. The chronic administration of melatonin augmented the spontaneous NK cell activity and also the circulating number of NK cells\textsuperscript{87}. The increased NK cell number brought about by melatonin administration was attributed partly to the increased production of cytokines by melatonin-stimulated T helper cells. IL-2, IL-6, IL-12 and IFN-\gamma have all been suggested as the possible cytokines that mediate melatonin-induced increase of NK cell number\textsuperscript{88}. Moreover, melatonin is a natural antioxidant
which exerts its many physiologic actions (e.g., scavenging of free radicals, interaction with cytosol proteins like calmodulin) by acting on membrane and nuclear receptors, the cause of significant anti-aging activities.

2. Zinc
Zinc is one of the most important trace elements in our bodies, and deficiencies in zinc also accompany many diseases, such as gastrointestinal disorders, renal disease, sickle cell anemia, alcoholism, some cancer types, AIDS, and burns. More than 300 enzymes require of zinc for the biological function, although its presence in nature does not exceed 0.02%. The major characteristics of zinc include a highly concentrated charge and rapid exchange of reactions, which enable zinc to play a major biological role as a catalyst. Zinc is present in “zinc finger domains” of many proteins, peptides, enzymes, hormones, transcriptional factors, and cytokines, which act in maintaining body homeostasis. Zinc is required to maintain enzymatic activity of inducible nitric oxide synthase. Zinc regulates G0/G1 phase of cell cycle by means of cyclin/CDK complexes in a dose dependent manner. Zinc also regulates the balance between gene expression of matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs). The expression of MMP genes is under the control of the TIMP gene products, α2 macroglobulin and 13-amyloid precursor protein, which encode zinccfinger motifs. Alterations in the balance between MMPs and TIMPs or α2 macroglobulin have been observed in cancer, infections, and aging.

The relevance of zinc is strictly linked to special proteins called metallothioneins (MTs). MT acts as an antioxidant which induces the transfer of zinc from MT-binding sites to other lower affinity proteins through the reaction of oxido-reduction. The redox properties of MTs and their effect on zinc in the clusters are crucial for the protective role of MTs in transient stress, as it may occur in young adult age. In contrast, their role is harmful in aging because of the stress-like condition and the constant oxidative damage. MT sequesters zinc and prevents the transfer to other proteins during aging. Abnormal high levels of MT and low zinc ion bioavailability are observed in syndromes of accelerated aging such as Down syndrome. Moreover, low zinc ion bioavailability is a risk factor for infection relapses in the elderly, who display decreased immune functions. Decreased chemotaxis by neutrophils and monocytes and impairment of cell-mediated immune responses, including thymic endocrine activity, NK activity and cytokine production, were observed with zinc-deprived diets. MTs play a pivotal role in zinc-related cell homeostasis because of their high affinity for this trace element, which is in turn relevant against oxidative stress and for the efficiency of the entire immune system, including NK cell activity. In aging, the liver extrathymic NK activity is also reduced because of the major quota of zinc ions bound with liver MTs in immunosuppressive persons.

Zinc–gene interaction also affects some relevant cytokines (IL-6 and TNF-α) and Hsp70 in aging, successful aging (nonagenarians) and in some age-related diseases (such as atherosclerosis and infections). Some regulatory or inhibitory transcription factors (Egr-1, Sp1, A20), which, together with other zinc-regulated transcription factors (NF-κB, STAT, HSF-1), are involved in the regulation of gene transcription of pro-inflammatory cytokines (IL-6 and TNF-α) and Hsp70 during inflammation and in the presence of antigenic stimuli. Therefore, zinc finger proteins are indispensable for transducing signals from the cytokine receptors into expression of response genes, and zinc deficiency in experimental animals or during a chronic inflammatory status, such as in aging, severe infections, or cardiovascular diseases.

An overall estimation of all experimental and clinical observations on the biological role of zinc seems to infer that zinc supply may be useful in reducing infection relapse, restoring immune efficiency in aging, and preventing age-related degenerative diseases. Zinc is not stored in the body, and excess intake results in reduced absorption and increased excretion. Nevertheless, there are documented cases of acute and chronic zinc poisoning.

**Rice bran (MGN-3/Biobran)**
MGN-3, a biological response modifier, is an arabinoxylan with a xylose in its main chain and an arabinose polymer in its side chain. It is derived from rice bran that has been enzymatically modified by an extract of the mushroom *Hyphomycetes mycelia*. An *in vitro* investigation revealed increased tumor necrosis factor-α and IFN-γ production by peripheral blood lymphocytes treated with MGN-3. MGN-3 was found to enhance anti-CD95 antibody-induced apoptosis in a human leukemic cell line. In addition, it has been studied in a limited number of patients with HIV disease or cancer, with improvement in NK cell function and disease activity over time. Animal model studies...
have reported increased NK cell activity in aged mice supplemented with rice bran (MGN-3/Biobran)\textsuperscript{111,112}. Further studies on NK function in aged humans are needed to ascertain the benefits of this biological response modifier on age.

**Conclusion**

Aging is a universal phenomenon that affects nearly all animal species. According to Helfand et al.\textsuperscript{113}, aging can be described as: (1) an inevitable consequence of being a multicellular organism; (2) being associated with a random, passive decline in function; (3) leading to a global loss of homeostasis over time; and (4) being associated with increasing mortality. This review article aimed to provide a new insight into NK/NKT activity with age progression in relation to longevity. Also, a rationale was provided for possible strategies and nutrient supplementations in subjects in order to keep the immune response under control for healthy aging and longevity.

**Acknowledgments**

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