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Effects of Immunoscenescence on Aging

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Abstract: Aging is an inevitable process as a result of which our body undergoes innumerable alterations, including our immune system. The gradual failure of the immune system to function efficiently with advancement in age is known as immunosenescence. It is an unquestionable fact that ageing is accompanied by alteration of the immune system, including reduced numbers of naive T cells, increased senescent or exhausted T cells and dysregulation of monocyte, neutrophil and natural killer cell function. Eventually these changes cause increased risk of infection, reduced immune memory, reduced immune tolerance and immune surveillance, with huge effects on the wellbeing in advanced age. This makes our body susceptible to various diseases and infections. Of late, we have come to know that the rate of deterioration of the immune system is flexible and can be influenced by pharmacological interventions. This review focuses on the impact of aging on immune system and therapeutic strategies that have been displayed to restore immune functioning in aged individuals.

Keywords: Aging, Immunosenescence, Immune system, T cells, Natural killer cell, Monocyte, Neutrophil, Dendritic cells, Macrophages

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Introduction

As we grow older our bodies go through a range of changes. One of the impactful transformations that occur with aging is the gradual decline, in our immune system, commonly known as "immunosenescence." Immunosenescence refers to the weakening of our function as we age, which makes us more susceptible to infections, illnesses and other health related complications. As our global population continues to age, understanding and combating immunosenescence has become an urgent and pivotal challenge in the field of immunology and gerontology. The desire to counteract the effects of aging on the system has sparked a realm of research and exploration, in pharmacology. This involves the potential to extend lifespan and enhance the quality of life for older individuals.

The main objective of this review is to explore and shed light on the nature of immunosenescence. It aims to provide insights,

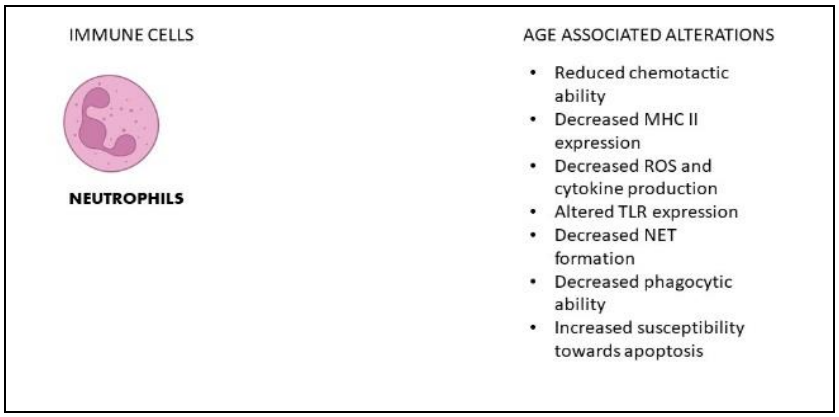

Fig. 1: Effect of aging on Neutrophils.

into the underlying mechanisms behind it while also discussing its implications and potential interventions. By exploring the network of immunosenescence, our aim is to uncover the obstacles it presents while also showcasing potential avenues, for creative solutions that can enhance healthy aging and elevate the well-being of our expanding elderly community. In the pages we will explore the recent advancements and promising opportunities, in the pursuit of reversing the effects of aging on our immune system. These discoveries could potentially revolutionize medicine and usher in an era of healthcare, for older adults.

Immune System

Immunity is the body's defense mechanism against invading pathogenic microorganisms and the range of cells, tissues and organs involved in order to protect our body against infections and diseases is known as immune system. Immunity is of two types, innate immunity and adaptive immunity. Innate immunity is the one which is present since birth and non-specific in nature while the adaptive immunity is the one which acquired during our lifetime as a response to a particular infection or disease and is specific in nature.

Aging and Immunosenescence

Aging is a complex biological process, results in numerous changes in the immune system. These changes can accumulate which eventually leads to a gradual decline in the ability of the immune system to fight off invading pathogen microorganisms and this age associated deterioration of the immune system is known as immunosenescence. Effect of aging on immune system is multi-faceted (Chan *et al*., 2019). Age specific dysregulation of the immune system occurs due to changes in the innate immunity cells and changes in the adaptive immunity cells. Immunosenescence results in the elevated susceptibility to infection, malignancy and autoimmunity, lowered immune surveillance and response to vaccination, as well as impaired wound healing (Busse *et al*., 2010).

Effects of Aging on the Innate Immune System

Neutrophils

These are short lived, active phagocytic cells which form first line of defence against invading microorganisms. These are one of the most abundant circulating leucocytes and usually are the first to reach a site if infection or inflammation. Though there is no significant changes in the number of neutrophils with increasing age, the neutrophils do undergo functional changes (Fig. 1). The changes include lowered chemotaxis, decreased ability to perform phagocytosis (Wenisch *et al*., 2000), dysregulation of TLR, increased apoptosis (Plackett *et al*., 2004), reduction in expression of MHC impaired signalling, impaired cytokine productionand ROS

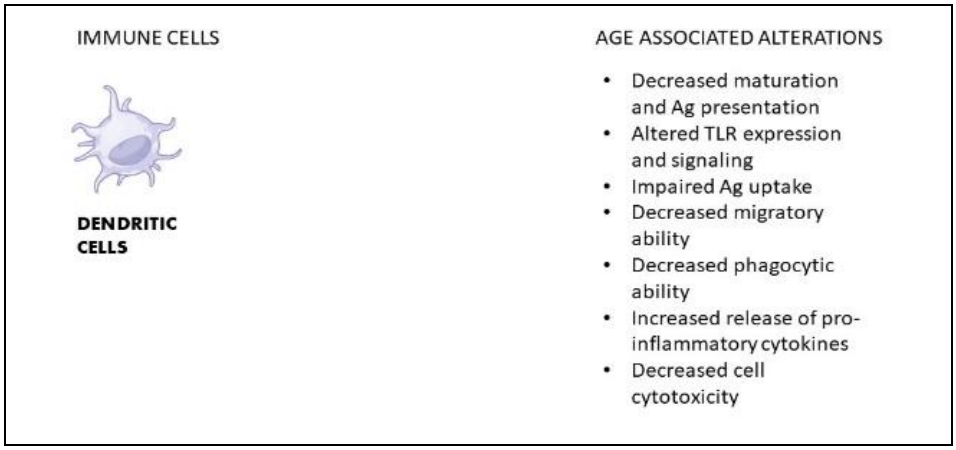

Fig. 2: Effect of aging on Dendritic Cells.

production. In addition, neutrophils of the elderly fail to produce the required amount of neutrophil extracellular traps (NET) which are required for binding and trapping extracellular pathogensto prevent infections (Tseng *et al*., 2012; Hazeldine *et al*., 2014).

Dendritic Cells

These are the professional antigen presenting cells which form a bridge between the innate and adaptive immune system. Few studies show that aging does not change the number of myeloid DCs (mDCs), but the number and function of plasmacytoid DCs get reduced (Shodell *et al*., 2002; Della Bella *et al*., 2007; Jing *et al*., 2009). In the elderly the ability to phagocytose antigens is reduced and alterations in antigen presentation and migratory capacity of DC have affected the adaptive immune response, during which T cells and DCs are involved in immune tolerance, and lead to autoimmune diseases (Pietschmann *et al*., 2000; Agrawal *et al*., 2008,2009).The dendritic cells of the elderly are characterised by decreased maturation and antigen presentation, impaired TLR expression and signalling, increased formation of pro-inflammatory cytokines like IL-6 and TNF-α, impairedproduction of cytokines and impaired signalling (Fig. 2).

Macrophages and Monocytes

Monocytes and macrophages (Fig. 3) are phagocytic cells which play major roles in antigen presentation. Monocytes circulate in the blood and then migrate into tissues where they mature into macrophages.

There is not much significant difference in the proportion of circulating monocytes in the peripheral blood of elderly population compared to that of young population, but there are fewer number of monocytes in the bone marrow of individuals between the age of 80-100 years. This can be due to the increased process of apoptosis and decreased cellularity with advancement in age. As we age, the expression of MHC-II by macrophages gets hampered due to epigenetic alterations and the surface expression of TLR1 and TLR4 gets decreased (Ponnappan *et al*., 2011). The phagocytic ability of macrophages gets reduced along with reduction in the release of reactive oxygen species, such as NO_2 and H_2O_2 (Fig. 3) and lowered secretion of proinflammatory cytokines like TNFα, IL-6 and IL-12 but elevated production of IL-10. Their ability to reach the site of infection gets impaired as a result of which the process of wound healing gets delayed.

Natural Killer Cells

Natural killer (NK) cells are a class of cytotoxic granulocytes (Fig. 4). They are significant in the recognition and killing of virus infected cells. Recent studies displayed that high NK cytotoxicity is associated with longevity and good health, while a low NK function is associated with an increase in morbidity and mortality, and consequently,

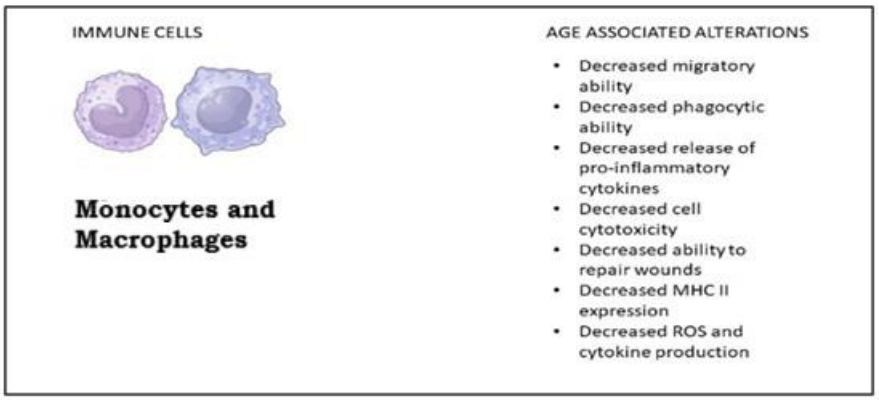

Fig. 3: Effect of aging on Monocytes and Macrophages.

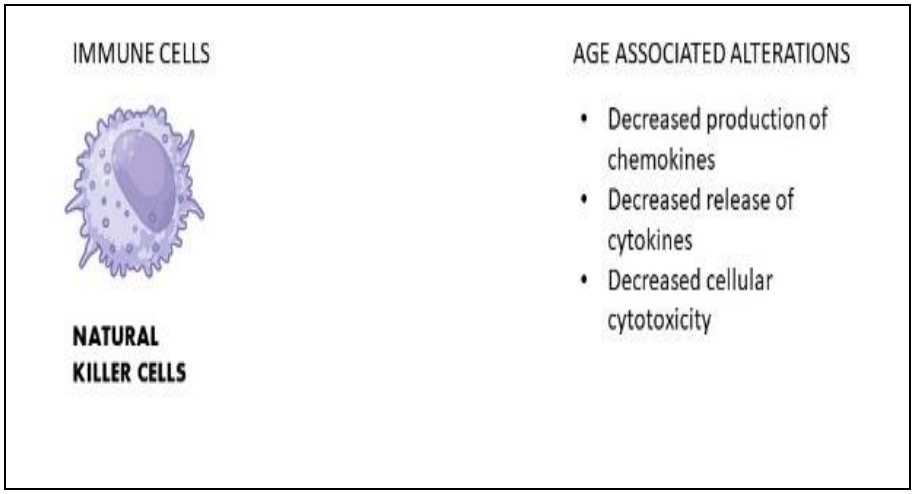

Fig. 4: Effect of aging on Natural Killer Cells.

infections, mechanisms of atherosclerotic and neurodegenerative diseases. NK cells cause cell lysis which in turn leads to the release of perforin and granzymes; resulting in the activation of caspases and induce apoptosis of target cells. During senescence there occurs the decrease of an important lymphokine for the lymphocyte activation processes like the IL-2 and also for the killing of the NK-resistant cell lines in response to IL-2. This decreases the number of normal numbers of nk cells and their functionality. (Borrego *et al*., 1999).

It has been reported that the number of NK cells in the elderly population gets increased but the cells fail to function effectively. Age related alterations in the NK cells include decrease in cellular cytotoxity and reduced signal transduction.The production and secretion of cytokines like MIP1α, RANTES, and IL-8 get reduced while that of IL-2, IFN-γ, TNF and IL-12 gets elevated (Fig. 4) (Dewan *et al*., 2012; Müller and Pawelec, 2014).

Effects of Aging on the Adaptive Immune System

Age Related Changes in Haematopoiesis

The haematopoietic stem cell (HSC) compartment of bone marrow is the site where B precursor cells and T precursor cells originate (Fig. 5). As we age, the HSC compartment undergoes alterations (Geiger *et al*., 2013) such that myeloid production increases while the lymphoid production decreases. Diminished production of IL-7 along with decreased production of stromal cell numbers cause the stromal matrix of aging bone

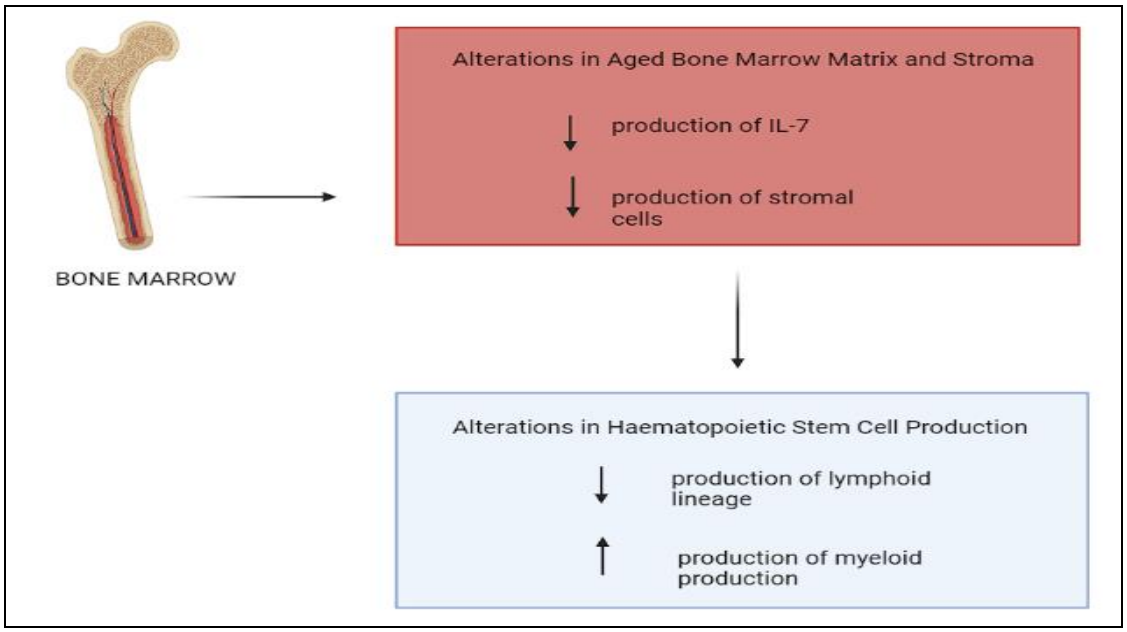

Fig. 5: Age related changes in haematopoiesis.

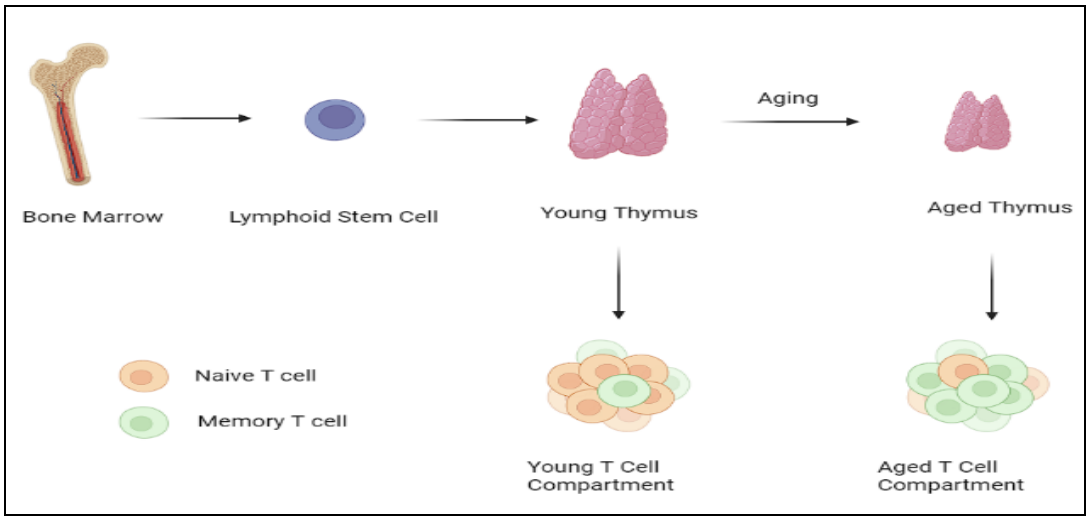

Fig. 6: Thymic Involution.

marrow to experience structural changes which in turn disrupts the HSC production (Pangrazzi *et al*., 2017).

Intrinsic changes in the HSCs and their microenvironment also contribute to the changes within the HSC compartments. Aged HSCs are characterised by age-related accumulation of DNA damage, epigenetic changes, and telomere attrition, accompanied by elevations in intracellular ROS (Dykstra and de Haan, 2008; Warren and Rossi, 2009).

Thymic Involution

Shrinkage of thymus due to aging is known as thymic involution. After puberty, a progressive decrement in the size of the thymus size takes place, areas of active thymopoiesis decrease and the organ decreases in size (Fig. 6)(Aspinall *et al*., 2010). This is brought about by increased levels of thymo-suppressive cytokines, such as leukaemia inhibitory factor, oncostatin M, and IL-6 (Sempowski *et al*., 2000), with a simultaneous decrease of IL-7 secretion. These result in

Fig 7: Effect of aging on T cells.

decreased number of thymic epithelial cells and lead to decreases in thymopoiesis. The contraction of thymic output and consequently failure to replace the circulating naïve T lymphocytes after their activation and differentiation is believed to be a key factor contributing to the development of immunosenescence (Aspinall *et al*., 2010; Müller and Pawelec, 2014).

Thymic involution is characterised by decreased efficiency of T-cell development, by the weakened migratory capacity of naïve T lymphocytes to the periphery and increased number of memory T cells.

Changes in T cells

T cells are the immune cells (Fig. 7) which are producing in the bone marrow and matures in the thymus. Depending on their functionality in the immune response, T cells are categorised into Helper T cells, Cytotoxic T cells and Regulatory T cells. Thymic involution has been associated with the decrease in the naïve T cell output which in turn causes loss of T cell diversity.

Helper T cells

T helper (Th) cell is characterised by the expression of cell surface marker CD4. Th cells are subdivided into Th1, Th2, Th9, Th17, Th22 and follicular helper T cells (Tfh). In aged humans, naive CD4 T cells have the tendency to proliferate and differentiate into effector memory Th9 cells that secrete increased cytokines IL-9 due to the upregulation of the TGFbR3 receptor, leading to higher PU.1, BATF and IRF4 expression. (Hu *et al*., 2019). The single-cell RNA sequencing unveils that aging promotes T cells from naive to effector subtypes, among which Th1 and Th17 cell subsets are dominant. These subgroups are highly correlated with IL-6, IL-27 and IFN, which promotes chronic inflammation and declines immunity partly. (Elyahu *et al*., 2019).

Reduced ICOS expression with aging can restrict the number of Tfhcells. (Choi *et al*., 2011). Elevated proinflammatory cytokines IL-12 with aging leads to the production of Tfh cells (Schmitt *et al*., 2013) and support differentiation of other Th cells, such as Th1 and Th17 cells (Ouyang *et al*., 2011).

Cytotoxic T cells

T cytotoxic (Tc) cell is characterised by the expression of cell surface marker CD8 which destroys intracellular antigens by producing perforins and granzymes (Zahran *et al*., 2022). As we age, Tc cell proliferation gets hampered along with the reduced naive cell marker (CD45RA and CD27), the lymphocyte adhesion molecule SELL (CD62L) and the lymphoid tissue homing chemokine receptor (CCR7), while there is an elevated expression of memory cell marker CD45RO and the senescent marker CD57 (Shin *et al*., 2019). Cytotoxicity of Tc cells is decreased with aging, which reduces the killing effect on virus and increases disease risk in the elderly (Frasca *et al*., 2020).

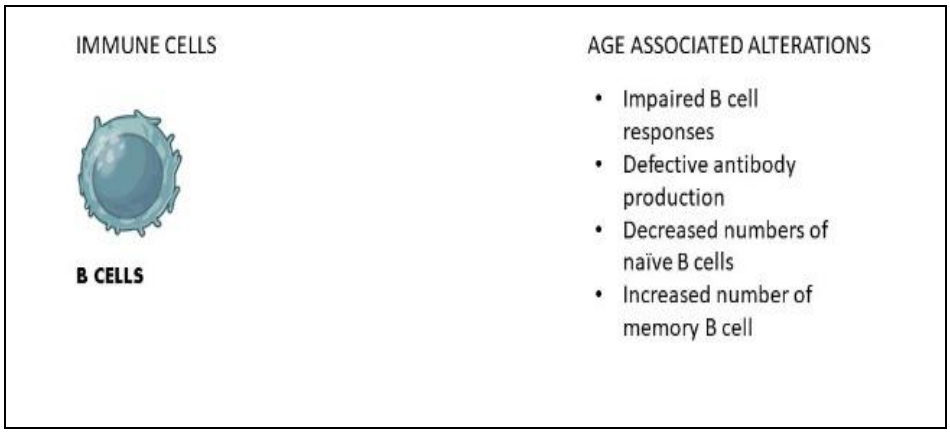

Fig. 8: Effect of aging on B Cells.

Regulatory T cells

Regulatory T cells, also known as Tregs are characterised by the expression of CD25 and FOXP3. In spite of age-related regression of thymus, the number and proportion of Treg cells increase in the elderly (Gregg *et al*., 2005; Lages *et al*., 2008). Treg cells are derived not only from the thymus but also the differentiation of peripheral CD4+T cells and the proliferation of CD45RO+Treg cells (Vukmanovic-Stejic *et al*., 2006).

A few studies have shown that Treg cell function reduces in the elderly, however, the overall data suggest that Treg function remains the same or even increases during aging, which is consistent with the fact that older individuals are more susceptible to infection and malignant tumors, while they are likely to develop autoimmune diseases due to Treg cell dysfunction (Jagger *et al*., 2014).

Changes in B Cells

The main function of the B cells (Fig. 8) is to produce antibodies as a response to infection caused by an invading microorganism (Tedder *et al*., 1997; Gitlin and Nussenzweig 2015). As we age, the B cells undergo numerous alteration which includes weakening of B cell responses and defective antibody production which are mirrored in the reduced ability of aged B cells to effectively respond against viruses and bacteria (Ademokun *et al*., 2010; Visentini *et al*., 2011; Buffa *et al*., 2013).

As a matter of fact, humoral immunity undergoes both quantitative and qualitative alterations (Colonna-Romano *et al*., 2008). The reduced function of B cells was thought being due to scarcity of helper T function in T-dependent responses while there are functions of B cells which are T-independent; like the response to the polysaccharide, which is pivotal for antibacterial protection and that seems to be inefficient as well (Antonaci *et al*., 1984).

Immunosenesence alters the number of B cells in the elderly such that there are reduced production of IgM and IgD (M and D type immunoglobulins) certainly associated with the transition from naive cells to memory B cells area (Weksler *et al*., 2000). On the contrary, there is an elevation in the production of IgG (G type immunoglobulins), especially of IgG1, IgG2 and IgG3; the level of IgA is also elevated (Paganelli *et al*., 1992).

The reduced number of plasma cells in the elderly bone (Pritz *et al*., 2015) causes a lack of antibody production, a reduced ability to respond to viruses and bacteria (Buffa *et al*., 2013) and an altered response to vaccines against B hepatitis virus (Rosenberg *et al*., 2013).

Pharmacological Interventions to Reduce Immunesenescence

Caloric Restriction Mimetics

Calorie restriction mimetics (CRM), also known as energy restriction mimetics, are a hypothetical

class of dietary supplements or drug candidates that would mimic the substantial anti-aging effects that calorie restriction (CR) has on many laboratory animals and humans. Although increasing lifespan and improving health in old age is a desire for most of us, a lifetime commitment to cut down on calorie diet is difficult to implement at a population level. As a result, CR mimetics are taken into consideration and several have already been identified including Resveratrol (SIRT1 activator), Metformin (AMP kinase activator) and Rapamycin (mTOR inhibitor).

Resveratrol: A polyphenolic sirtuin activator (De la Lastra and Villegas, 2005) which has been shown to increase lifespan in numerous species, occurs naturally in various plants including red grapes, peanuts and berries. Although there is not much studies done on the impact of resveratrol on immunity *in vivo*, several *in vitro* studies have demonstrated immune modulating effects, these include a suppressive effect of resveratrol on neutrophil chemotaxis, superoxide generation (Cavallaro *et al*., 2003), T cell proliferation and cytokine production (Gao *et al*., 2001) and an enhancement of NK cell cytotoxicity (Lu and Chen, 2010). Resveratrol's immunomodulating properties are dose dependent manner, with low concentrations exerting a positive effect while higher concentrations exerting a negative effect (Falchetti *et al*., 2001). Additionally, anti-inflammatory effects of resveratrol have been reported in animal studies (Das and Das, 2007; Tung *et al*., 2015). Another example of resveratrol as an anti-inflammatory agent has been mentioned in a study displaying that the long-term treatment with resveratrol significantly attenuated the development of senescence-associated secretory phenotype (SASP) in senescent fibroblasts; reducing the release of proinflammatory cytokines (Pitozzi *et al*., 2013) by modulation of mRNA splicing (Latorre *et al*., 2017). Resveratrol is inexpensive and commercially available but studies in healthy humans are limited (Gualdoni *et al*., 2014).

Rapamycin: It is a mTOR inhibitor, which mimics the effects of CR. Decreased signalling through mTOR has been associated with increased longevity in invertebrates (Powers *et al*., 2006), and mammalian species (Harrison *et al*., 2009). Rapamycin is used clinically as an immune suppressant in transplant patients and mTOR mediated immunosuppression is mediated by modulation of effector and regulatory CD4 T cell subsets (Araki *et al*., 2011). To date there has been one placebo-controlled trial in humans that has used low doses of a m-TOR inhibitor (RAD001) given daily for 6 weeks before the influenza vaccination in older adults. The treatment was shown to increase the antibody response by 20% for 2 out of 3 strains (Mannick *et al*., 2014) with few side effects. This drug may have benefits for immunity in old age as well as broader positive health effects through mTOR modulation.

Metformin: It is a treatment for type 2 diabetes, which can mimic CR via its ability to activate AMP kinase and has also been shown to extend lifespan and healthspan in several species including rodents (Martin-Montalvo *et al*., 2013). Clinical data have also revealed that diabetics taking metformin have significantly lower mortality than diabetics on alternative sulphonyl urea therapies (Campbell *et al*., 2017). Regarding immunity, recent clinical studies have found out an anti-inflammatory role of metformin (Saisho, 2015) and an attenuating effect of metformin on Th17 cell generation and upregulation of Tregs in mice models of arthritis (Son *et al*., 2014).

Reversal of Thymic Involution

Thymic regeneration or maintenance would be a rational target for improving immune competence in older adults. Potential mechanisms for thymic regeneration include; IL7 or growth hormone replacement therapy (Aspinall and Mitchell, 2008), and enhanced keratinocyte growth factor signalling (Seggewiss *et al*., 2007). Studies carried out in old mice have displayed that IL7 therapy reversed thymic atrophy, increased thymopoiesis and raised numbers of naive T cells in blood (Henson *et al*., 2005; Aspinall *et al*., 2007).

Administration of IL7 in preliminary human studies produced an increase in thymic T cell output and expansion of naive T cells in patients with lymphopenia, cancer, chronic viral infections and following transplant (Mackall *et al*., 2011). IL7 has also been recognised as an effective vaccine adjuvant that can increase antigen specific responses post vaccination recombinant lentivector immunised mice (Colombetti *et al*., 2009). The clinical evidence so far in humans has implicated that rhIL7 is safe with few side effects (Lundstrom *et al*., 2012), providing compelling evidence for testing rhIL7 as a therapeutic agent to restore thymic output in healthy older adults. Recently IL22 has been identified as another potential target for restoring thymic function since it promotes proliferation and survival of thymic epithelial cells, supporting a microenvironment required for thymopoiesis (Chaudhry *et al*., 2016). Additionally, exogenous administration of recombinant GH has been reported to promote thymus regrowth in HIV infected adults (Napolitano et al. 2008), though the increased risk of cancer with GH may prevent its long-term use.

Statins

It is HMG-CoA reductase inhibitors that have favourable effect of statins in preventing cardiovascular events by blocking cholesterol synthesis (Thavendiranathan *et al*., 2006). Recent studies have shown that statins also possess anti-inflammatory properties and can decrease inflammatory markers, especially IL6 and CRP both during chronic inflammatory conditions (Nawawi *et al*., 2003; Montecucco and Mach, 2009) and also in healthy older individuals (Mora *et al*., 2010). This widely used drug may be a promising intervention for fighting inflammaging. A recent study has reported a beneficial effect of statins *in vitro* and *in vivo* in restoring neutrophil migratory accuracy which reduces with advancing age (Sapey *et al*., 2017). Additionally, statins are now also considered as modulators of telomerase activity in study conducted on 230 older adults and can slow telomere shortening, they showed that with every 1-year increment in age, a decrement by 0.058 Kb was observed in the no statin group compared with 0.033 Kb in the statin group (Boccardi *et al*., 2013). However, a major side effect of using statins that needs to be considered is statin-induced myopathy which is the most common cause of statin discontinuation and has been observed in 10–15% of statin users (Abd and Jacobson, 2011).

PI3 Kinase Blockers

Phosphoinositide 3-kinase (PI3K) activity controls neutrophil functions as chemotaxis, phagocytosis, and superoxide production (Hannigan *et al*., 2004). Erroneous neutrophil chemotaxis in elderly has been linked to an increase in constitutive inhibitors of this pathway and PI3Kd signaling provide restoration precision of migration without adversely affecting other functions of neutrophils (Sapey *et al*., 2014). PI3K inhibiting treatments present a fresh approach to enhancing neutrophil function in senior citizens and may contribute to results throughout an infection and lessen inflammation (Lefebvre and Nicaccache, 2014). Nevertheless, utilizing PI3K inhibitors may have the disadvantage that they may be detrimental to other immune cells, for example, DC phagocytosis requires PI3K, andrelocation. Compared to neutrophils, aged DCs have lower PI3K pathway activation with age (Agrawal *et al*., 2007) and additional suppression may be harmful.

p38 MAP Kinase Inhibition

According to recent research, T cells with senescent traits become older and show constitutive p38 MAPK activation (Henson *et al*., 2015). This is because MAP kinases and the sestrin family of proteins form a complex that activates MAP kinases (Lanna et al. 2017). Additionally, T cell proliferative ability was restored by sestrin knockdown (Lanna *et al*., 2017) or p38 MAP kinase suppression (Lanna *et al*., 2014), and aged sestrin knockout mice responded better to immunization than wild type mice. Clinical preliminaries utilizing p38 inhibitors have been tried for a brief time frame in inflammatory circumstances like rheumatoid joint

pain, ongoing obstructive aspiratory illness and therewere no reports of expanded risk of harm (Patterson et al. 2014), which is a worry in re-establishing proliferative limit all the more by and large. StrangelyTNFa has been displayed to repress neutrophil movement by means of initiation of the p38MAP kinase pathway (Lokutaand Huttenlocher, 2005), proposing that this pathway could likewise designated to reestablish age related defects inneutrophil capability.

IL15 Treatment

IL15 is known to assume a part in directing resistant homeostasis and goes about as a lymphocyte endurance factor, especially for naivewhite blood cells (Wallace *et al*., 2006). IL15 likewise assumes a basic part in the turn of events andsupport of NK cells (Cooper *et al*., 2002) and as expressed above NK cell cytotoxicity declines with age (Hazeldine *et al*., 2012). *In vitro* examinations analysing the impact of IL15 on NK cells from intense myeloid leukaemia patients revealed an expansion in articulation of NK cell receptors NKp46 and NKp30 (Sanchez Correa *et al*., 2016). Clinical assessment of IL15 in disease treatment has displayed to incite extension of nearby Lymphocytes and invasion of seemingly perpetual memory White blood cell limit (Pilipow *et al*., 2015). These discoveries propose the chance of utilizing cytokine adjustment to further develop NK cell reactions and increment naive memory Lymphocyte proportion in elderly.

Conclusion

The resistant framework is significantly renovated with maturing prompting a decrease in viability with progressing age, bringing about expanded hazard of constant infections, contaminations, autoimmunity and antibody disappointment. Changes in nourishment and way of life can be a viable approach towards working on resistant result in elderly however might be difficult to accomplish at a population level. Research in the field of mediations to target resistant senescence is gathering pace and further developing in susceptible reactions like immunizations might be utilized as an early biomarker for against maturingimpacts. A great many pharmacological specialists with hostile to immune senescence properties have been distinguished and preliminaries with specialists, for example, rapamycin analogs are in progress. In this way, immunomodulation addresses a promising restorative way to deal with work on the wellbeing of elderly.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The author declares no conflicts of interest.

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