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Review

Targeting immune dysfunction in aging

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ABSTRACT

Human aging is a multifactorial phenomenon that affects numerous organ systems and cellular processes, with the immune system being one of the most dysregulated. Immunosenescence, the gradual deterioration of the immune system, and inflammaging, a chronic inflammatory state that persists in the elderly, are among the plethora of immune changes that occur during aging. Almost all populations of immune cells change with age in terms of numbers and/or activity. These alterations are in general highly detrimental, resulting in an increased susceptibility to infections, reduced healing abilities, and altered homeostasis that promote the emergence of age-associated diseases such as cancer, diabetes, and other diseases associated with inflammation. Thanks to recent developments, several strategies have been proposed to target central immunological processes or specific immune subpopulations affected by aging. These therapeutic approaches could soon be applied in the clinic to slow down or even reverse specific age-induced immune changes in order to rejuvenate the immune system and prevent or reduce the impact of various diseases. Due to its systemic nature and interconnection with all the other systems in the body, the immune system is an attractive target for aging intervention because relatively targeted modifications to a small set of cells have the potential to improve the health of multiple organ systems. Therefore, anti-aging immune targeting therapies could represent a potent approach for improving healthspan. Here, we review aging changes in the major components of the immune system, we summarize the current immune-targeting therapeutic approaches in the context of aging and discuss the future directions in the field of immune rejuvenation.

1. Introduction

Scientific and medical developments during the last century allow humans to live healthier and longer. The latest data from the United Nations reveals that one in eleven people in the world is over age 65 (9%) and by 2050 this will rise to one in six (16 %). Additionally, the number of humans over 80 is projected to triple, from 143 million in 2019 to 426 million in 2050 (United Nations, 2019). Unfortunately, the aging of the global population is accompanied by an increase in the incidence of age-related diseases which in turn impair the quality of life of the elderly. One of the biggest challenges of this century is promoting healthy aging, which is achievable both by changes in lifestyle and therapeutic interventions.

Aging is a multifactorial phenomenon that affects virtually all cells and organ systems in the human body resulting in a progressive functional impairment and loss of homeostasis. One of the most dysregulated systems in aging is the immune system, with alterations in several

biological and physiological processes that have significant repercussions on the overall well-being of the organism (López-Otín et al., 2013) (Fig. 1). The main roles of the immune system include the defense of the host against pathogens, the maintenance of homeostasis with clearance of dead cells and the regulation of healing processes. These activities are performed by specialized cells, that can activate general immune responses (innate immunity) or build specialized long-lasting defense against specific antigens (adaptive immunity). The progressive deterioration of the immune system affects both of these systems in elderly individuals, increasing susceptibility to infections, cancer and inflammatory diseases, while delaying wound healing processes and reducing the ability to build an antibody response to some types of vaccination (Barbé-Tuana et al., 2020; Pereira and Akbar, 2016; Weyand and Goronzy, 2016). Indeed, the incidence of several infectious diseases, both bacterial and viral, increases with age and can be modeled based on immune system decline (Palmer et al., 2018). In the same computational study, Palmer et al. showed that this is also true for cancer, indicating
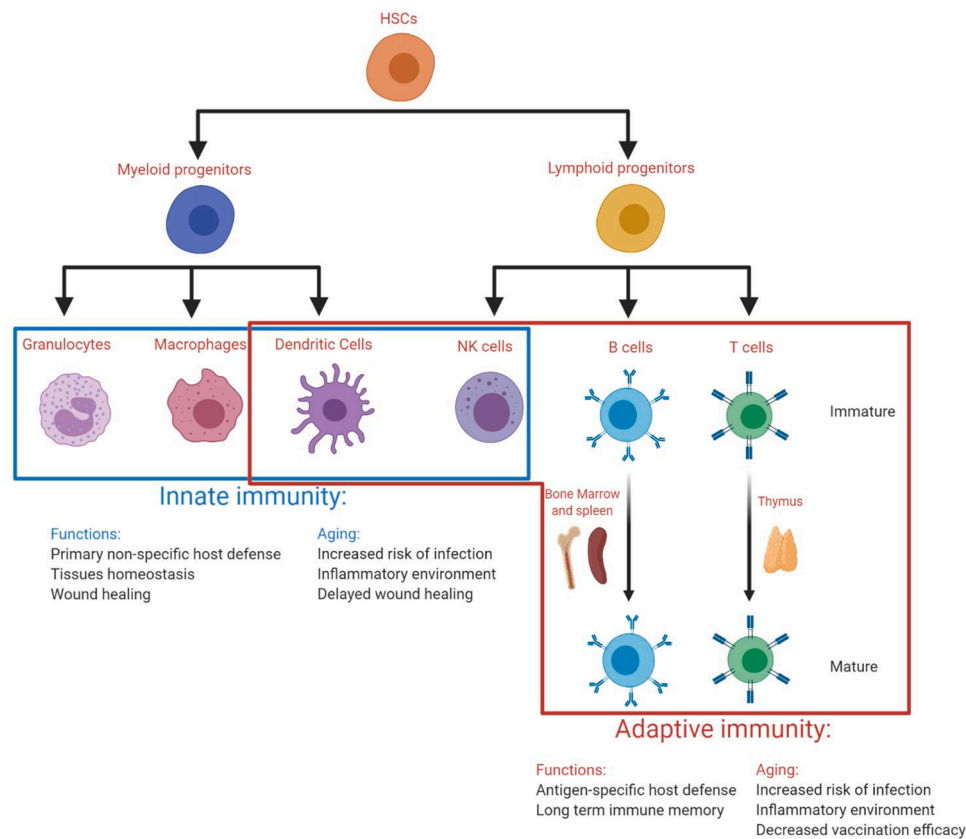
Fig. 1. Immune cells and general changes in aging. Schematic representation of the immune system, with the differentiation of distinct immune cells, their physiological role in innate and adaptive immunity and the consequences of alterations during aging.

that the alteration of the immune system in aging may contribute to increased cancer incidence in the elderly (Palmer et al., 2018). This work expands the scientific evidence on the relation between aging, immunity and cancer, but the exact ways in which they affect and influence each other remains debatable (De Magalhães, 2013; Fane and Weeraratna, 2020). Also autoimmune diseases have been investigated in the context of aging, with some evidence suggesting that they tend to be less frequent and less severe in elderly individuals (Watad et al., 2017), consistent with an overall decline in immune cell activity.

Another notable example of the importance of robust immune response in healthy aging is the recent COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that has a drastic effect on the elderly, especially those with co-morbidities. Indeed, age has been defined as a strong risk factor for disease severity and mortality upon infection with SARS-CoV-2, and this is strongly connected to the immune dysfunction that characterizes the elderly (Cunha et al., 2020; Domingues et al., 2020; Verity et al., 2020). Notably, an inefficient antigen-specific response, caused by alterations of cells of the adaptive immunity (particularly naïve T cells) in patients older than 65, contributes to poor disease outcome (Rydyznski Moderbacher et al., 2020). Additionally, individual differences in immune features of COVID-19 patients add a further layer of complexity (Mathew et al., 2020): immune dysfunction in the elderly cannot be generalized and individual differences can affect the outcome, vaccine efficacy and treatment response.

The dysfunctional immune system in aging has been associated with two processes defined as "immunosenescence" and "inflammaging". Immunosenescence, first proposed more than 40 years ago, is defined by

the gradual deterioration of the immune system, which loses its ability to respond to infections and build effective long-lasting immune memory (Aiello et al., 2019; Aw et al., 2007; Walford, 1969). More recently, studies have highlighted how several cell types of the innate and adaptive immune system undergo phenotypic changes during aging that impair their basic functions. At the beginning of 2000, a second phenomenon that affects the immune system in aging was proposed, termed inflammaging (Franceschi et al., 2000). While inflammatory processes are essential for the defense against foreign pathogens and clearance of dead and aberrant cells, their dysregulation and overactivation in the elderly causes a chronic inflammatory state that persists and promotes the development of inflammatory diseases associated with aging. These two processes are deeply interconnected, and can influence and maintain each other to create an imbalanced immune environment that is not only dysfunctional, but even acts as a driver for diseases development (Fulop et al., 2018). Individual differences are now starting to delineate a personalized way of aging that adds complexity to the investigation of deregulated processes (Ahadi et al., 2020; Mathew et al., 2020; Sayed et al., 2019). In this view, the identification of different immune ageotypes will help define subpopulations of elderly individuals with characteristic immune signatures and their longitudinal monitoring might help develop potential personalized anti-aging treatments (Alpert et al., 2019). In this review, we report and discuss the contributions of different immune cells in aging and address the latest therapeutic options that have been proposed with the overall goal to rejuvenate or at least revitalize the immune system and slow down or even reverse immune aging.

2. Therapeutic targeting of immune precursors

Hematopoietic Stem Cells (HSCs) are responsible for the production of all blood cells in vertebrates, being able to differentiate into both myeloid and lymphoid precursors. Balancing their self-renewal and differentiation potential, they maintain immune homeostasis in the body throughout the whole lifetime of an organism. Even though extremely resilient, the HSC compartment is highly affected by aging, losing some of its fundamental properties during the aging process (Lee et al., 2019) (Fig. 2). Being the source of all immune cells, changes in HSCs can drastically affect several immune processes and populations. In old mice, phenotypic and functional changes in the adaptive immune system are primarily driven by HSCs aging (Leins et al., 2018). In a recent article, the deletion of *Ercc1*, an important DNA repair protein, in murine HSCs induced a selective increase of DNA damage in immune cells and early immunosenescence. This resulted not only in impaired immune function but also in systemic premature aging, which could be attenuated by young immune cells transplantation (Yousefzadeh et al., 2021).

While healthy HSCs are able to maintain appropriate proportions of the downstream lineage-specific progenitors, in the elderly HSCs differentiation is skewed towards the myeloid lineage, resulting in a reduced output of lymphoid progenitors (Pang et al., 2011). Additionally, aging reduces HSCs self-renewing potential, progressively decreasing their capacity to repopulate the blood after stress (De Haan and Lazare, 2018). Indeed, in younger mice HSCs perform much better compared to older mice HSCs after transplantation, indicating higher potency (Dykstra et al., 2011; Rossi et al., 2005; Verovskaya et al., 2013). The reason for this reduced potential has been intensely investigated, and several factors have been found to play a role. One is DNA damage, with evidences of an increase in double strand DNA breaks in

aged human HSCs (Rübe et al., 2011). Similarly, aging HSCs produce higher levels of reactive oxygen species (ROS), which induces oxidative stress in HSCs, promoting senescence and apoptosis (Lee et al., 2019). Particularly relevant in this context is p38, a mitogen-activated protein kinase which has been found to have high activity in aged tissues and is known as a key regulator of stress pathways and as a strong ROS inducer (Hsieh and Papaconstantinou, 2002; Li et al., 2011). Indeed, p38 inhibitors are able to rejuvenate murine HSCs and increase their potency (Ito et al., 2006; Jung et al., 2016). Other important proteins involved in oxidative stress control are sirtuins. Specifically, Sirt3 is downregulated in the HSCs of aged mice and correlates with increased ROS-stress. Its overexpression reverts the phenotype, decreases ROS levels and increases the potency of these cells (Brown et al., 2013). Recently it was also reported a central role of chaperone-mediated autophagy (CMA), a selective type of autophagy that involves motif-specific lysosomal degradation of proteins, in the sustainment of HSCs functions (Dong et al., 2021). In HSCs from old mice CMA activity is drastically decreased, and its pharmacological reactivation restores HSCs function both in mice and humans (Dong et al., 2021). An additional factor for the reduced potency and replication abilities of HSCs during aging may be the progressive shortening of telomeres. Indeed, it was demonstrated in mice that HSC proliferation is accompanied by a decrease in telomere length and that telomerase is essential in maintaining HSC proliferative capabilities (Allsopp et al., 2003, 2001). HSCs from mice with short telomeres show high DNA damage levels and become senescent (Wang et al., 2014). Pot1, a telomere-binding protein, has been reported to be essential in maintaining HSCs activity in aging and its overexpression promoted self-renewal and reduced the DNA damage response and ROS production *in vitro* (Hosokawa et al., 2017). Moreover, telomere dysfunction causes drastic changes in mouse bone marrow promoting aging, including myeloid skewing and increased cytokines production
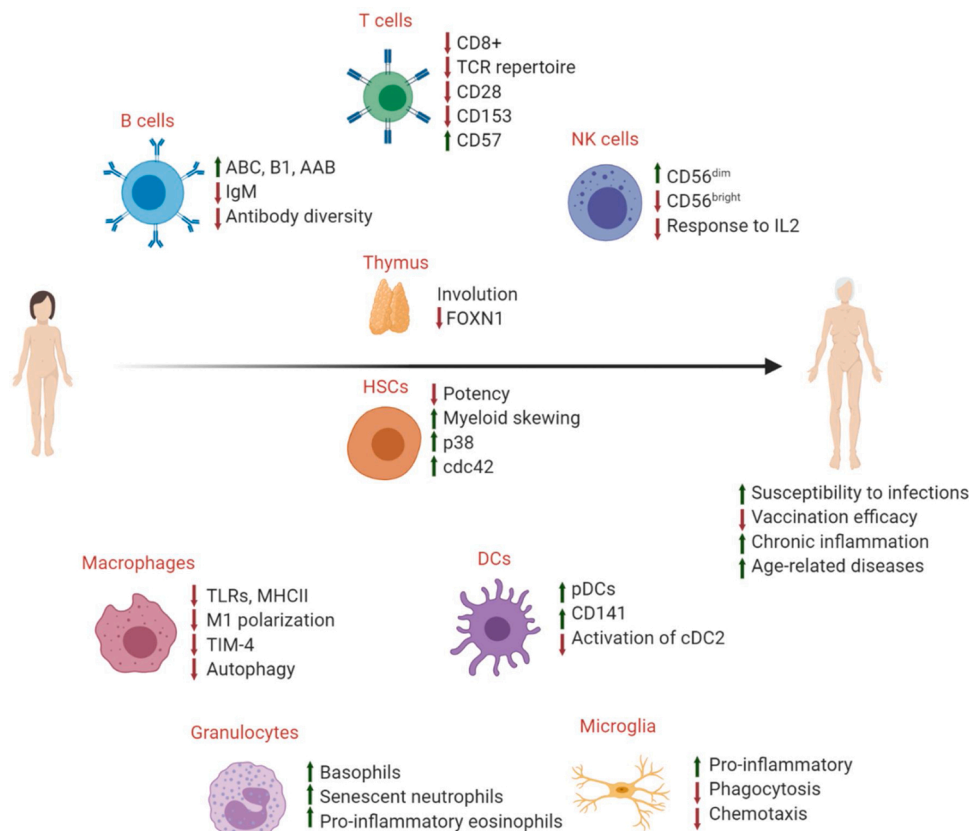

Fig. 2. Immune alterations during aging. Depiction of the main alterations that affect immune cells during aging, which ultimately result in higher susceptibility to infections, increased incidence of age-related diseases as cancer and diabetes, chronic inflammation, and reduced vaccination efficacy.

(Ju et al., 2007). Targeting this dysfunction by gene therapy-mediated telomerase activation was sufficient to replenish the blood cell counts and improve survival in a mouse model of anemia (Bär et al., 2016). Similar approaches could potentially be applied to aging, bearing in mind that telomerase expression might promote cancer initiation and should therefore be carefully implemented to avoid detrimental effects.

Recent studies in mice demonstrated a central role of cell division control protein 42 (cdc42) in HSC aging (Florian et al., 2018; Leins et al., 2018). Elevated cdc42 activity in these cells causes loss of polarity and a reduction in the number of lymphoid precursors (Florian et al., 2013). Consistently, cdc42 inhibition successfully reverts the phenotype and promotes rejuvenation of the HSC compartment, as well as reconstitutes the immune system activity (Leins et al., 2018). Among several inhibitors available to target this protein, the small-molecule CASIN shows great potential for its ability to specifically target cdc42 and mobilize murine HSCs (Liu et al., 2019). In addition, CASIN administration in aged mice restores the physiological level of cytokines and is able to increase overall lifespan (Florian et al., 2020). Targeting cdc42 is beneficial in reversing aging not only in HSCs, but also in other stem cells compartments, such as mesenchymal stem cells derived from rat and human adipose tissues (Chaker et al., 2018; Umbayev et al., 2018). This suggests that cdc42 is a promising target for general rejuvenating therapies that influence multiple systems, though further studies are needed regarding its applicability to humans and potential side effects.

Another approach proposed for the rejuvenation of the HSCs compartment is bone marrow (BM) transplant. Indeed, BM transplant from young donors to old mice is able to increase lifespan by 30 % (Kovina et al., 2019). Also, BM transplant is able to improve learning and memory in old mice, suggesting this approach may be beneficial in the treatment of age-associated neurodegenerative diseases (Das et al., 2019). In humans, DNA methylation age of reconstituted blood following allergenic HSCs transplantation reflects the age of the donor and not the one of the recipient, even 17 years after transplantation (Søraas et al., 2019). This shows a potential for HSCs transplantation from younger donors to older individuals that may have a rejuvenating effect on the immune system. As cellular precursors of all immune cells, HSC rejuvenating therapies are showing great promise: restoring a more normal phenotype and rebalancing the immune system at source with effects on several downstream immune processes (Fig. 3).

3. Therapeutic targeting of the lymphoid lineage

3.1. T cells

T lymphocytes, together with B cells (described in detail below), are the main players in adaptive immunity. Through their unique T cell receptor (TCR), T cells are responsible for the recognition of foreign antigens displayed by antigen presenting cells (APCs), and the activation of specific host defense measures. The two main T cells populations, CD4+, mostly involved in orchestrating the response of other immune cells, and CD8+, generally exerting their cytotoxic effect on infected or damaged cells, are affected differently during aging (Fig. 2). In terms of blood count numbers, while CD4 + T cells are not affected, the CD8+ cytotoxic subset shows a strong decrease in the elderly, and can be considered one of the markers of immune aging (Goronzy and Weyand, 2019; Whiting et al., 2015). Additionally, activated CD8+ cells display features of cellular senescence and gain a virtual differentiated memory phenotype, therefore reducing the functional naïve T cells compartment, and influencing their ability to respond to new infections (Quinn et al., 2018; Sprent and Surh, 2011). The dynamics inside specific subpopulations is also strongly influenced by aging: in mice, the CD4+ subsets is skewed towards the extremes, with accumulation of pro-inflammatory CD4 + T cells with acquired cytotoxic phenotype (CTLs) and anti-inflammatory T regulatory cells (Tregs) (Elyahu et al., 2019). Tregs changes during aging are still being debated. On one hand, it has been shown that in aged mice Tregs are higher in number and
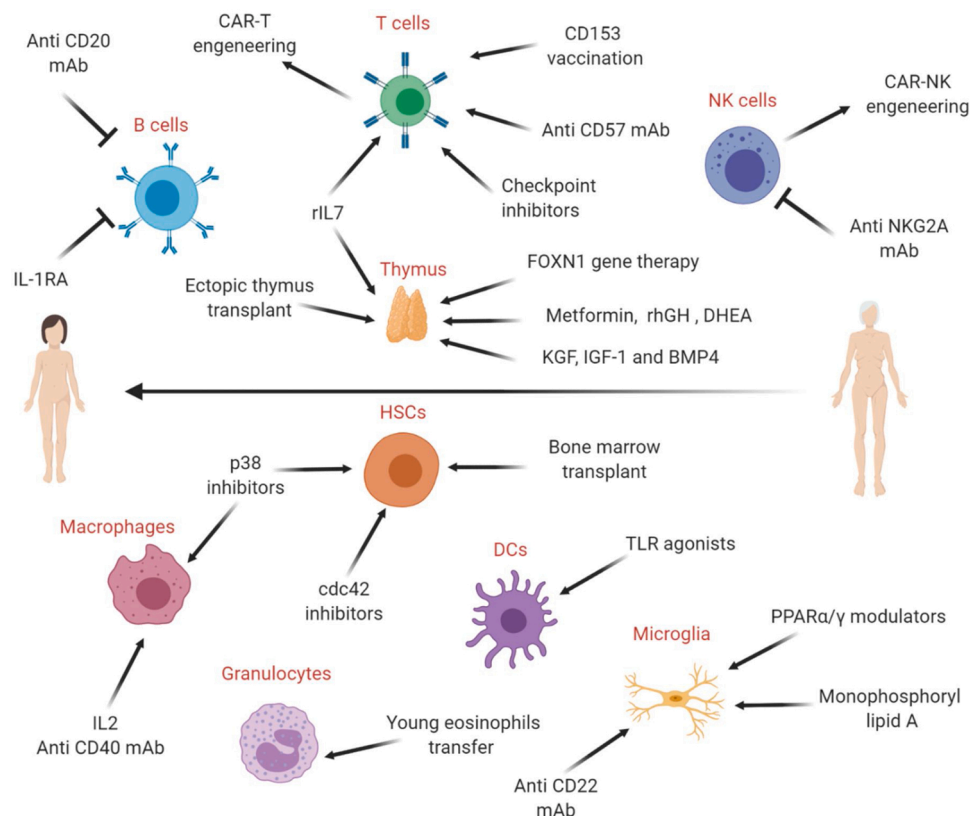

Fig. 3. Immune interventions to reverse immune aging. Representation of the most promising therapeutic interventions targeting immune cells. Rejuvenation of the immune system could be achieved from different directions and combining drugs that target distinct dysfunctional cell types.

more suppressive compared to Tregs from young mice (Garg et al., 2014). On the other hand, it was reported that Tregs senesce more than other T cells, and Tregs from old mice are less able to exert their suppressive function compared to their young counterparts, contributing to increased inflammaging (Guo et al., 2020). Finally, other CD4+ subtypes such as T helper type 1 and type 17 cells have been shown to be dysfunctional in the elderly and may contribute to increased susceptibility to infections (Coakley et al., 2019; Dillon et al., 2020).

Circulating T cells are known to proliferate in response to IL7 produced in lymph nodes and the thymus. However, the levels of this cytokine progressively decreases with age (Fry and Mackall, 2005). The age-induced fibrosis of lymph nodes, combined with a decrease in IL7R on T cells, results in a further reduction of T cell numbers in the elderly (Kityo et al., 2018; Ucar et al., 2017). Clinical trials in HIV patients demonstrate that recombinant human IL7 treatment increases both CD4+ and CD8 + T cells, as well as induces their activation (Rosenberg et al., 2006; Lévy et al., 2012). This approach could also be tested in healthy elderly patients to restore the physiological levels of T lymphocytes (Nguyen et al., 2017).

T cells function through recognition of antigens presented on the MHC (major histocompatibility complex) molecules on target cells through their TCR. Upon aging the number of T cells with different TCRs is highly reduced, decreasing the ability to recognize a broad spectrum of antigens, and this correlates with impaired immune responses (Yager et al., 2008; Yoshida et al., 2017). Notably, in old individuals clonal populations of T cells with the same TCR may rise up to as much as 25 % of the total CD8 + T cell compartment (Aiello et al., 2019). The shrinkage of the CD8+ repertoire has been also associated with chronic infections in humans, with CMV-seropositive individuals showing accumulation of CD8+ clonal populations (Hadrup et al., 2006). This may drastically decrease the recognition power of CD8 + T cells, increasing the susceptibility to new infections and cancer development.

Upon aging, differentiated T cells gain some specific features such as increased DNA damage, short telomeres, and increased production of inflammatory cytokines which can be associated with a senescence-like state (Pangrazzi and Weinberger, 2020). These T cells become highly inflammatory, while at the same time reducing their antigen specificity, harming healthy tissues (Covre et al., 2020). Even though no combination of markers is currently validated to characterize senescent T cell subsets completely and exclusively, some important suggestions have been proposed. Lymphocytes with a reduced expression of CD28, a co-stimulatory molecule required for T cells activation, show a "senescence-like" phenotype, are associated with several age-related diseases and show reduced antigen-dependent proliferation, short telomeres and increased inflammatory cytokine production (Pangrazzi and Weinberger, 2020). Additionally, it has been proposed that a subpopulation of human CD28- cells characterized by the increased expression of CD57 shows even more senescent-like features such as higher production of pro-inflammatory molecules and high ROS level (Pangrazzi et al., 2020). Other groups characterized the loss of the co-stimulatory marker CD27 as an additional senescence-related marker on CD28- T cells. It is now proposed that the loss of both of these markers defines a more differentiated and senescent-like population of T cells (Pangrazzi and Weinberger, 2020; Weng et al., 2009). Attempts to characterize CD4+ senescent cells identified CD45RA + CD27− as a subpopulation with typically senescent features (Henson et al., 2014). These markers were also recently confirmed in CD8+ cells, identifying CD45RA + and CD27 as more general senescent markers for human T lymphocytes (Callender et al., 2018). Notably, during aging senescent-like CD8 + T cells switch from the typical TCR-mediated activity to a NK-like activity by expressing protein complexes typical of NK cells (Pereira et al., 2020). The expression of NK receptors and the concomitant reduction in TCR levels allows these cells to recognize and kill other cells in an antigen-independent way, however reducing their contribution to the adaptive immune response. This phenotypic switching is mediated by sestrins (stress-inducible proteins that regulate metabolism through sensing nutrient levels and redox status) and their blockade is able to restore T cells functions, as well as enhance influenza vaccine response in old mice (Lanna et al., 2017; Pereira et al., 2020).

The presence of specific protein markers that identify senescent T cells could open the possibility for therapies targeting these specific populations without affecting normal immune system functions. A notable example is the recent development of a CD153 peptide vaccine, that using a specific peptide was able to induce high production of anti-CD153 antibodies (Yoshida et al., 2020). CD153 has been proposed as a marker of senescent-like T cells infiltrating the adipose tissue, responsible for increased inflammation and metabolic disorders (Shirakawa et al., 2016). CD153 vaccination was found to be well tolerated and effective in the reduction of CD153+ senescent T cells in the adipose tissue of diet-induced obese mice, as well as in the restoration of metabolic balance to improve aging and obesity-related metabolic disorders (Yoshida et al., 2020).

As discussed for HSCs, T cells are also affected by telomere shortening. Indeed, T cells from healthy centenarians show longer telomeres and higher telomerase activity in response to stimulation compared to other centenarians (Tedone et al., 2019). Additionally, a specific subset of T cells, characterized by CD28 expression, is able to maintain a strong telomerase activity upon stimulation, in agreement with the identification of the loss of CD28 as one of the T cell senescent markers previously mentioned (Huang et al., 2017; Pangrazzi and Weinberger, 2020). Several therapeutic strategies for telomere elongation or telomerase induction are currently under investigation (Martínez and Blasco, 2017). Among others, sestrin inhibition shows great promises by increasing telomerase activity and elongating telomeres in murine senescent T cells via p38 inhibition (Lanna et al., 2017). The development of new anti-senescence therapies and their application in T-cell re-activation could help strengthening adaptive immunity in the elderly (Fig. 3).

3.2. B cells

B cells are essential for adaptive immunity through their antigen presenting and antibody production capacities. It is widely accepted that during aging B cells produce less antibodies and with lower affinity, impairing the ability of the elderly to respond to new infections and vaccinations (Kogut et al., 2012) (Fig. 2). In particular, the decrease in vaccination efficacy with age is caused by a reduction in the IgM repertoire and their levels in the bloodstream upon immunization (Park and Nahm, 2011). Recently, a subset of B cells renamed aged-associated B cells (ABCs) were identified. In mice, the number of ABCs in the bone marrow and spleen increases with age (Ratliff et al., 2013) and these increased levels closely correlate with immune senescence as well as inflammaging (Cancro, 2020). It was reported that specific toll-like receptors (TLRs), responsible for pathogens recognition, such as TLR7 and TLR9, are required for ABC differentiation, together with stimulatory cytokines such as IL-21 and IFNγ (Naradikian et al., 2016). This suggests that these markers may be suitable targets for anti-aging therapies that aims to specifically deplete this subpopulation, without interfering with the normal B cell compartment (Rubtsov et al., 2017). Also the B-1 subpopulation of B cells, important in antimicrobial and housekeeping antibody production, decreases during human aging (Rodriguez-Zhurbenko et al., 2019). Apart from B-1 changes in number, their ability to secrete IgM is highly impaired, implicating them in increased susceptibility to infection and reduced quality of life (Holodick and Rothstein, 2015; Rodriguez-Zhurbenko et al., 2019). Another recent age-associated subpopulation of B cells is the aged adipose B cells (AABs), resident in fat associated lymphoid clusters and phenotypically different from ABCs (Camell et al., 2019). AABs express high levels of IL-1R and are induced by IL-1β and IL-18. Both an antibody treatment against the B cell marker CD20 and the IL-1R antagonist (IL-1RA) reduce AABs and increase lipolysis in mice, showing promise as anti-aging therapies (Camell et al., 2019).

The balance between B cell subpopulations might therefore be a prominent factor in aging, but further studies are needed to advance novel ways to specifically target age-promoting populations of B cells such as ABCs and AABs. In addition, overall B cell depletion with a cocktail of B cell specific markers CD19, B220 and CD22 showed promising results by inducing the rejuvenation of the B cell compartment through the reactivation of B cell lymphopoiesis in murine bone marrow (Keren et al., 2011). However, while this approach rejuvenated the circulating B cells compartment, it was not able to restore immune competence and vaccination responses in old mice (Avivi et al., 2019). Therefore, further studies are needed to demonstrate if a combination of B cell depletion with other anti-aging strategies may be effective in the restoration of immune competence in elderly individuals (Fig. 3).

3.3. Natural killer cells

Natural Killer (NK) cells are an important lymphoid population involved in innate immune defense. However, due to their ability to retain antigen-specific memory, NK cells are now considered also part of the specialized adaptive immune system (Nikzad et al., 2019; Paust and Von Andrian, 2011). NK cells have been shown to undergo several phenotypic and functional changes during aging (Xavier Camous et al., 2012) (Fig. 2). NK cells are characterized by the expression of the adhesion protein CD56 and the level of expression of this marker can distinguish two subpopulations with different functions: CD56^{bright} cells, mostly involved in cytokine production, and CD56^{dim} proficient cytotoxic cells (Gounder et al., 2018). The ratio of CD56 NK cells is important for the maintenance of a functioning immune system, and it is impaired in aging with a decrease of CD56^{bright} and an increase in the number of CD56^{dim} cells (Borrego et al., 1999; Gayoso et al., 2011). In addition, IL-2 induction of NK cells in the elderly fails to evoke sufficient proliferation and activation, with a switch in cytokine production (Almeida-Oliveira et al., 2011; Rink et al., 1998). NK cells are also thought to be pivotal in the removal of senescent cells in the organism, and their alteration during aging results in an accumulation of these deleterious cells (Song et al., 2020). Indeed, strategies targeting NKG2A, a receptor involved in the inhibition of NK cell cytotoxic activation, show promising effects in reducing the number of senescent cells in mice by restoring NK cellular immunity (André et al., 2018; Kamiya et al., 2019; Pereira et al., 2019) (Fig. 3). Additionally, the possibility to engineer chimeric antigen receptor (CAR)-NKs (Wang et al., 2020) specifically towards cellular senescence targets may represent a novel way to safely reduce the effects of aging and the accumulation of senescent cells.

4. Therapeutic targeting of the myeloid lineage

4.1. Macrophages

Macrophages are essential cells of the innate immunity compartment involved in protection against foreign pathogens, as well as one of the main APCs important in T cells activation. Several studies have shown that during aging macrophage functions are reduced or impaired, impacting the ability of these cells to build up a proper immune response (Fig. 2). Indeed, macrophages in elderly have reduced TLRs (Renshaw et al., 2002), increasing susceptibility to infections, as well as lower expression of MHC II, resulting in a decreased ability to present antigens to T cells (Herrero et al., 2002). Additionally, aged macrophages have altered inflammatory cytokine production, and increased release of suppressive cytokines such as IL-10 and prostaglandins (Stahl and Brown, 2015). This is confirmed by a reduced ability of macrophages to polarize towards the M1 pro-inflammatory phenotype and to properly activate an inflammatory response (Allavena et al., 2008). However, aged murine macrophages maintain enough plasticity to be induced through targeted IL-2/anti-CD40 therapy and are able to regain their T cell activation capacities (Jackaman et al., 2013). Conversely, aged macrophages also show high-inflammatory features characteristic of the M1 phenotype, in line with the general inflammatory state persistence in the elderly (Clark et al., 2020). Changes in macrophage phenotypes upon aging are also related to metabolic alterations. Among other cell types, macrophages are highly affected by decreased autophagy, altered nutrient sensing abilities and mitochondrial dysfunction associated with aging (van Beek et al., 2019). Caloric restriction or metabolic targeting drugs such as metformin, resveratrol and rapamycin might therefore exert their effect on lifespan through a direct action on the macrophage population (Fabbiano et al., 2016; Vasamsetti et al., 2015). Importantly, inflammation resolution is highly impaired and longer lasting in the elderly (De Maeyer et al., 2020). The cause of this impaired inflammation resolution can be identified in a reduction of TIM-4 receptor on macrophages caused by hyperactive p38 activity. Notably, an orally administered p38 inhibitor in the elderly is able to decrease TIM-4 expression and may help to restore macrophage ability to resolve inflammation (De Maeyer et al., 2020). In addition, inhibition of p38 is able to reduce local inflammation through a decrease of CCL2-mediated inflammatory monocyte recruitment, therefore increasing specific antigen responses (Chambers et al., 2021). This novel approach could represent an efficient therapeutic option to treat inflammatory age-related diseases, but additional studies with larger cohorts are needed to prove efficacy and identify potential side effects (Fig. 3).

4.2. Dendritic cells

Dendritic cells (DCs) are proficient APCs involved in both innate and adaptive immunity and tolerance. In their unique role, they are capturing antigens in different tissues and then migrate to the lymph nodes to interact with T and B lymphocyte to build up the adaptive immune response (Hammad and Lambrecht, 2008; Novak et al., 2010). They are subdivided in myeloid DCs (mDCs), a peripheral subset resident in tissues, and plasmacytoid DCs (pDCs), mostly found in the circulation. While they have overlapping functions, they are specialized in the production of particular cytokines and present different TLRs on their surface (Agrawal et al., 2018; Sallusto and Lanzavecchia, 2002). While overall DCs numbers are not altered during aging, specific subsets have been shown to change. Notably CD141+ DCs, known to be involved in viral response, are decreased in the elderly, which can be one of the reasons of increased susceptibility to viral infection at advanced ages (Agrawal et al., 2016). In addition, post-menopausal women have lower numbers of pDCs, their DCs produce less cytokines compared to young women and are less responsive to stimulation (van Splunter et al., 2019). A recent study identified a subset of DCs, cDC2, that may be responsible for the reduced vaccination efficacy in the elderly. Indeed, when this subset activity was boosted with imiquimod, a TLR7 agonist, the vaccination efficacy in mice was partly restored (Stebegg et al., 2020). As DCs are just one of the players involved in antibody responses, the combination of this drug with strategies targeting other immune populations might help in restoring a functional antigen-response for long-term vaccination efficacy in elderly (Fig. 3).

4.3. Granulocytes

Granulocytes (neutrophils, basophils, eosinophils and mast cells) are innate immunity cells that are able to activate efficient inflammatory programs upon pathogen infection or loss of tissue homeostasis. While their role in aging has been less studied compared to other immune cells, several changes have been identified in the elderly and their importance in maintaining aged tissue homeostasis (Fig. 2). Aging impacts the neutrophil compartment inducing changes in their basic activities, such as peroxide production, chemotaxis and apoptosis (Fulop et al., 2004; Tortorella et al., 1998). Additionally, aged mice display higher levels of senescent neutrophils, characterized by high expression of the chemokine receptor CXCR4 and low expression of the naïve marker CD62 L (Frisch et al., 2019). Also, the number of basophils increases with age and the expression of specific surface markers are altered, impairing

their activity (Van Beek et al., 2018). Finally, recent data also highlighted the important role of eosinophils in aging (Brigger et al., 2020). This novel study showed that eosinophils from aged adipose tissue display impaired tissue homeostasis ability, promoting systemic inflammation. Notably however, eosinophils transfer from young mice rescued these phenotypes and resulted in a striking systemic rejuvenation of the recipient mice mediated by restored IL-4 production (Brigger et al., 2020).

4.4. Microglia

Microglia are specialized cells in the central nervous system responsible for maintenance of homeostasis and immune responses. Opposite to macrophages, microglia cells are known to have increased inflammatory properties during aging, with high production of pro-inflammatory cytokines in response to external stimuli, but reduced phagocytosis and chemotaxis capabilities (Rawji et al., 2016). These alterations have been extensively associated with age-related neurodegenerative diseases such as Alzheimer's disease (Norden and Godbout, 2013). Indeed, monophosphoryl lipid A, an inducer of chemotaxis and phagocytosis, increases microglia's phagocytosis capability and improves Alzheimer's clinical outcome in mice (Michaud et al., 2013). In addition, the promotion of a regulatory phenotype with the selective nuclear receptor PPARα/γ modulator DSP-8658 induced better clinical outcomes, through decreased secretion of pro-inflammatory cytokines and increased phagocytic abilities in a murine model of Alzheimer (Yamanaka et al., 2012). CD22 expression, a negative regulator of phagocytosis, is elevated in microglia. CD22 antibody blockade successfully reversed the transcriptional signature of aging brains in mice and improved cognitive functions (Pluvinage et al., 2019). Given the high expression of CD22 in Alzheimer's human brain (Friedman et al., 2018), CD22 could be a promising candidate for targeted therapies aiming to rejuvenate the human brain through the restoration of microglial phagocytic functions. Recent data also shows a role of prostaglandin E2 signaling in microglia and macrophages in mouse brain aging and cognitive decline (Minhas et al., 2021). In aged mice, inhibition of prostaglandin E2 receptor EP2 in the myeloid compartment restored cognitive functions, through a rejuvenation of cellular metabolism as well as systemic and neural inflammation (Minhas et al., 2021).

5. Other immune-targeting strategies

5.1. Thymus regeneration

The thymus is an immune organ involved in T cell maturation. It atrophies at puberty and progressively loses functionality during adulthood, reducing its ability to eliminate self-reacting T cells responsible for increased inflammation (Thomas et al., 2020). Thymus function is strongly regulated by FOXN1, a transcription factor expressed by thymic epithelial cells responsible for thymocyte development and differentiation (Vaidya et al., 2016) (Fig.2). FOXN1 expression in the thymus decreases with age and is the main cause of thymus involution, which occurs relatively early during the life course (Rode et al., 2015; Sun et al., 2010). The importance of this single factor in thymic function makes it an extremely attractive target for thymic rejuvenation therapies. Gene therapy inducing FOXN1 overexpression in the murine thymus reverses the aged thymus phenotype and restores its function (Sun et al., 2010). Similarly, the transplant of thymus epithelial stem cells with high expression of FOXN1 reverses age-related murine thymic involution (Kim et al., 2015). Of note, ectopic thymus created from reprogrammed fibroblasts also increases the number of naïve T cells in mice and expands the possibilities for thymus rejuvenation (Bredenkamp et al., 2014). Additionally, FOXN1 reprogrammed embryonic fibroblasts engrafted in the thymus of aged mice rejuvenates the overall thymic architecture, reduces both the number of senescent T

cells and inflammaging (Oh et al., 2020). These findings open new clinical possibilities to reverse thymic involution in humans using autologous reprogrammed fibroblasts to restore central tolerance and reduce inflammation in the elderly. In another thymus reconstitution study, decellularized rat thymi stuffed with ex vivo expanded thymic epithelial and interstitial cells of human origin were successfully transplanted into humanized immunodeficient mice (Campinoti et al., 2020). In mice followed for over five months after transplantation, the transplanted thymi show capacity to support T cells development and maturation into physiological human CD4+/CD8+ ratio. Also, supplementation of exogenous factors such as KGF, IGF-1 and BMP4 improves thymic functionalities in mice, thus representing putative regenerative strategies that should be investigated for their potential in humans (Chu et al., 2008; Min et al., 2007; Wertheimer et al., 2018). Of particular interest are cytokine therapies using IL-7 and IL-22, which are under investigation considering their involvement in thymus homeostasis regulation. IL-7 is a cytokine produced by stromal cells that stimulates survival and differentiation of thymocytes and T cells. It has been reported that IL-7 supplementation reverses age-associated thymus atrophy and reactivate its functionality in old mice (Andrew and Aspinall, 2001; Henson et al., 2005). However, while clinical trials studying the effect of IL-7 administration in humans showed an increase in lymphocytes numbers in several disease settings, no specific effect on thymus was observed (Rosenberg et al., 2006; Sportès et al., 2010; Trédan et al., 2015). Specific studies are therefore required to investigate IL-7 immune-rejuvenating effects on healthy elderly.

However, the beneficial effects of thymus rejuvenation can be counteracted by secondary lymphoid organ degeneration (Thompson et al., 2019). Efficient strategies should therefore aim to combine thymus with lymph nodes regeneration: anti-fibrotic or senolytic drugs might help in this direction by reducing lymph node fibrosis and remodeling their degenerated structure. Alternatively, synthetic lymph nodes may efficiently acquire the properties of the lymphatic tissues in vivo and restore immune functions (Lenti et al., 2019). This approach could open novel possibilities for the rejuvenation of the lymphatic system and could be combined with other strategies to allow a long-lasting restoration of the immune function (Fig. 3).

5.2. Targeting immune metabolism

During aging, cells of the body undergo metabolic reprogramming that allows them to modify their nutrient sensing capabilities and to modulate their need for energy (Barzilai et al., 2012; López-Otín et al., 2013). Several metabolic-targeting approaches have been shown to promote health and lifespan in different models by targeting organismal or cell-specific processes (Gonzalez-Freire et al., 2020; Partridge et al., 2020). Immune cells are not an exception, and several studies highlighted the importance of metabolic alterations in immune cells during aging, as well as proposed ways to target this phenomenon. An approach that is gaining attention for its potential in increasing overall health-span and perhaps life-span is caloric restriction (CR), which involves a reduction in caloric intake or fasting. Indeed, CR increases life-span in most model organisms tested to date, also showing health benefits in primates (Madeo et al., 2019). CR exerts its anti-aging functions through several pathways, including mTOR inhibition, sirtuins activation and enhanced AMP kinase function, which in turn induces autophagy, a major deregulated process in aging (Barbosa et al., 2019; Cantó and Auwerx, 2011; Guarente, 2007). CR also attenuates the effect of age on immune cells in mice, particularly on NK cells and T lymphocytes (White et al., 2017). In addition, CR may be implicated in immune suppression, resulting in increased susceptibility to infections in fruit flies (Ayres and Schneider, 2009). A preliminary trial suggests this is not the case in humans (Meydani et al., 2016), however CR in humans remains poorly studied and more data is needed to delineate its benefits and risks for healthy aging.

From a therapeutic perspective, several agents that mimic the effect

of CR have been identified and tested successfully for their anti-aging effects (Madeo et al., 2019). At the center of attention is metformin, a drug approved for the treatment of type 2 diabetes with a still unclear mechanism of action, that includes the activation of AMPK, induction of autophagy and inhibition of mitochondrial respiration (Rena et al., 2017). Additionally, the intestinal microbiome has been identified as a target of metformin, which could in turn mediate its effect on aging through the modulation of pro- and anti-inflammatory factors (Cabreiro et al., 2013; Prattichizzo et al., 2018). Metformin is also able to increase the lifespan in *C. elegans* (Cabreiro et al., 2013) and in mice, both alone (Martin-Montalvo et al., 2013) and when administered in combination with rapamycin (Strong et al., 2016). Additionally, retrospective epidemiological studies correlated metformin treatment with reduced incidence of age-related diseases, such as cardiovascular diseases and cancer (Partridge et al., 2020), as well as with a reduction in all-cause mortality (Campbell et al., 2017). Metformin has been also used in combination with rhGH and DHEA in a small clinical trial to revert the epigenetic age of old healthy individuals. Notably, the treatment cocktail was able to induce thymus regeneration, changes in immune phenotype and reversal of the epigenetic age of the individuals, resulting in an increase predicted lifespan (Fahy et al., 2019). Due to the limited sample size, a follow-up trial (NCT04375657) with a bigger cohort is ongoing to assess the significance of the results.

Recently, it was reported that T cell mitochondrial dysfunction caused by the TFAM transcription factor deficiency promotes senescence in mice, inducing aging-related disorders and inflammaging (Desdín-Micó et al., 2020). While immunometabolism has been extensively studied in other contexts, such as cancer and autoimmune diseases, this is the first report directly linking metabolic alterations in immune cells to aging. Additionally, it was also reported that metformin exerts a positive effect on CD4 T cells from old individuals as a way to revert inflammaging. Strikingly, the increased autophagy and the normalized mitochondrial function induced by metformin on CD4+ T cells switched the highly inflammatory elderly-derived T cells to a "young-like" phenotype (Bharath et al., 2020). A larger clinical trial, the Targeting Aging with MEtformin (TAME) initiative (https://www.afar.org/tame-trial), is predicted to start soon and recruit 3000 elderly to extensively test the benefits of metformin in aging and aging-related disease onset (Partridge et al., 2020).

Another well studied anti-aging drug target is mTORC1, a central protein in several metabolic pathways. Rapamycin, a specific mTORC1 inhibitor and CR mimicker, is able to increase longevity in various model organisms (Blagosklonny, 2019; Johnson et al., 2013). Among its effects, rapamycin is effective in restoring the HSC renewing capacities in old mice and in increasing influenza vaccination efficiency, reversing immunosenescence (Chen et al., 2009). An initial test in human volunteers revealed that the mTORC1 inhibitor RAD001 was able to reduce immunosenescence and improve the response to influenza vaccine (Mannick et al., 2014). Additionally, a clinical trial using a combination of the mTORC1 inhibitors RTB101 and RAD001, confirmed these findings showing enhanced immune function in old individuals, upregulated antiviral response and increased influenza vaccination efficiency (Mannick et al., 2018). However, despite the successful phase 2a and 2b clinical trials, the recent phase 3 trial with RTB101 was unsuccessful in enhancing immune functions in the elderly to reduce respiratory illnesses (Kaeberlein, 2020; Mannick et al., 2021). Further studies are planned to test rapamycin efficacy in reducing the clinical effects of aging and could help obtain data on immune-related effects (NCT04488601).

Another CR agent that is drawing interest is resveratrol, a natural polyphenolic compound of plant origin present in high quantities in berries and grapes (Baur and Sinclair, 2006). Resveratrol is able to increase lifespan in mice on a high-fat diet (Baur et al., 2006; Howitz et al., 2003). In nonhuman primates resveratrol reduces the inflammatory effects of high-fat diet and induces sirtuins expression (Mattison et al., 2014; Rajman et al., 2018). The anti-inflammatory effect of resveratrol

is mediated by its effect on several immune cells, including macrophages, T and B lymphocytes and NK cells by promoting immunomodulatory and anti-inflammatory cytokine production, as well as increasing Treg counts (Malaguarnera, 2019). Another CR mimicking agent is the endogenous metabolite spermidine, a known inducer of autophagy that is able to increase lifespan in mice (Eisenberg et al., 2016). In addition, it was also demonstrated that administration of spermidine in mice is able to reduce B cell senescence (Zhang et al., 2019).

Finally, alpha-ketoglutarate, an endogenous metabolite, has a potent effect on the modulation of chronic inflammation. Indeed, its administration in old mice induces IL10 secretion from T cells, reducing morbidity and extending lifespan (Asadi Shahmirzadi et al., 2020).

All these reports indicate that immunometabolism is playing a central role in the aging of the immune system, and several drugs targeting various metabolic processes could hold a high therapeutic potential for immune rejuvenation strategies.

5.3. Targeting senescent cells

Senescent cells are characterized by cell cycle arrest, increased metabolic activity, upregulation of anti-apoptotic pathways and a senescence-associate secretory phenotype (SASP) that accumulate during aging in several tissues (Kirkland and Tchkonia, 2017). SASP includes production of several pro-inflammatory cytokines and chemokines that contribute to inflammaging and the development of age-related diseases (Coppé et al., 2008). Senolytic drugs specifically target senescent cells, therefore being a powerful tool to reduce both tissue-specific and systemic inflammation. Senescent cells are responsible for tissue aging and inflammation in young mice, and senolytics have been shown to improve health and increase lifespan in old mice (Xu et al., 2018). Additionally, the same senolytic cocktail was efficient in reducing senescent cell burden in a human clinical trial in individuals with diabetic kidney disease (Hickson et al., 2019). Several other senolytic agents, including HSP90 or BCL-2 and BCL-XL inhibitors, show promising results in mice and should be further investigated for their applicability and efficacy in humans (Fuhrmann-Stroissnigg et al., 2017; He et al., 2020; Kirkland and Tchkonia, 2020).

While the age-mediated accumulation of senescent cells in many tissues is a widely accepted phenomenon, senescent immune cells have not been deeply characterized. Robust criteria for distinguishing senescent immune cells from highly differentiated but non-senescent immune cells remain unknown. Immune cells are known to express classical senescence markers, such as senescence-associated beta-galactosidase (SA-beta-gal) (Biran et al., 2017; Frasca et al., 2021; Hall et al., 2016; Rajagopalan and Long, 2012; Ye et al., 2012). Recently, an age-associated increase of SA-beta-gal activity was observed in all subsets of peripheral blood mononuclear (PBMC) cells, including T lymphocytes, plasmacytoid dendritic cells (pDCs), natural killer (NK) cells, monocytes, and B cells (Martínez-Zamudio et al., 2021). Strikingly, the number of CD8 + T cells with a high level of SA-beta-gal activity in healthy subjects increases from 30 % in their 20 s to 64 % in their 60 s. Targeting senescent cells with a prodrug processed into a cytotoxic compound by β-gal has been proven to be extremely effective in reducing inflammation and restoring physical function in old mice (Cai et al., 2020). Notably, this effect was also partly mediated by depletion of SA-beta-gal positive macrophages from aged tissues (Cai et al., 2020). Comparing classical senescence markers such as SA-beta-gal with the immunological markers mentioned above might help define immune senescence and provide additional therapeutic options.

Additionally, it was recently reported the development of specific CAR-T cells directed against senescent cells expressing the plasminogen receptor uPAR on their surface (Amor et al., 2020). This opens the possibility to engineer T cells to recognize specific senescence-associated markers and create new senolytic approaches based on the CAR technology.

5.4. Targeting immune epigenetics

Changes in the epigenetics state of cells have been defined as one of the hallmarks of aging and correlate with lifespan in several organisms (López-Otín et al., 2013). Notably, the DNA methylation state can be used to assess the biological age of the cell and this is claimed to be more accurate than any other method investigated, such as telomere length or other transcriptomic or proteomic biomarkers (Horvath and Raj, 2018; Jylhävä et al., 2017). In the immune compartment, epigenetics plays a pivotal role in mediating several processes such as lineage differentiation (Allan et al., 2012; Pace et al., 2018) and immune memory formation (Abdelsamed et al., 2018; Scharer et al., 2017). During aging, HSCs become globally hypomethylated, while at specific loci, such as the Polycomb Repressive Complex 2 binding sites and IL7R gene, there is hypermethylation (Beerman et al., 2013; Taiwo et al., 2013; Ucar et al., 2017). Other reports suggest the hypomethylation of FoxP3 leads to an increase in the number of Tregs in older mice (Garg et al., 2014). Also, chromatin modifications have been associated with aging. Indeed, increased H3K4me3 levels affects genes involved in HSCs identity and renewal, while overall H3K9me3 decrease leads to phenotypical changes in the HSCs compartment (Djeghloul et al., 2016; Sun et al., 2014).

Another epigenetic driver of inflammaging has been identified in transposon activation. During aging, retrotransposable elements become transcriptionally active and promote IFNγ-mediated inflammation, and their pharmacological repression reverses this phenotype in mice (De Cecco et al., 2019). Additionally, the derepression of these transposable elements is mediated by SIRT6 (Simon et al., 2019). This suggests that SIRT6 activating therapies might show anti-aging effects through the reduction of systemic inflammation by restoring epigenetic repression of retrotransposons.

While additional studies are needed to pinpoint the importance of immune cells epigenetics in aging, it is clear that epigenetic changes have a prominent role in shaping the phenotype of the cells they are affecting (Jasiulionis, 2018; Keenan and Allan, 2019). Several epigenetic drugs have been developed in recent years to target epigenetic changes in different diseases and contexts (Ganesan et al., 2019). Investigating their effect in aging and particularly in the modulation of immunosenescence could add additional therapeutic approaches to the fight against aging, providing novel ways to rejuvenate the immune system.

6. Future directions

Our understanding of immune alterations during aging is increasing exponentially. In the last few years, several new immune populations have been identified to drastically change during lifetime and influence each other and the overall immune competence of the organism. New anti-aging therapeutic approaches targeting specific immune dysfunctions in the elderly are being proposed at a growing pace, with many of them showing promising pre-clinical results (Table 1). While their clinical application and long-term safety remain to be proven in clinical trials, current evidence suggests that immune targeting approaches may revolutionize the longevity field. Due to its interconnection with all other systems in the body, its relevance for homeostasis maintenance and the primary role in fighting infections and cancer, the immune system represents the ideal target to comprehensively address many hallmarks of aging. For this reason, anti-aging immune targeting therapies could represent a potent approach for improving healthspan. The therapeutic strategies described in this review can be summarized as: I. Rejuvenating strategies to replenish aged immune tissues or cells (e.g., rejuvenation of the thymus and the HSCs compartment or young cell transfer) II. Immunosuppressive strategies to tune down dysregulated populations that promote inflammaging III. Immunostimulatory

Table 1
Aging-related immune changes and reported therapeutic strategies.

| Cell types	Alterations	References	Therapeutic approach	Species	References
HSCs	Reduced potency and myeloid skewing	Leins et al., 2018; Pang et al., 2011; Lee et al., 2019; Ju et al., 2007; Florian et al., 2018	p38 inhibition	Mouse	Ito et al., 2006; Jung et al., 2016
			cdc42 inhibition	Mouse	Leins et al., 2018; Florian et al., 2020
			HSCs transplant	Mouse	Kovina et al., 2019; Das et al., 2019; Yousefzadeh et al., 2021
T cells	Decreased number and activity	Goronzy and Weyand, 2019; Kityo et al., 2018; Ucar et al., 2017	IL-7 administration	Human	Rosenberg et al., 2006, Y Lévy et al., 2012
	Increased senescence	Pangrazzi and Weinberger, 2020; Covre et al., 2020; Lanna et al., 2017; Callender et al., 2018; Shirakawa et al., 2016	CD153 vaccination	Mouse	Yoshida et al., 2020
	Decreased telomere length	Tedone et al., 2019; Huang et al., 2017; Pangrazzi and Weinberger, 2020	Sestrin inhibition	Mouse	Lanna et al., 2017; Pereira et al., 2020
				Mouse	
B cells	Increase in aging-promoting populations	Ratliff et al., 2013; Camell et al., 2019; Rodriguez-Zhurbenko et al., 2019	B cell depletion	Mouse/Human	Keren et al., 2011; Avivi et al., 2019
			IL-1R antagonists	Mouse	Camell et al., 2019
NK cells	Reduced activity	Song et al., 2020; Gayoso et al., 2011; Almeida-Oliveira et al., 2011	NKG2A blockade	Mouse/Human	André et al., 2018; Kamiya et al., 2019; Pereira et al., 2019
Thymocytes	Involution	Thomas et al., 2020; Rode et al., 2015; Sun et al., 2010	FOXN1 induction	Mouse	Sun et al., 2010; Kim et al., 2015)
			Thymus reconstitution	Mouse	Bredenkamp et al., 2014; Oh et al., 2020; Campinoti et al., 2020
Macrophages	Altered secretory activity and polarization	Stahl and Brown, 2015; Allavena et al., 2008; Clark et al., 2020	IL-2/CD40 therapy	Mouse	Jackaman et al., 2013
	Increased p38 activity	De Maeyer et al., 2020	p38 inhibition	Human	De Maeyer et al., 2020; Chambers et al., 2021
DCs	Reduced cDC2 activity	Stebegg et al., 2020	TLR agonists	Mouse	Stebegg et al., 2020
Granulocytes	Altered activity and inflammatory phenotype	Fulop et al., 2004; Frisch et al., 2019; Brigger et al., 2020	Eosinophil transfer	Mouse	Brigger et al., 2020
Microglia	Increased inflammation	Rawji et al., 2016	Monophosphoryl lipid A	Mouse	Michaud et al., 2013
			PPARα/γ modulation	Mouse	Yamanaka et al., 2012
	Reduced activity	Pluvinage et al., 2019; Friedman et al., 2018	CD22 blockade	Mouse	Pluvinage et al., 2019
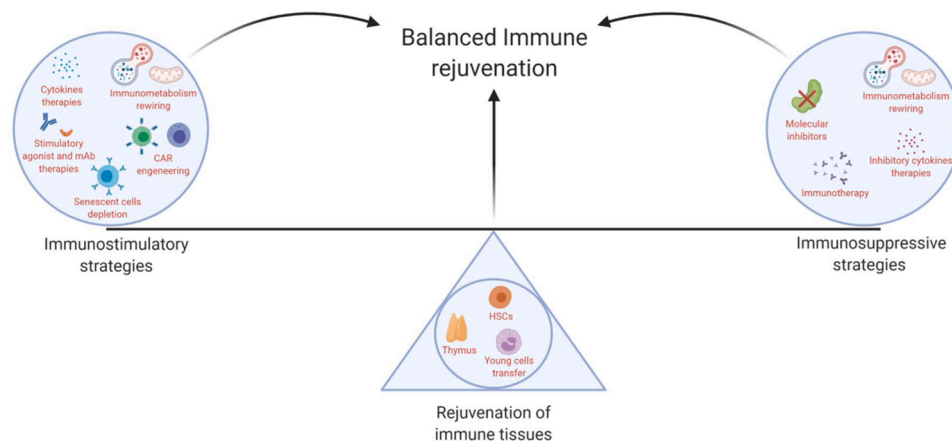
Fig. 4. Combining and balancing immune rejuvenation strategies. Rejuvenating strategies should combine both generalized and cell-specific approaches in order to have a balanced modification of the immune system. Immunostimulatory and immunosuppressive strategies can address different dysfunctional areas of the immune system and combine their effects towards a sustainable immune rejuvenation.

strategies to re-activate, eliminate, or replace senescent cells (Fig. 4). While some of the therapies in development target defined immune cell types or even specific subpopulations, other approaches are directed against general dysregulated processes that are common to many different cell types. Examples are metabolic or epigenetic targeting drugs that will affect multiple immune and non-immune cells, likely with distinct effects on their phenotype. When considering these treatments, it will be essential to assess the full spectra of effects, both in the cell type of interest and potential off-target effects.

Another aspect to consider is the strong differences between individuals, including at the level of heterogeneity of immune system changes with age. In several medical areas, treatments are now based on individual characteristics of the patient, thanks to multi-omics analysis that provide genetic and epigenomic personalized information. Precision medicine is now the standard approach for several types of cancers where treatments are decided based on the mutational profile of the patient (Friedman et al., 2015). In aging, distinct individuals respond differently to metformin, indicating that there might be specific genetic or epigenetic characteristic that can influence the treatment efficacy (Soukas et al., 2019). Stratification of the aged population based on biomarkers identified from multi-omics data could therefore define subgroups that might benefit from specific treatments and allow more effective personalized approaches.

The strong relevance of the immune system in aging therapy is reflected also by the flexibility of gene therapy and engineering of immune cells *ex vivo*. Because changes to the immune system will have systemic affects, *ex vivo* gene therapy of immune system cells has great potential as a therapy for aging. The development of CAR-T cells has already demonstrated its efficacy in cancer therapy (Singh and McGuirk, 2020) and autoimmune diseases (Ellebrecht et al., 2016; Kansal et al., 2019) and recent evidence suggest the potential application in aging and treatment of age-associated diseases (Amor et al., 2020). The flexibility of the CAR technology, potentially adaptable to any senescence marker, and the rise of other gene therapy approaches for stable T cells engineering (Bailey and Maus, 2019; Honaker et al., 2020) open new possibilities for a stable modification of the immune system to restore active immune surveillance and clearance of senescent and other dysfunctional cells.

Given the complexity of the immune system and aging, the biggest challenge for the years to come will be to find the right combination of the various therapeutic approaches described in this review and to identify the group of individuals that would benefit the most from each of them. Targeting multiple components of the immune system at once will require an extremely balanced approach to avoid undesired side effects. On the one hand, exaggerating immune suppression to reduce

inflammaging could result in an increased susceptibility to infections or loss of basic immune homeostatic functions. On the other hand, a strong stimulation of the immune system to re-gain its full functionality could result in an increased risk of autoimmune diseases or acute inflammatory side effects. To maintain the right balance in the immune system, rejuvenating approaches need to be fine-tuned to affect the right components without being detrimental on others (Fig.4). Personalized combinatorial approaches will allow different immunological processes to be affected leading to efficient and durable effects. Extensive preclinical and clinical studies are needed to define the approaches that will yield the best health outcomes with the least side effects, but given the large amount of targeting possibilities and the promising recent developments in the field, immune rejuvenation can already be considered a realistic biological milestone to be achieved in the near future.

Declaration of Competing Interest

Simone Borgoni, Ksenia S. Kudryashova, Ksenia Burka and João Pedro de Magalhães work/consult for Centaura AG, a company focused on development of radical anti-aging interventions.

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