Published in final edited form as:

Int Rev Immunol. 2014 ; 33(3): 162–173. doi:10.3109/08830185.2013.829469.

Immunosenescence and Immune Response in Organ Transplantation

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Abstract

The immune system undergoes a complex and continuous remodeling with aging. Immunosenescence results into both quantitative and qualitative changes of specific cellular subpopulations that have major impact on allorecognition and alloresponse, and consequently on graft rejection and tolerance. Here, we are going to review the immunological changes associated with the aging process relevant for transplantation. Interventions to selectively target changes associated with the senescence process seem promising therapeutic strategies to improve transplantation outcome.

Keywords

aging; elderly; immunosenescence; transplantation

INTRODUCTION

The number of older people is increasing dramatically. In the world, by year 2050 the number of older people will surpass the number of younger (<35 years of age) people for the first time [1]. The exponential increasing proportion of elderly individuals in our society and the shortage of organs impose significant challenges to organ transplantation.

The elderly is the fastest growing segment of the population with end-stage organ disease [2]. In the United States, transplant recipients of any solid organ older than 65 years represented in 2012 9.3% of all recipients, while in 1988 they represented only 2.1%. Likewise, the percentage of solid organ donors older than 65 years increased more than 8 times in the same period, representing 7.1% in 2012 [2].

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Immunosenescence is the process of progressive dysfunction of the immune system that increases the susceptibility of the elderly to infection, autoimmune disease, and cancer, contributing significantly to morbidity and mortality of the elderly [3–5].

Here, we are going to update the literature and discuss the complex remodeling of the immune system in the elderly by describing most significant changes of key players, and its impact on both rejection and tolerance.

CHANGES OF THE IMMUNE SYSTEM WITH AGING

The aging process causes important anatomical and functional changes in a number of systems that result in reduction of the functional reserve and inability to cope with stress. As the functional reserve decreases, organs are exposed to overload during stress conditions, resulting in a vicious cycle activating the immune system while contributing to tissue injury and reduction of function [6, 7].

The immune system undergoes a complex and continuous remodeling with aging. Immunosenescence changes result into both quantitative and qualitative modifications of specific cellular subpopulations rather than a global deterioration of the immune system, as previously thought [8, 9]. Even stem cells, despite their extensive proliferative and regenerative capacity, show signs of aging [10, 11].

The most striking alterations are found in phenotypes and functions of T-cell components and less frequently in components of the natural (innate) immune system. Consequently, chemotaxis, phagocytosis, natural cytotoxicity, and complement activity are relatively well preserved in elderly individuals [12]. Most alterations of B cells seem secondary to T-cell dysfunction [4].

The most relevant age-related immunological modifications are on T cells, since they play a pivotal role in tolerance and rejection [13]. Regarding the changes in the absolute number of lymphocytes with aging there is some controversy [14], whereas there is sufficient evidence for an alteration of specific cell subsets. Changes in T-cell subtypes include increased amounts of CD3+, CD4+, CD8+ T cells, decreased CD28+ T cells, and a shift from naïve to memory phenotypes, leading to a limited T-cell repertoire [3, 9, 12]. With aging, the diversity of TCR- β chains drops 1 000-fold in individuals older than 70 years [15].

It is hypothesized that aging is associated with chronic activation of the immune system [16]. The cytokine network undergoes profound and complex changes with aging [17]. It has been shown that there is a shift toward the production of pro-inflammatory cytokines (IL-6, IL-1 β , TNF- α , and IFN- γ), and reduction of the expression of several adhesion molecules and chemokine receptor expression with increasing age [18]. In addition, aging of the endocrine and neurological systems are closely associated with aging of the immunological system and may contribute to chronic allograft deterioration [18, 19].

Aged Memory Cells

The number of memory cells increases with age, possibly reflecting an accumulation of antigenic experiences. In neonates, 99% of T-cells are naïve, while in the age group from 50

to 70 years only 35% are naïve, and in centenarians about 20% [12, 20]. Alloreactive memory cells, generated either by previous sensitization to alloantigens or through heterologous immunity, are barriers to achieve graft tolerance [20]. Unlike naïve T-cells, memory cells can be fully activated in the absence of costimulation [21, 22], can recirculate in peripheral nonlymphoid tissues, and be able to initiate early responses directly in the graft. Memory cells response to antigens has greater magnitude and efficacy than response from naïve T cells [23]. It has been shown that a high number of memory cells are associated with increased incidence and severity of rejection [24].

With aging, the number of immature B cells decrease and there is a significant loss in diversity of the B-cell receptor [25, 26]. The numbers of memory B cells (CD27+) are increased with aging [27]. An increased proportion of mature B cells may also account for the increased resistance to tolerance induction in the elderly [28–31].

MHC expression in aged cells—MHC class II plays a key role in regulating and restricting the immune response [32–34]. Optimal levels of MHC expression are crucial for the proper functioning of cellular and humoral immune responses. MHC class I protein levels increase significantly with age on both peripheral blood and spleen (T cells and B cells) lymphocytes, whereas the percentage of MHC class II-expressing spleen lymphocytes markedly decreases [35–37]. This decrease was due to a decrease in the relative proportion of B cells compared to T cells in the spleen lymphocyte population of older animals [35]. The ease of B-cell tolerance induction decreases with aging in native, and lethally irradiated and thymectomized mice recipients of B cells from donors of different ages. This age resistance of the peripheral B-cell population to tolerance induction might be, at least in part, accounted for the increased incidence of auto-antibodies [38, 39].

Aged T-regulatory cells—Regulatory T cells (Tregs) play crucial roles in the induction and maintenance of allograft tolerance. There is growing evidence indicating that Tregs control the activation of primary and memory T-cell responses. The literature on changes of Treg with aging is limited and controversial [40]. There are studies showing both increase and decrease in the numbers of Tregs [41–45]. It has been shown in aged porcine thymi that there are fewer regulatory cells to inhibit alloreactive cells [42]. Regarding Treg function, most studies showed that aged Tregs are dysfunctional and unable to suppress aged T-effector cells. In a mouse model, one study indicated that the percentages, phenotypes, the size of TCR repertoire, and function of CD4+ CD25+ Treg cells were altered significantly with aging. It showed that CD4+ CD25+ Treg cells of aged mice displayed significantly lower inhibiting ability on alloantigen-induced delayed-type hypersensitivity reaction or on inflammatory cytokines (IL-2 and IFN- γ) production, but not on cell proliferation of effector T cells [43]. In addition, there was a direct correlation between the expansion of Treg cells and the aged immune deficiency, and the authors speculated that depletion of these cells might be critical for restoring immune responses in aged animals [44]. In a clinical study, it was found that Tregs, accumulated as a result of aging, were capable of suppressing cytotoxic activity of CD8+ T and NK cells, and production of IL-2 [45].

It has been shown that Tregs in aged individuals may have a restricted TCR repertoire [46]. Studies in humans demonstrated that the suppressive activity of CD4+CD25+ Tregs declines

with age [47]. Other study showed that thymocytes of aged mice have a significant increase in the percentage of CD4+ CD25+ cells than in young mice [48]. In this study, the expression of surface markers also changed with aging. CD4+ CD25+ cell expression of CD69, CD5, CD28, and FoxP3 was lower, whereas the expression of CTLA-4 and CD28 was higher. *In vitro* studies showed that these aged CD4+ CD25+ cells maintained their potential to suppress the proliferation of activated responder lymphocytes of young mice, but not the proliferation of responder T cells from aged animals, implying that the response dysfunction may lie in changes of the CD4+ CD25– effector T-cell population’s ability to proliferate or respond to Tregs [48, 49].

Dendritic cells and costimulatory pathways in the elderly—Dendritic cells (DCs) are the most effective antigen presenting cells to initiate the immune response and play an important role on both rejection and tolerance, depending on the graft microenvironment [50]. Costimulatory signals, originating exclusively from professional antigen presenting cells, set the stage for either rejection or tolerance. Through “positive” costimulatory molecules and “negative” T-cell costimulatory pathways, the function of the immune system can be activated or down-regulated, respectively. In the elderly, the costimulatory system is dysfunctional [51]. It has also been shown that aging DCs have impaired migration to draining lymph nodes [52]. Data on age-associated changes in the number and function of DCs are controversial and vary depending on the subset of DCs and in the compartment in which they are located [52]. DC function is increased in healthy aged humans and mice, and may enhance allorecognition to compensate for an impaired function of senescent T cells [53–55]. However, in frail elderly patient, DC function deteriorates, reducing antigen presentation, expression of costimulatory molecules, and IL-2 production [16].

Della Bella et al. observed that DCs from aged individual have a more mature phenotype with higher expression of costimulatory molecules CD86 and CD83 [56]. Varas et al. observed a decrease in the density of thymic stromal DC with aging. They found reduced expression of MHC-II, CD40, CD86, and CD54 in thymic DCs from aged mice along with decreased allostimulatory capacity [57]. These stromal thymic DCs play a critical role in selection of Tregs and might explain differences in the subset of Tregs and resistance to tolerance. In accordance to this hypothesis, another study showed that different expression of CD80, CD86, and CD40 on DCs of old mice may explain the elevation of the percentage of natural Tregs in the thymus with aging [58].

With aging, the CTLA4 molecule is increased [59], whereas CD28, CD40-CD40L, MHC class II expression are reduced [35, 60–62]. At birth, CD28 costimulatory molecule is expressed on more than 99% of T cells, and at ages 70 to 90 it is reduced to 71% [60].

Innate immune system in the elderly—There is increasing data on the importance of the innate immune response in both rejection and tolerance [63–69]. All of components of the innate immune system are also affected by advanced age [70–73]. There is evidence that aging is associated with a hyperinflammatory state that may exacerbate chronic conditions such as atherosclerosis. [74]. There is an increase in pro-inflammatory cytokines, such as IL-6, IL-1B, TNF- α , C-reactive protein. The cytokine expression shifts toward an IL-17 alloimmune responses with aging [75]. Adhesion molecules and chemokines play an

important role in homing of lymphocytes and consequently in graft activation and rejection. They are generally increased by cellular stress [18]. It has been shown that T lymphocytes from elderly donors exhibited increased CD49d, CD50, and CD62L [76]. The vascular endothelium also regulates the postinflammatory fibroproliferative process [77]. Aging by itself enhances the sensibility of the endothelial cells to apoptotic stimuli and promotes morphological changes [78]. It has been shown that natural killer (NK) cells, key players of the innate immune system, have a decreased proliferative response upon stimulation with IL-2 [79].

Cells from the immune system are influenced by a variety of agents (hormones, cytokines, chemokines, adrenergic and cholinergic agonists, fatty acids, and immunoglobulins). The levels of many of these agents change with aging and can have a major impact on cell function. According to the theory proposed by Matzinger, the immune system recognizes any kind of cellular damage [80]. Thus, the aged microenvironment with increased cellular stress triggers “danger signals” and may facilitate activation of effector cells of the immune system instead of tolerogenic pathways. In addition, aged grafts are more susceptible to ischemia reperfusion injury because of increased production of reactive oxygen species, dysfunctional protective and repair mechanisms, leading to more damage and immune response [81, 82].

It has been shown that the aging process is associated with changes in the intracellular redox balance as a consequence of reduced capacity to produce active heat-shock proteins and reactive oxygen radicals scavengers [83, 84]. The healing process is also impaired with aging [85]. Cycles of injury and repair may have reached their limits, thus resulting in atrophy, uncontrolled proliferation, fibrosis, and impaired function [86, 87]. More recently, it has been shown that expression of Toll-like receptors, one of the receptors of the innate immune system, is altered in aged individuals [65, 74, 88, 89].

Aging and rejection—Both the age of donor and recipient play important role in allogenic response. In a large-multivariate analysis, donor age was identified as the most important risk factor for chronic kidney allograft failure [90]. The utilization of kidneys from old donors is also associated with an increased risk of delayed graft function (DGF) and acute rejection [91, 92]. It has been shown that donor age alone is representing a significant risk factor for patient death with a functioning kidney allograft, and it has been speculated that the poor function of the aged graft could lead to hypertension and an increased incidence of cardiovascular events [93]. Organs from elderly donors are particularly susceptible to ischemia/reperfusion injury, and associated with a higher incidence of DGF. For every 6 hours of cold ischemia, there is a 23% increase in the risk of DGF, thus increasing the risk for both, acute rejection and chronic graft deterioration [94].

Regarding the recipient age, it was commonly believed that older transplant recipients have a decreased risk to develop both acute and chronic rejection based on the concept of global deterioration of the immune system with aging [95]. To date, the reduced incidence of acute rejection has been confirmed in many experimental and clinical trials in cornea, kidney, cardiac, liver, and lung transplantation [92, 96]. The reduced incidence of acute rejection has been directly associated with an age-related immune dysfunction. Possible mechanisms to

explain the decreased incidence of acute rejections in the elderly include: reduced numbers of naïve T cells, dysfunctional memory cells, increased sensibility to immunosuppression, reduced TCR-V and defective T-cell signaling, increased T-suppressor cells, and altered cytokine profiles.

Because of the reduced incidence of acute rejection in older recipients, allocation of older organs to older recipients may provide a better “immunological matching.” Graft survival was best among elderly recipients, after adjustment for death with a functioning graft. The frequency of acute rejection declined with every cohort of increasing recipient age. Donor age, in contrast, was associated with gradually increasing frequencies of rejection. This effect is blunted when old organs are transplanted into old recipients, and old recipients receiving old organs have excellent rates of graft and overall survival [92]. Thus, an “old-for-old” program has been established in Europe—the Eurotransplant Senior Program [97], and proposed in the United States [98].

On the other hand, it has been shown that recipient age is also a strong and independent risk factor for the development of chronic allograft failure [99].

Important changes of the immune system that may increase the incidence of chronic rejection include increased numbers of memory T cells, low CD4+/CD8+ ratio, 31/32 shift [100], increased APC activation [19–21], upregulation of HLA-DR [101], production of antidonor HLA antibodies [42, 43], and increased pro-inflammatory cytokines (TNF- α , IL-4, IFN- γ , TGF β -1, and IL-6) [99]. Age-related nonimmunological changes include impaired antioxidative and repair-remodeling abilities, and associated comorbidities (lipid disorders, diabetes, cardiovascular disease, hypertension, etc.). It has been shown that increased concentrations of homocysteine, apolipoproteins, and altered insulin-like growth factors accelerate the progression of arteriosclerosis in the elderly [99]. Age-related hormonal changes can also adversely affect the prognosis of transplantation in the elderly [19, 97, 102, 103].

Aging and tolerance—Billingham and Medawar long ago showed that age interferes with immunologic tolerance. They showed that a “window of opportunity” for immunologic tolerance exists for transplantation in neonates [104]. On the other hand, the aging immune system undergoes a series of changes that interfere with both the immune response of the recipient and the immunogenicity of the graft, which lead to reduced graft survival [5, 105].

The phenomenon of neonatal tolerance is multifactorial and there are many theories [106–110]. Based on findings from Burnet, Billingham, and Medawar, it has been theorized that experimental neonatal tolerance may occur by negative selection in the same way as natural self-tolerance develops [104, 106]. Another fact is that the neonate immune system is associated with decreased expression of MHC class II antigens and may not effectively presents antigens [109]. In addition, the neonatal immune system has little antigenic experience (naïve) and consequently reduced numbers of memory cells [111]. Memory cells are ready to mount a destructive response and constitute barriers to achieve graft tolerance. However, Ridge and Matzinger challenge this concept, proposing that tolerance is not an intrinsic property of the newborn immune system, but rather that the conditions under which

the antigen is introduced determine whether the outcome is neonatal tolerance or immunization [110].

Aging is not only associated with increased resistance to achieve tolerance to foreign antigens [112] but also with loss of self-tolerance (autoimmunity). Aged animals and humans exhibit a decreased T-cell activation response although they have increased susceptibility to loss of self-tolerance. [38, 113–115].

Data on the effects of age on induction of tolerance to allografts is scarce. Most of the data on the effects of aging on immunologic tolerance come from animal experiments of oral tolerance to antigens. It has been shown in these studies that there is an age-dependent resistance to tolerance induction [116–124]. In transplantation, resistance to tolerance has been shown in a pancreas islet allograft model in the rat. Nine-month-old Lewis recipients were more resistant to intrathymic tolerance in comparison to 3- and 6-month-old recipients [41]. A study using anti-CD4 mAb (RIB 5/2) to induce tolerance to full-mismatched grafts of different age combinations in the rat showed that both the aged immune system and old graft interfere with tolerance and that these changes can be adoptively transferred to young recipients of young grafts [125]. Another study demonstrated that anti-CD45RB mAb therapy was ineffective in preventing rejection of cardiac grafts in aged recipients, although prolonged survival was similar to that observed in thymectomized young recipients [126]. In a large animal model for induction of tolerance to kidney allografts using cyclosporine, advanced age inhibited the establishment of tolerance [127]. Some studies showed that aged individuals may be rendered tolerant but may require that virtually all the potentially responsive cells be turned off and that the nature of antigen presentation sets the stage for immunization or tolerance [110, 116].

Changes in the innate and adaptive immune responses associated with aging may be obstacles to achieve immunologic tolerance. Potential mechanisms for this increased resistance are: (1) changes in frequencies and/or function of specific cellular subsets of the immune system deleting/anergizing; (2) different level of expression of adhesion, costimulatory, and MHC molecules, and heat-shock proteins; (3) the aged innate immune system/microenvironment (hormonal deficits, pro-oxidant and pro-inflammatory milieu), and (4) impaired ability of cellular repair.

MODULATION OF THE AGED IMMUNE SYSTEM

The increased resistance to achieve tolerance in aged individuals may be reversible. Modulation of the aged immune system by pharmacological or other means may represent a new avenue for prolongation of graft survival. Staples and colleagues showed successful induction of tolerance in older thymectomized and irradiated mice repopulated with lymphoid cells from young animals [118]. Other study showed that if aged mice resistant to tolerance induction are thymectomized, irradiated, and repopulated with spleen or bone marrow cells of young mice, they can become tolerant to specific antigens [118]. In another experiment, using a model of vascularized thymic transplantation in MHC inbred miniature swine it was shown that thymectomized recipients and aged recipients do not respond to an established protocol of tolerance induction with short-term tacrolimus. Surprisingly, aged

thymic grafts transplanted into young recipients could be rejuvenated both histologically and functionally, suggesting that host environmental factors play an important role in thymic senescence. Interestingly, rejuvenated aged thymus could restore the ability to induce tolerance to kidney grafts across MHC class I mismatch [42]. Thymic function is reduced with aging but it is not lost, suggesting that therapeutic approaches to enhance thymic function may be successful even in very aged hosts [128].

Traditionally, approaches to improve the immune response in the elderly have focused on thymic rejuvenation [129–131]. It has been shown that many approaches can enhance thymopoieses including: administration of hormones and cytokines (growth hormone, prolactin, ghrelin, keratinocyte growth factor, vitamin D, and IL-7), androgen ablation, caloric restriction, bone marrow transplantation, and thymic tissue transplantation [131–140]. In the future, gene therapy and stem cell transplants may yield even better results.

A newer potential approach to enhance immunologic tolerance in the elderly is by modulation of tolerogenic cells. The potential of tolerogenic cells (regulatory T cells or tolerogenic DCs) transfer for the treatment of T-cell-mediated diseases (e.g. transplant rejection) in humans has gained momentum in recent years [141, 142].

It is unclear whether any single agent administered into older subjects can rejuvenate the immune system. However, combination of therapies to boost the aged immune system and reduce graft immunogenicity may improve outcomes.

CONCLUSIONS AND FUTURE PROSPECTS

Aging should be seen as a global and interconnected process of deterioration of all immune compartments. The aging process causes important anatomical and functional changes that result in reduction of the functional reserve and inability to cope with physiological and pathological stresses. In addition, changes associated with immunosenescence and the aging microenvironment may interfere with antigen recognition and efficient presentation, which in turn modifies both rejection and tolerance. The changes associated with immunosenescence are just beginning to be revealed.

Despite the aging population in most parts of the world, elderly patients continue to be underrepresented in transplant clinical trials [143]. To optimize the outcomes of transplantation in the elderly, it is necessary to test new protocols in the elderly population. Individualization of the immunosuppressive treatment and interventions to selectively target and reverse the crucial dysfunctions of the aging immune system and aged grafts are promising therapeutic strategies to improve graft and patient survival of the elderly transplant population.

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