Impact of Donor and Recipient Age on Allograft Tolerance

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Abstract

The elderly represent the fastest growing segment of the population with end-stage organ disease and the use of aged grafts increased exponentially. Since aging of the immune system, or "immunosenscence" is generally associated with weaker immune responses, one might expect the elderly to be less reactive against transplanted organs than younger patients and therefore to show better results in terms of transplant outcome. Paradoxically, however, experimental studies and clinical data of organ transplantation show that old age of either the recipient or the donor is associated with poorer outcomes. On the other hand transplant tolerance is easier to be induced in the neonatal period. One potential reason for this discrepancy may lie in the effects of immunosenescence on the induction of tolerance. While the impact of aging on acute and chronic allograft rejection has been extensively studied, its role on establishing transplant tolerance is not well known. Since tolerance is an active process, and not just the absence of an immune response, the immunologic changes associated with the aging process may interfere with graft survival. In experimental and clinical transplantation, most successful tolerance induction protocols have been tested on young individuals, using grafts from young donors. However, some experiments that have utilized aged animals have demonstrated resistance to tolerance induction. Extrapolation of these results to humans suggests that protocols for clinical tolerance induction may not be effective in the elderly and may need to be revised for this population. The resistance to achieving immunological tolerance with aging is complex and multifactorial. Here, we review the age associated changes that may interfere with immunologic tolerance. Understanding this phenomenon may help in developing novel therapeutic approaches to reverse the crucial dysfunctions of the aging immune system and achieve effective tolerance regimens for the elderly.

Key words: *Aging, Tolerance induction, Transplant, Immunosenescence*

The exponential increase of older individuals in our society and the shortage of organs present significant challenges for organ transplant. Elderly individuals are the fastest growing subgroup of the population with end-stage organ disease (1, 2). In 2008, in the United States, patients older than 65 years represented 13.2% of candidates for any solid-organ transplant, and donors older than 65 years represented 9.3% (OPTN-UNOS 2008).

The effects of aging on acute and chronic allograft rejection have been extensively studied (2). It has been established that the increasing age of both donors and recipients adversely affects graft survival. Older donor age has been identified as the most important risk factor for chronic kidney allograft failure (3-5). Although advanced recipient age alone is associated with fewer episodes of acute rejection, it is a strong and independent risk factor for the development of chronic allograft failure (6). However, the effects of aging on transplant tolerance induction protocols are not well known. Data on the effects of age on immunosuppression-free protocols are scarce. In experimental and clinical transplant studies, most tolerance induction protocols (long-

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term immunosuppression-free regimens) have been tested on young individuals, and grafts from young donors have been used. Thus those protocols may not be effective in elderly patients.

Because immunologic tolerance is an active process and not just the absence of an immune response, immunologic changes associated with aging may also interfere with graft accommodation. Defective steps can occur early at the level of antigen recognition and presentation or later at the level of effector-cell modulation. Because of the intrinsic changes associated with aging, it has been suggested that age-adapted immunosuppression may be necessary to improve results (2, 7-10).

Neonatal Immune System: A Window of Opportunity for Immunologic Tolerance

It has been known since the early experiments of Billingham and Medawar that age interferes with immunologic tolerance. Those authors showed that a window of opportunity for immunologic tolerance exists for transplant in neonates (11). However, the aging immune system undergoes a series of changes that interfere with the immune response of the recipient and the immunogenicity of the graft, and those changes lead to reduced graft survival (2). The phenomenon of neonatal tolerance is multifactorial and the subject of many theories (12-16). Based on the findings of Burnet, Billingham, and Medawar, it has been theorized that experimental neonatal tolerance may occur by negative selection, as does natural self-tolerance (11, 12). The neonatal immune system exhibits decreased expression of major histocompatibility complex (MHC) class II antigens and may not effectively presents antigens (15). In addition, the neonatal immune system is naïve (ie, it demonstrates little antigenic experience) and consequently has a reduced number of memory cells (17). These cells mount a destructive response against the graft and constitute a barrier to achieve graft tolerance. However, Ridge and colleagues challenged that concept by suggesting that tolerance is not an intrinsic property of the newborn immune system but rather that the conditions under which an antigen is introduced determine whether neonatal tolerance or immunization results (16).

Immunosenescence and Increased Resistance to Antigen Tolerance

Because immune responsiveness decreases with age, it is reasonable to assume that older individuals would be more easily rendered tolerant of transplanted organs, as stated previously (18). However, the opposite seems true. Aged recipients are less likely to become tolerant of specific antigens. Aging is associated not only with increased resistance to achieving tolerance to foreign antigens (19) but also with a loss of self-tolerance (autoimmunity). Aged animals and humans exhibit a decreased T-cell activation response yet demonstrate increased susceptibility to the loss of self-tolerance (20-23).

Data on the effects of age on the induction of tolerance to allografts are few. Most data on the effects of aging on immunologic tolerance are derived from experiments involving oral tolerance to antigens in animal models. Those studies have shown that there is an age-dependent resistance to tolerance induction (24-41). In a study by Qian and colleagues, resistance to tolerance was demonstrated in a pancreas islet allograft experiment in the Lewis rat (42). Those authors showed that 9-month-old recipients were more resistant to intrathymic tolerance than were 3- or 6-month-old recipients (42). A study using anti-CD4 mAb (RIB 5/2) to induce tolerance to full mismatched grafts of different age combinations in rats showed that an aged immune system and an old graft interfered with tolerance and that those changes were adoptively transferred to young recipients of a young graft (43). Another study demonstrated that anti-CD45RB mAb therapy was ineffective in preventing the rejection of cardiac grafts in aged recipients, although prolonged survival was similar to that in thymectomized young recipients (44). In a large animal model to study the effectiveness of cyclosporine in inducing tolerance to kidney allografts, advanced age inhibited tolerance (45). Aging also abrogates the protective effects of graft ischemic preconditioning (46-50). In addition, older animals are not only more resistant to developing immunologic tolerance but may also exhibit a different response to immunosuppression (7,8,51).

As we noted above, many experiments have demonstrated that aged individuals cannot be rendered tolerant to specific antigens. However, that theory might not be absolutely true. New immunological concepts show that the induction of tolerance requires that virtually all potentially responsive cells be rendered inactive and that the nature of antigen presentation sets the stage for

immunization or tolerance. Thus, the higher success of tolerance induction in younger individuals may be associated with the dose and quality of the cells transferred. For example, a neonate has only a few thousand native T cells; thus, after the adoptive transfer of 5×10^6 spleen cells, there are 100 antigen-presenting cells for every neonate recipient T cell. However, an adult has 2000 times more T cells than does a neonate; thus the same inoculum in an adult has less than 1 antigen-presenting cell for every 10 T cells. This means that the tolerizing dose for an adult may be much higher than that for a neonate (16). One study has shown that aged mice are refractory to oral tolerance induction; they require 100 times more antigen than do younger littermates to induce unresponsiveness (52).

Changes in the Aged Immune System That Contribute to Increased Resistance to Tolerance

Age-associated changes in the immune system have a crucial role in the susceptibility to tolerance induction. However, age-related comorbid conditions (diabetes, hypertension, steatosis, arteriosclerosis) that cause poor organ function can interfere with tolerance induction, regardless of changes in the immune system. Organ damage after brain death has also been shown to interfere with tolerance induction (53).

Changes during the immunosenescence process result in both quantitative and qualitative modifications of specific cellular subpopulations rather than a global deterioration of the immune system, as was previously thought. The most striking changes are found in phenotypes and the functions of T-cell components and less frequently in components of the innate immune system (54, 55). Thymic involution is particularly associated with resistance to tolerance.

The immune status of the recipient may influence which tolerance mechanism (deletion, anergy, ignorance, exhaustion, suppression) operates in any particular situation. Tolerance induction is a dynamic and active process, and any or all of those mechanisms may be operating at different stages of induction and maintenance (56). In the elderly, changes in innate and adaptive immune responses may interfere with those tolerance mechanisms and can render them more resistant to immunologic tolerance. Possible reasons for that increased resistance are: 1) changes in the frequency and/or function of specific cellular subsets of the immune system (memory and regulatory cells); 2) a different level of expression of adhesion, costimulatory, and MHC molecules and heat-shock proteins; 3) changes in the innate immune system and the aged microenvironment (hormonal deficits, alterations in the prooxidant and proinflammatory milieu) (4) impaired cellular repair. Those factors will be discussed separately in subsequent sections of this review.

Aged memory cells

The frequency of memory cells increases with age; this reflects an accumulation of antigenic experiences. In neonates ,99% of T cells are naïve (CD3 CD45RA+ cells) while in people aged 50 to 70 years they represent 35%, and in centenarians 20%, (57, 58). Alloreactive memory cells, which are generated either by previous sensitization to alloantigens or by heterologous immunity, are barriers to achieving graft tolerance (59). Unlike naïve T cells, memory cells can recirculate in peripheral nonlymphoid tissues. They can be rapidly recruited, and they initiate early responses directly in the graft. Memory cells can be fully activated in the absence of costimulation (60, 61), and they are more differentiated and less susceptible to apoptosis (59). The response of memory cells to antigens has greater magnitude and efficacy than does the response of naïve T cells (62). High frequencies of memory cells are associated with increased incidence severity of rejection (63).

Age-related impairment of Fas/Fas ligand (FasL)-mediated apoptosis (which results from a th1/th2 shift of cytokines), aberrant T-cell receptor/CD3 downstream signaling pathways, and altered CD28/B7-mediated T-cell costimulatory signals have been noted. CD 27+ (memory marker) B cells increase in number with age (64). An increased proportion of mature B cells may also account for the increased resistance to tolerance induction in the elderly (65-68).

MHC expression in the aged

MHC molecules are of major importance in both tolerance and rejection. MHC class II molecules have a key role in regulating and restricting the immune response (69-71). Optimal levels of MHC expression are crucial for the proper functioning of cellular and humoral immune responses. MHC class 1 protein

levels increase significantly with age on both peripheral blood and spleen (T cell and B cell) lymphocytes, but the percentage of MHC class 2-expressing spleen lymphocytes markedly decreases (72-75). That decrease was shown to result from a decrease in the proportion of B cells relative to T cells in the spleen lymphocyte population of old mice (72).

Some studies have demonstrated that the ease of B-cell tolerance induction decreases with age in both native and lethally irradiated, thymectomized mouse recipients of B cells from donors of different ages (23,76). The age resistance of the peripheral B-cell population to tolerance induction might account in part for the increased incidence of autoantibodies in those studies.

Aged regulatory T cells

Regulatory T cells (Tregs) have a crucial role in the induction and maintenance of allograft tolerance. Cumulative evidence indicates that regulatory T cells control the activation of primary and memory T-cell responses. However, very little is known about whether there is an association between regulatory T cells and impaired immune responses in the aged.

One study showed that anti-CD45RB therapy was ineffective in preventing the rejection of cardiac grafts in aged recipients (43). The authors suggested that this finding might be due to the age-associated reduction of thymic regulatory T-cell production. Previous experiments have suggested that in aged porcine thymi, there are fewer regulatory cells to inhibit alloreactive cells or they are slower in generating donor-specific regulatory cells and in deleting or anergizing new alloreactive thymocytes (77).

In a mouse model, one study demonstrated that the percentages, phenotypes, and size of the T-cell receptor (TCR) repertoire and the function of CD4+ CD25+ regulatory T cells changed significantly during aging (78). The study results showed that when CD4+ CD25+ regulatory T cells in young and old mice were compared, the cells in the old mice exhibited significantly less inhibition of alloantigen-induced delayed-type hypersensitivity reactions and inflammatory cytokine (IL [interleukin] 2 and interferon gamma) production but not significantly less inhibition of effector T-cell proliferation. Another study (79) showed that a great accumulation of regulatory T cells prevented the activation of immune responses and the rejection of immunogenic tumors in aged animals. There were significantly more CD4+CD25+FoxP3+ and CD8+CD25+FoxP3+ regulatory T cells in the spleen and lymph nodes of the old animals (as opposed to the younger animals). In addition, there was a direct correlation between the expansion of regulatory T cells and immune deficiency in the old subjects, and the authors suggested that the depletion of those cells might be critical to the restoration of the immune response in aged animals. In a clinical study, regulatory T cells that had accumulated as a result of aging and/or medical conditions suppressed the cytotoxic activity of CD8+ T and natural killer cells and the production of IL-2 (80).

Older individuals have more suppressor cells (regulatory T cells) but achieve allograft tolerance with relative difficulty, perhaps because in the elderly, regulatory T cells (though increased in number) have a restricted TCR repertoire, are dysfunctional (ie, exhibit reduced activity), and cannot suppress aged T-effector cells. Hausman and colleagues showed a long time ago that suppressor T cells induced in young mice suppressed the response after stimulation in young but not old mice. Similarly, suppressor T cells induced in old mice decreased the response in old but not young mice. Those findings suggest that aging is associated with changes in the idiotype repertoire that can influence the specificity of the suppressor T cells in tolerant mice (81). One study in humans showed that the suppressive activity of CD4+CD25+ regulatory T cells decreases with age (82). In a comparison of the thymus in young and old mice, another study revealed that the thymi of aged mice had a 2-fold increase in the percentage of CD4+ CD25+ thymocytes (83). In that study, the expression of surface markers, which is usually used to characterize regulatory cells, changed with aging. In aged mice, CD4+ CD25+ cell expression of CD69, CD5, CD28, and FoxP3 was lower, and the expression of CTLA-4 and CD28 was higher than that in young mice. "In vitro" studies showed that these aged CD4+ CD25+ cells maintained their potential to suppress the proliferation of activated responder lymphocytes from young mice but not the proliferation of responder T cells from aged mice. This implies that the response dysfunction may lie in the altered ability of CD4+ CD25– effector T cells to proliferate or respond to regulatory T cells (83, 84).

Costimulatory Pathways in the Elderly

Dendritic cells are the most effective antigen-

presenting cells that initiate an immune response. They have an important role in both rejection and tolerance, depending on the graft microenvironment (85). Costimulatory signals, which are produced only by 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 (86). Data on age-associated changes in the number and function of dendritic cells are controversial and vary according to the subset of dendritic cells and the compartment in which they are located (87). Dendritic cell function is increased in healthy older humans and mice and may enhance allorecognition to compensate for the impaired function of senescent T cells (88-90). However, in frail elderly patients, dendritic cell function deteriorates; this reduces antigen presentation, the expression of costimulatory molecules, and IL-2 production (91). Della Bella and colleagues observed that dendritic cells from aged individuals have a relatively more mature phenotype with a higher expression of the costimulatory molecules CD86 and CD83 (92). Varas and colleagues noted that a decrease in the density of thymic stromal dendritic cells occurs with aging (93). Those authors found reduced an expression of MHC-II, CD40, CD86, and CD54 and a decreased allostimulatory capacity in thymic dendritic cells from aged mice. These stromal thymic dendritic cells have a critical role in the selection of regulatory T cells and might explain differences in the subsets of regulatory T-cells and the resistance to tolerance. Another study showed that variations in the expression of CD80, CD86, and CD40 in the dendritic cells of old mice may explain the increase in the percentage of natural T regulatory cells in the thymus that occurs with aging (94).

As an individual ages, the number of CTLA4 molecules increases and (95) and the number of CD28 (96) and CD40-CD40L) molecules decreases (97, 98), as does MHC class II expression (72). At birth, the CD28 costimulatory molecule is expressed on more than 99% of T cells, but in an individual 70 to 90 years of age, that molecule is expressed on 71% of those cells (96). Blocking the costimulatory pathways used to activate memory T cells such as ICOS-B7h, CD134-CD134L, and CD70-CD27 seems to be a promising method by which immunologic tolerance can be established (59). That method may be particularly useful for inducing tolerance in the elderly transplant population, who have an increased number of memory cells.

Innate Immune System in the Elderly

Data on the importance of the innate immune response in both rejection and tolerance are increasing (99-103). The innate immune system is also affected in advanced age (103-107). There is evidence that aging is associated with a hyperinflammatory state (108), there is an increase in the number of proinflammatory cytokines such as IL-6, IL-1B, tumor necrosis factor α, C-reactive protein, and prostaglandins; this creates a microenvironment that might not be favorable for tolerance induction. It has been shown that the expression of Toll-like receptors, which are a type of receptor in the innate immune system, is altered in aged individuals (101, 108-111). Grafts from aged donors have been shown to be more susceptible to ischemia reperfusion injury (112, 113).

Cells from the immune system are influenced by a variety of agents (hormones, cytokines, chemokines, adrenergic and cholinergic agonists, fatty acids, immunoglobulins). The levels of many of those agents change during aging and can greatly impact cell function. According to Matzinger, the immune system recognizes damage (114). Thus the aged microenvironment, which is characterized by increased cellular stress, triggers danger signals and may facilitate the activation of effector arms of the immune system instead of tolerogenic pathways.

There is a very close interplay between the innate response and the adaptive response. The ability to control the activation of regulatory T cells has emerged as a key function of innate immunity (115). There is also evidence that strongly supports the role of innate immunity in B-cell tolerance (116). One study showed that natural killer cells seem to be required for the induction of tolerance to islet allografts (117).

Adhesion molecules and aging

Adhesion molecules have an important role in the homing of lymphocytes and consequently in graft activation and rejection. They are usually increased in number by cellular stress. It has been shown that T lymphocytes from elderly donors exhibit increased CD49d, CD50, and CD62L (118).

The endothelium, which is the first contact between host and graft, has an important role in both rejection and tolerance. The vascular endothelium also regulates the postinflammatory fibroproliferative process (119). Aging itself enhances the sensitivity of endothelial cells to apoptotic stimuli and promotes morphologic changes (120).

Heme oxygenase-1 and tolerance induction in the elderly

Heme oxygenase-1 (HO-1) is considered to be the most critical cytoprotective mechanism that is activated when a cell is subjected to any type of stress. HO-1 may act as a master switch" for many cellular defense strategies against injury (121,122). Many reports have shown the beneficial effects of HO-1 in transplant recipients, in whom that agent reduces ischemia-reperfusion injury, inflammation, apoptosis, allo-mediated cell toxicity, and graft-versus-host disease (123).

The changes in HO-1 expression in the elderly remain controversial (124) and may depend on cell type. One study demonstrated that enhanced oxidative stress during aging is accompanied by the compensatory induction of HO-1 via activation of the nuclear factor kappa B (NFkB) pathway (125). Therapy for the induction of HO-1 has been shown to increase graft survival in young as well as aged animals (126-128). Grafts from old donors, who are intrinsically low HO-1 responders (129), could benefit from the stimulation of HO-1 expression.

Clinical observations that age may interfere with tolerance induction

To our knowledge, prospective randomized trials evaluating immunosuppressive drug protocols for tolerance induction in the elderly are not available. The elderly are often excluded from clinical trials because their comorbid conditions, altered drug pharmaco-kinetics, and higher incidence of adverse effects and complications may be confounding factors that render data analysis more complicated. However, there is increasing clinical evidence of the effects of age on tolerance induction (Table).

It has been shown that the in utero transplant of hematopoietic stem cells is a promising fetal therapy for the treatment of leukemia and genetic disorders such as immune deficiencies and inborn errors of metabolism. Because the fetus is immunoincompetent, the engraftment of transplanted stem cells is possible without immunosuppression. In addition, there is enough space in fetal bone marrow to permit the homing of transplanted stem cells (130,131). A prospective clinical study showed that the proportion of CD4(+)CD25(high) regulatory T cells in kidney transplant recipients was higher when the donor was young than when the donor was older than 65 years (132).

Table. Possible mechanisms of age-related tolerance induction resistance.

Thymic involution
Increased frequency of memory cells
Antigen-presenting cell dysfunction (Ag presentation, signaling, costimulation)
Regulatory T-cell dysfunction (limited repertoire, reduced suppression)
Inflammatory milieu (increased danger signals)
Reduced cytoprotective, antioxidant, and repair mechanisms
Increased major histocompatibility complex and adhesion molecule expressio

Data from all 30 216 kidney transplants performed in United States between 1997 and 2004 showed that the 5-year graft survival rates for recipients aged 1 to 10 years, 18 to 34 years, and older than 65 years were 83%, 72.3%, and 59%, respectively. The 5-year graft survival rates were 69%, 75.8%, and 49.5% when the donor was between 1 and 10 years of age, 18 to 34 years, and older than 65 years, respectively (UNOS-OPTN). Data from the UNOS database show that the projected half-life of a kidney graft was highest (18 years) in patients younger than 2 years. In teenagers, the projected graft half-life was lower (7 years) than that in adults and children (133). However, the low projected graft expectancy in teens was not due to the status of the immune system, because that age group has one of the best 1-year graft survival rates; instead, it reflects noncompliance (the highest rate among all age groups) with immunosuppressive therapy (134).

Further evidence supporting the finding of easier tolerance induction in immunologically immature individuals comes from the results of ABO-incompatible transplants. It has been reported that the requirement for ABO compatibility in heart transplant does not apply to infants because they often tolerate an allograft (135-139). It has been reported that after an ABO-incompatible living donor kidney transplant, the graft survival rates are better in patients < 15 years (100%, 89%, 78%, and 78% at the ages of 2, 5, 10, and 15 years, respectively) than in patients > 15 years (77%, 77%, 64%, and 59%, respectively) (138). In another ABO-incompatible liver transplant study, the 5-year survival rates in patients < 1 year old, ≥ 1 to < 8 years, ≥ 8 to < 16 years, and ≥ 16 years old were 76%, 68%, 53%, and 22%, respectively (139).

Most reported cases of clinical operational (prope) tolerance are from younger patients (140-145) In a

recent clinical report on the medical history of 10 kidney transplant recipients who exhibited an immunosuppressive drug-free operational tolerance for 9.4 ± 5.2 years, the recipient and donor ages were younger (median age, 33.9 and 25 years, respectively) than those in the general transplant population. This suggests that young age and graft quality may facilitate the induction of operational tolerance (140). Another clinical study on the induction of tolerance with donor bone marrow and a conditioning regimen in kidney recipients used younger patients (mean age, 30.8 years for recipients) (141). In that study, in 4 out of 5 recipients, it was possible to discontinue all immunosuppressive therapy 9 to 14 months after the transplantation, and renal function has remained stable for 2.0 to 5.3 years after transplantation.

Pediatric transplant recipients may be the easiest population in which to induce tolerance, and those patients may experience even greater benefits from tolerance induction than would adult patients. Mazariegos and colleagues, using a protocol to withdrawal immunosuppression after liver transplant in 28 patients, showed that the majority of the successfully weaned patients (22/28, 79%) were transplanted as children before the age of 18 (age range: 0.1 to 49.9 years, mean±SD: 11.8+/-15.5 years) (142). A study of avoidance of immunosuppression would be particularly interesting in pediatric transplant recipients because they have high rate of treatment noncompliance and a relatively greater need for prolonged graft survival and because in that population, the adverse effects of long-term immunosuppression (eg, poor linear growth, increased incidence of posttransplant lymphoproliferative disorders, cosmetic effects) are especially detrimental (146).

Besides the differences in the susceptibility to tolerance induction there is increasing evidence supporting the concept of age-adapted immunosuppression (8, 9). Aged grafts are more susceptible to ischemia and acute rejection episodes (147,148), and may require treatment with more immunosuppressive drugs. However, aged recipients experience fewer episodes of acute rejection and may require less immunosuppression (2, 9).

Modulation of the Aged Immune System

The increased resistance to tolerance in aged individuals may be reversible. Although it is currently not used in clinical practice, modulation of the aged immune system by pharmacologic or other means may represent a new avenue to prolong graft survival. However, it is unclear to what extent immune function can be therapeutically enhanced in aged individuals.

Staples and Talal demonstrated the successful induction of tolerance in older thymectomized, irradiated mice that had received lymphoid cells from younger mice (30). Another study showed that if aged mice that were resistant to tolerance induction were thymectomized, irradiated, and repopulated with spleen or bone marrow cells from young mice, the older subjects became tolerant to specific antigens (30). In another experiment using a vascularized thymic transplant in MHC-inbred miniature swine, the investigators showed that thymectomized recipients and aged recipients did not respond to an established protocol of tolerance induction with short-term tacrolimus. Surprisingly, aged thymic grafts transplanted into young recipients were rejuvenated both histologically and functionally; this suggests that host environmental factors have an important role in thymic senescence. Interestingly, a rejuvenated aged thymus was shown to restore the ability to induce tolerance to kidney grafts across an MHC class 1 mismatch (77). One study tested T-cell regenerative capacity after bone marrow transplant in a setting devoid of peripheral (homeostatic) expansion. To accomplish that, TCR-transgenic (Tg+) T-cell–depleted bone marrow was administered to aged and young recipients lacking an antigen specific for the Tg+ TCR. The aged recipients regenerated approximately 50% of the TCR Tg+ cells that were regenerated in young bone marrow transplant recipients. This provides evidence that even very aged thymi retain the capacity to regenerate significant numbers of mature T-cell progeny. Some authors therefore suggest that thymic function decreases during aging but is not lost and that therapeutic approaches that enhance thymic function may be successful even in very aged hosts (149).

Traditionally, approaches that improve the immune response in the elderly have focused on thymic rejuvenation (150-156). It has been shown that many such treatments (the administration of hormones and cytokines [growth hormone, prolactin, ghrelin, keratinocyte growth factor, vitamin D, IL-7]), androgen ablation, caloric restriction, bone marrow transplant, and thymic tissue transplant) can enhance thymopoiesis (157-165). In the future, gene therapy and stem cell transplants may yield even better results.

Donor or graft pretreatment is another method of improving graft acceptance. Preventing and minimizing existing damage to grafts reduce immunogenicity and may facilitate tolerance induction (166,167). A newer approach to enhancing immunologic tolerance in the elderly involves the modulation of tolerogenic cells (regulatory T cells or tolerogenic dendritic cells). The potential of tolerogenic cell transfer for the treatment of T-cell–mediated conditions (such as transplant rejection) in humans has gained momentum in recent years (168,169).

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

Conclusions

Defining ideal approaches and challenges to establish immunological tolerance in the lab will provide information to translate it into the clinical setting (170-174). The advanced age of donors and recipients is an obstacle to tolerance induction in experimental transplants. Changes associated with immunosenescence and the aging microenvironment may interfere with antigen recognition and efficient presentation and with the triggering of molecular pathways that favor tolerance. Tolerance protocols for the elderly should not be tested in the clinical setting until those barriers have been overcome. Tolerance induction protocols would be more successful in and more beneficial to pediatric transplant patients. Further definition of the molecular changes in the immune system that are associated with aging is also required. Therapeutic agents that can reverse the crucial dysfunctions of the aging immune system (such as aberrant immune responses and the reduced immunogenicity of aged grafts) are needed to enable tolerance induction in the elderly. Approaches including the induction of tolerogenic dendritic cells, the promotion of thymic rejuvenation, and stem cell transplants are promising (175).

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