DOWNLOAD PDF AGING AND THE IMMUNE RESPONSE

Chapter 1 : Aging Horse Vaccines and Immune Response | Purina Animal Nutrition

The effects of aging on the immune system are manifest at multiple levels that include reduced production of B and T cells in bone marrow and thymus and diminished function of mature lymphocytes in secondary lymphoid tissues. As a result, elderly individuals do not respond to immune challenge as.

This blog entry focuses on research on T-cells. The research is relevant to aging because it challenges the traditional view that T-cell numbers and potency decrease with advanced aging making the body ever-more susceptible to diseases, and that essentially nothing can be done about this. Overview â€" the immune systems and T cells Like the US Departments of Defense and Homeland Security, our immune systems involve many complex interacting subsystems and components. In fact, humans have two interacting immune systems, the innate immune system which is older and common to more primitive species, a system that offers fixed responses to pathogens and an adaptive immune system that not only defends against pathogens but learns about them so as better to protect the body in the future. This means that the cells of the innate system recognize and respond to pathogens in a generic way, but unlike the adaptive immune system , it does not confer long-lasting or protective immunity to the host. The adaptive immune response provides the vertebrate immune system with the ability to recognize and remember specific pathogens to generate immunity , and to mount stronger attacks each time the pathogen is encountered. They can be distinguished from other lymphocyte types, such as B cells and natural killer cells NK cells by the presence of a special receptor on their cell surface called T cell receptors TCR. Several different subsets of T cells have been discovered, each with a distinct function ref. Each plays its own specialized role in the adaptive immune system. B cells and T cells are the major types of lymphocytes. However, in nearly all other vertebrates , B cells and T-cells are produced by stem cells in the bone marrow. Thymopoiesis is the process in the thymus by which thymocytes differentiate into mature T lymphocytes T cells ref. Complex transcription factors and miRNAs are involved in the selection of destination-type T-cells ref ref. Chemokines produced by thymic stromal cells and chemokine receptors on the thymocytes play an indispensable role in guiding developing thymocytes into the different microenvironments ref. For one matter, thymic involution starts at an early age. There are strong age-related changes in hormone production ref. Older people may take anti-inflammatory medications like prednisone which inhibit immune function. And changes in patterns of epigenetic markers alter gene activation so as to reduce responsiveness of T cells with age. Our results show that the aberrant activation and proliferation status was related to lower sjTREC numbers a peripheral proliferation marker and both, higher CD57 expression levels and shortened telomeres replicative senescence-related markers. Elderly individuals show a greater contraction of the CD8 naive T cell numbers and all homeostatic alterations were more severe in this compartment. In addition, we found that low functional thymus show a CD4-biased thymocyte production. Taken together, our results suggest a homeostatic deregulation, affecting mostly the naive CD8 T cell subset, leading to the accumulation of age-associated defects in, otherwise, phenotypically naive T cells. Malnutrition, nutritional imbalances and other triggers of thymic involution. The publication Nutritional imbalances and infections affect the thymus: The thymic microenvironment the non-lymphoid compartment that drives intrathymic T-cell development is also affected in malnutrition: Profound changes in the thymus can also be seen in deficiencies of vitamins and trace elements. Taking Zn deficiency as an example, there is a substantial thymic atrophy. In conclusion, the thymus is targeted in several conditions of malnutrition as well as in acute infections. These changes are related to the impaired peripheral immune response seen in malnourished and infected individuals. Recent research It may be possible to discover safe ways to halt or reverse thymic involution and therefore keep the thymus gland active in producing T-cells in aging people. For several years now researchers have been pursuing approaches to preserving age-related T-cell functionality via slowing, halting or reversing thymic involution. Dysregulation of T-cell function is thought to play a critical part in these processes. One of the consequences of an aging immune system is the process termed thymic involution, where the thymus undergoes a progressive reduction in size due to profound changes in its anatomy associated with loss of thymic epithelial cells and a decrease in thymopoiesis. This

decline in the output of newly developed T cells results in diminished numbers of circulating naive T cells and impaired cell-mediated immunity. Although to date no interventions fully restore thymic function in the aging host, systemic administration of various cytokines and hormones or bone marrow transplantation have resulted in increased thymic activity and T-cell output with age. These strategies include the use of sex steroid ablation, the administration of growth and differentiation factors, the inhibition of p53, and the transfer of T cell progenitors to alleviate the effects of thymus dysfunction and consequent T cell deficiency. Male hormone blocking One of the approaches to thymic renewal has been based on blocking male hormone since such hormones appear to be implicated in the process of thymic involution. Treatments that block male sex hormone have in some circumstances been shown to reverse age-related thymic involution but with side effects. We have investigated the influence of testosterone on the ectopic synthesis of glucocorticoids GCs in thymocytes, an activity recently shown by us to be important for the homeostatic regulation of these cells. It appears that glucocorticoids can play different roles. Basal GC levels might promote growth of early thymocytes in young mice, and increased levels, generated through a stress reaction, apoptosis in these cells. A gradual loss of GC synthesis in TECs during aging might contribute to thymic involution, a process so far unexplained ref. Relative to reversing immune system aging, functional senescence of immune system cells may not be associated with telomere shortening and may be reversible. However, the mechanism that regulates the end-stage differentiation of these cells is unclear. This suggested that telomerase activity was actively inhibited in this population. The research, published in the September issue of the Journal of Immunology, opens up the possibility of temporarily reversing the effects of aging on immunity and could, in the future, allow for the short-term boosting of the immune systems of older people. Because our immune systems become less effective as we age we suffer from more infections and these are often more severe. This takes a serious toll on health and quality of life. These caps, called telomeres, get shorter each time a white blood cell multiplies until, when they get too short, the cell gets permanently deactivated. This means that our immune cells have a built-in lifespan of effectiveness and, as we live longer, this no longer long enough to provide us protection into old age. This told the researchers that there must be another mechanism in the immune system causing cells to become deactivated that was independent of telomere length. It was like a football manager finding out that some star players who everyone thought had retired for good could be coaxed back to play in one last important game. Medicines which block this pathway are already being developed and tested for use in other treatments so the next step in this research is to explore further whether white blood cells could be reactivated in older people, and what benefits this could bring. It is perfectly normal for our immune systems to become less effective and there are good evolutionary reasons for this. This work has discovered a new and unforeseen process controlling how our immune systems change as we get older. By increasing the incidence and severity of infection, weakened immunity seriously damages the health and quality of life of older people so this research is very valuable. Peripheral maintenance of naive T cells over the lifespan is necessary because their production drastically declines by puberty, a result of thymic involution. We report that this maintenance is not random in advanced aging. These high-avidity precursors preferentially responded to infection and exhibited strong antimicrobial function. Thus, T-cell receptor avidity for self-pMHC provides a proofreading mechanism to maintain some of the fittest T cells in the otherwise crumbling naive repertoire, providing a degree of compensation for numerical and diversity defects in old T cells. The finding may lead to targeting these cells with vaccinations that increase their number and improve protection against disease in older adults. Improving T cell function can result in improved immunity. See Restoration of the thymic cellular microenvironment following autologous bone marrow transplantation. It appears that thymic involution like so many other aging-related changes is to a large extent dependent on epigenetic factors, so age-related changes are potentially stoppable or reversible by epigenetic interventions. There appears to be a significant amount of current research related to epigenetic mechanisms and gene-activation pathways relating to T-cell genesis and homeostasis. For example, a number of publications have been concerned with Foxp3 and NF-kappaB expression in regulatory T-cells. From DNA methylation controls Foxp3 gene expression: Certain dietary supplements appear to be protective against thymic involution and facilitate thymopoiesis in aged individuals One such supplement is zink, as suggested in the publication Correlation between zinc status

and immune function in the elderly. We hypothesized that impaired zinc status associated with aging would mediate the decline in thymic function and output and that restoring plasma zinc concentrations via zinc supplementation would improve thymopoiesis and thymic functions. There are remarkable parallels in the immunological changes during aging and zinc deficiency, including a reduction in the activity of the thymus and thymic hormones, a shift of the T helper cell balance toward T helper type 2 cells, decreased response to vaccination, and impaired functions of innate immune cells. Many studies confirm a decline of zinc levels with age. Most of these studies do not classify the majority of elderly as zinc deficient, but even marginal zinc deprivation can affect immune function. Consequently, oral zinc supplementation demonstrates the potential to improve immunity and efficiently downregulates chronic inflammatory responses in the elderly. These data indicate that a wide prevalence of marginal zinc deficiency in elderly people may contribute to immunosenescence. This was suggested in-vitro studies some time ago. The publication Protection from glucocorticoid induced thymic involution by dehydroepiandrosterone reports: Research in our laboratory has demonstrated evidence for an antagonistic interaction between DHEA and glucocorticoids GC in liver and brown adipose tissue. Effects of GC on the immune system include involution of the thymus when given in animals in vivo and death of thymic lymphocytes in vivo with exposure to these steroids. Results of in vitro experiments confirmed protective effects of DHEA in pretreated animals. We conclude from these studies that DHEA protects against at least one GC anti-immune effect, thymic lymphocyte lysis. The publication Melatonin and the immune system in aging relates: Innate, cellular and humoral immunity all exhibit increased deterioration with age. Circulating melatonin decreases with age, and in recent years much interest has been focused on its immunomodulatory effect. Melatonin stimulates the production of progenitor cells for granulocytes and macrophages. The production and release of various cytokines from natural killer cells and T helper lymphocytes are enhanced by melatonin. Melatonin has the potential therapeutic value to enhance immune function in aged individuals. From his publication Neuroimmunomodulation of aging. A program in the pineal gland: In the last decade we have shown that the pineal gland is a main adapter and fine synchronizer of environmental variables and endogenous messages into physiological modifications of basic functions. In particular the pineal gland itself seems to regulate, via circadian, night secretion of melatonin, all basic hormonal functions and also immunity. We have shown with several in vivo models that this fundamental role of the pineal gland decays during aging. Aging itself seems to be a strictly pineal-programmed event similar to growth and puberty. Some commercial cocktails of herbal substances are claimed to have thymus-strengthening and immunity-enhancing powers. I have not so far undertaken to investigate these. For example, the publication Tumor-induced oxidative stress perturbs nuclear factor-kappaB activity-augmenting tumor necrosis factor-alpha-mediated T-cell death: Further investigations suggest that neutralization of tumor-induced oxidative stress and restoration of NF-kappaB activity along with the reeducation of the TNF-alpha signaling pathway can be the mechanism behind curcumin-mediated thymic protection. Thus, our results suggest that unlike many other anticancer agents, curcumin is not only devoid of immunosuppressive effects but also acts as immunorestorer in tumor-bearing host. There has been limited progress with hormonal and transplantation approaches to thymic renewal and much has been learned. However, it appears that we are not really there yet in terms of advanced immune competency-extending interventions.

Chapter 2 : Aging | UPMC Immune Transplant and Therapy Center

Researchers have uncovered one of the mechanisms by which aging may compromise the ability of the immune system to fight infections and respond to vaccines. The study, conducted in aging mice.

Much of the discussion of the age-related decline of the immune system that can be found in the Fight Aging! But the innate immune system also becomes damaged and dysfunctional with age. Here is a quick summary of the functional difference between these two components of the immune system: The immune system protects organisms from infection with layered defenses of increasing specificity. Most simply, physical barriers prevent pathogens such as bacteria and viruses from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals. If pathogens successfully evade the innate response, vertebrates possess a third layer of protection, the adaptive immune system, which is activated by the innate response. Here the immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the adaptive immune system to mount faster and stronger attacks each time this pathogen is encountered. In short, the innate immune system responds the same way to each new attack and wakes the adaptive immune system to action. The adaptive immune system changes in response to new threats and remembers how to respond to old threats. This process of adaptation is in fact what brings that component of the immune system to its knees eventually. But there are different and less well understood mechanisms at work that undermine the innate immune system: Elderly individuals display increased susceptibility to chronic inflammatory diseases and microbial infections, such as periodontitis and oral aspiration pneumonia. The resurgent interest in innate immunity in the s has been accompanied by parallel studies to understand the impact of aging on the function of the innate immune system, which not only provides first-line defense but is essential for the development of adaptive immunity. This review summarizes and discusses our current understanding of age-associated molecular alterations in neutrophils and macrophages , key inflammatory phagocytes implicated in both protective and destructive host responses. The analysis of recent literature suggests that, in advanced age, phagocytes undergo significant changes in signal transduction pathways that may affect their ability to perform antimicrobial functions or regulate the inflammatory response. These abnormalities are expected to contribute to the pathology of oral infection-driven inflammatory diseases in the elderly. Moreover, the elucidation of age-associated defects in the innate immune system will facilitate the development of intervention therapeutic strategies to promote or restore innate immune function and improve the quality of health in old age. This all ties into research on inflammaging , a term for the characteristic increase in levels of chronic inflammation coupled with a weakened immune system seen in the old. This is the outcome of systematically malfunctioning components of the immune system - which means that once researchers understand why this is happening, it will be possible to intervene and restore an age-damaged immune system to a more youthful state of operation. Too Old to Fight? Aging and its Toll on Innate Immunity. Molecular oral microbiology, 25 1 , PMID:

Chapter 3 : Aging impairs innate immune response to flu

aging changes and their effects on the immune system As you grow older, your immune system does not work as well. The following immune system changes may occur.

In their May issue, the AOA shared information about the decline of immune system capabilities in aging individuals and the increased chances of acquiring infection and cancer. Three key facts from Nutrition, Immunity, and Aging: The nutritional compromise that is common in older adults with chronic medical problems directly contributes to immune compromise Aging affects innate and adaptive immunity, which increases risk of infections, malignancy, and autoimmune disorders Aging is characterized by an overall decline in T-cell function, and T-cell receptor diversity decreases dramatically after age 65, with significantly reduced function jclinicalinvest The Journal of Clinical Investigation is a venue for discoveries in basic and clinical biomedical science that advance the practice of medicine. Older individuals are not immunodeficient, but they often do not respond as efficiently to antigens People of advanced age do not fight off the flu as well as younger people and have a poor response to the flu vaccine Aging also affects patterns of gene expression in mature B and T cells ScienceDaily ScienceDaily shares breaking news about the latest discoveries in science, health, environment, and technology. In this scholarly paper on the effects of aging on the immune system, the authors explain that researchers have found that the innate immunity of older people is negatively impacted by aging. One suggestion to remedy the weakened immune systems of older adults is to reactivate the function of innate immune cells to improve their response to pathogens and vaccinations. Three key facts from Innate Immunosenescence: The effects of aging on the immune system include a decline in the production of fresh, naive T cells; more restricted T cell receptor TCR repertoire, and weak activation of T cells There are some potential approaches to restore immunity in older adults via therapeutic interventions The efficacy of the immune system decreases as we age ScienceDaily This scholarly paper from the Norwich BioScience Institutes reports on a detailed study that looks into how your intestinal tract changes as you age. The study also considers how the aging intestinal tract determines our overall health. In particular, immune cells that line the gut work to maintain the integrity of the barrier, as well as maintaining a balance that provides a healthy environment for beneficial bacteria, but reacts to combat invasion by pathogenic microbes. Systematic Review and Meta-Analysis is a scholarly paper that considers the fact that aging adults are more vulnerable to infections than younger adults, and they often have more severe and irregular episodes. Studies suggest that probiotics have a role in preventing infection in older adults. Systematic Review and Meta-Analysis: Older people are more susceptible to infections and often have more sever and unusual episodes because their immune systems are compromised Infections are a major cause of morbidity and mortality in the elderly Older people who receive probiotic supplements for three months have a reduction in the average duration of an infection and a reduction in the frequency of common infectious diseases, especially upper airway infections RSocPublishing The Royal Society Publishing is a publisher of the life and physical sciences and includes the oldest journal in the world. Their Evolution of the Immune System in Humans from Infancy to Old Age showcases the immune system as a body system that matures and then declines as humans move through childhood and into adulthood and eventually into old age. The paper also highlights the fact that changes in the immune system occur as you age that impacts your risk of infection, autoimmune disease, and cancer. Vaccines for Aging Populations Dr. Because your immune system has decreased capacity and you have waning immunologic memory, older people may respond less well to immunizations than younger folks. Three key facts from Vaccines for Aging Populations: While adults have encountered pathogens and have developed immunity to them, older adults are susceptible to new diseases and exposure to new pathogens if they travel or have not encountered them before because of their compromised immune systems Aging adults should stay up to date with vaccines because their immune systems are weaker and need to be stimulated so they are better protected from infection and disease Videos, Slideshows, and Multimedia Resources about Aging and the Immune System senstweet The SENS Foundation works to develop, promote, and ensure widespread access to rejuvenation biotechnologies which comprehensively

address the disabilities and diseases of aging. Janko Nikolich-Zugich, who gives an overview of the immune system and the pathogens it protects us from. Nikolich-Zugich explains, the immune system becomes less effective as we age, but there are some promising techniques for overcoming age-related immune decline. Three key facts from Aging of the Immune System â€" Dr. In this video, she explains how her research can be used to treat common age-related diseases like rheumatoid arthritis and cancer. Three key facts from Research Shorts: The Immune System and Aging: The body also considers consuming things like glucose and fat and damaged immune cells when it does not have enough energy to run itself. Aging impacts the immune system and prevents it from operating at peak efficiency Vaccines, especially those for influenza and pneumonia, help protect aging people from getting sick Exercise, even in the form of a daily walk, stimulates the production of antibodies and white blood cells TuftsUniversity Tufts University is recognized as a premier research university in the United States. In this slideshow on the connection between nutrition, aging, and the immune system, Simin Nikbin Meydalni, director of the Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts, shares dietary strategies for improving immune response and infection resistance in older adults. Older people have an impaired immune response, especially in the T cell-mediated function Changes in gut microflora also impair the immune system when you age Otherwise benign viruses become pathogenic in older adults who have a weakened immune system SharecareInc A digital health company that offers tools to help you manage your health, Sharecare features answers from three medical doctors in this multimedia resource for learning more about the effects of aging on the immune system. All three doctors agree that our immune system becomes weaker as we grow older, which makes the elderly especially susceptible to infection and disease. Delves offers an overview of the immune system in addition to comparisons of the immune systems in newborns versus older people in this interactive article. Three key facts from Effects of Aging on the Immune System: As the article explains, gerontologists are working to determine why the immune system changes as we age, and more research needs to be done to determine whether changing immune response in seniors would be advantageous. Three key facts from Immune System: They provide education and resources to older individuals and their families, including this article on the lymphatic system and aging. Three key facts from Lymphatic System and Aging: As we age, our lymphatic system is less effective at protecting us against disease and infection As we age, our T cells become less responsive and fewer respond to infection or an invasion by pathogens The antibody levels in older individuals do not rise as quickly after an infection developers, which makes them more vulnerable to viral and bacterial infections UpToDate UpToDate is an evidence-based clinical decision support system authored by physicians to help clinicians make the best decisions at the point of care. They offer a free preview of a report on immune function in older adults reminds us that the study of age-related changes in immune function is fairly new, and most of the research shows that the immune system is less capable in older adults, which increases their susceptibility to infections, cancer, disease, and autoimmune disorders. Three key facts from Immune Function in Older Adults: Their article, Effects of Aging on Our Immune System, features statistics on the decline of the immune system with age. The article also examines the changes our immune systems undergo as we get older and explains how those changes make us more vulnerable to illness. He blogs about aging and anti-aging firewalls and has been researching anti-aging literature for more than a decade. In this article, Vince focuses on T-cell research and suggests that there are steps we can take to combat the changes the immune system undergoes when we age. Specifically, the adaptive immune system grows weaker as we age, which results in a decline in the production of new naive T and B lymphocytes It may be possible to discover safe ways to stop or reverse the decline of the thymus glad and help it remain active in producing T cells as we age Some research has found that certain white blood cells survive longer and better protect older people against infections such as the flu.

Chapter 4 : Aging changes in immunity: MedlinePlus Medical Encyclopedia

Immunity & Aging. In the recent decades, there has been an increase in the aging population across the world coupled with declining birth rates and an increased lifespan of individuals.

Find articles by Colvin, M. Find articles by Smith, C. Find articles by Tullius, S. Find articles by Goldstein, D. Although organ transplantation is an effective therapy for older patients i. Here, we provide an overview of the impact of aging on both the allograft and the recipient and its effect on the immune response to organ transplantation. We describe what has been determined to date, discuss existing gaps in our knowledge, and make suggestions on necessary future studies to optimize organ transplantation for older people. Introduction The number of people over 65 years of age seeking and receiving organ transplants is growing. Presently, the average age of those receiving kidney transplants is approximately 50 years 1. A similar trend is observed with other organ transplants: Along these lines, clinical studies have demonstrated that solid-organ transplantation is an effective treatment for selected older patients 3 â€" 8. However, older transplant recipients succumb to more infections and are more susceptible to post-transplant malignancies 9 , Despite a growing body of evidence on the complex effects of immunosenescence 15 , 16 , there have been relatively few studies that have focused on aging and the immune response to organ transplantation. In addition, most therapeutic trials in organ transplantation have not included patients over 65 years of age. Older organs can exhibit more pronounced immunogenicity, respond differently to stress, and repair less well than younger organs subsequently to transplantation 17 , These limits are due to the deleterious effects of aging on organ function, the vasculature, and alterations of resident immune cells, all of which limit the expansion of the donor pool for patients awaiting organ transplantation. Here, we describe how aging alters the immune response to organ transplantation in both the allograft and the recipient. Although biological aging represents a spectrum and clinical studies define age differently, we characterize older individuals as those greater than 65 years of age, unless stated otherwise. Impact of aging on the donor Clinical impact. Advanced donor age has historically been associated with poor outcomes after transplantation, although the impact of donor age can vary by organ 19 , In heart and kidney transplants, increased donor age is a risk factor for mortality and delayed graft function Donor age affects both quality and longevity, and its effect on patient survival in kidney transplantation has been shown to be greater than that of the histocompatibility difference between donor and recipient Donor hearts greater than 40 years of age are four times more likely to have chronotropic incompetence requiring permanent pacer implantation, and donors older than 50 years are more likely to be CMV seropositive, all of which may impact post-transplant graft function and longevity 24 , Use of lungs from donors greater than 60 years of age leads to acceptable outcomes, but there is a trend toward shorter survival at 10 years after transplant in older recipients compared with younger recipients The Eurotransplant Senior Program was developed to optimize use of organs and decrease waiting time by age-matching kidneys 27 , Based on this study, age-matching of organs is associated with less optimal but acceptable short-term and long-term outcomes. The cell necrosis that occurs during IRI leads to the release of intracellular contents e. Several innate immune pathways have been implicated in IRI after organ transplantation, for which Toll-like receptor TLR pathways are particularly important 31 , Specific gene knockout studies e. Moreover, deletions of MyD88 in donor animals or the graft have been shown to reduce alloimmunity These studies demonstrate that TLR signaling via MyD88 is a central pathway controlling innate and subsequent adaptive alloimmunity Aging may influence the consequences of IRI by affecting the initial inflammatory response within the graft. Aging has complex effects on the innate immune system 36 , and most of its impact is focused on immune cells such as DCs and macrophages Generally, innate immunity declines with aging 36 , but a low-grade elevated inflammatory phenotype consisting of the release of inflammatory cytokines e. The source of the inflammatory cytokines with aging remains unclear, but possibilities include the adipose tissue and the vasculature The mechanism responsible for the IL-6 response of aging aortas 40 has been shown to be the activation of MyD88 within vascular smooth muscle cells. In organ transplantation, innate immune activation within an allograft may be mediated via the vasculature, cardiomyocytes in the case of heart transplantation or

other stromal cells, or passenger immune cells. Yet no experimental studies have determined the impact of aging on any of these compartments during IRI. Thus, future research will be needed to determine whether altered innate immunity with aging within an allograft impacts IRI and subsequent antidonor immunity. Aging may also affect the capacity of an organ to respond to repair mechanisms based on altered metabolic, bioenergetic, and functional reserves within an older organ. Experimental studies in ex vivoâ€”perfused rat cardiomyocytes, for example, have demonstrated that aging is linked to augmented damage during hypoxia leading to impaired oxidative phosphorylation, increased ROS, and defective mitochondrial function 17 , A general decline in SIRT1 activity with aging may also contribute to compromised myocardial repair 43 , Aging also leads to a decline in other protective cellular mechanisms. For example, impaired liver IRI with aging has been associated with a reduction in the cytoprotective chaperone HSP Thus, it appears that an aging allograft exhibits fewer protective mechanisms capable of enduring any extremes of IRI. Increasing donor age, independent of recipient age, increases the rate of acute allograft rejection This finding is also supported by an experimental study in which, after implantation into young recipients, older murine cardiac allografts donors 18 months of age underwent a faster tempo 1â€”5 days faster vs. By deletion of immune cells in the donor either via lethal irradiation or via pharmacological approaches i. Moreover, DCs from the spleens of old donor mice exhibited increased expression of costimulatory molecules e. These findings were consistent with a prior study that found that aged DCs induced higher levels of graft-versus-host disease than young DCs 46 , 47 , although direct examination of DCs from aged cardiac allografts was not performed in the former study Assessing tissue-resident immune cells is important for understanding how aging impacts immune responses within organs, as there is an increasing appreciation of the contribution of these cells in maintaining organ homeostasis 18 , 48 , Finally, targeting IL â€” a cytokine that contributes to Th cytokine responses, especially chronic rejection after organ transplantation 50 , 51 â€” in recipient mice either genetically or via antibody depletion also prolongs the survival of older grafts The above study examining the age of cardiac allografts partly contrasts with an earlier experimental murine skin allograft study, in which older skin grafts donor age of 18â€”22 months were rejected at a similar tempo to that of young skin allografts donor age of 2â€”4 months Furthermore, DCs purified from the spleens or propagated from the bone marrow of aged mice did not enhance T cell alloimmunity in contrast to DCs from young mice Differences between the two studies could be due to the experimental transplant models used heart vs. Despite the differences between these two studies, it is likely that aging exerts important effects on passenger immune cells or stromal cells within a donor allograft. What is not known is whether, in contrast to young allografts, aged allografts have an altered ability to induce infiltration of immune cells into allografts as compared with young allografts. Furthermore, comparison of different organs e. Donor age and chronic allograft injury. Clinical studies have established that the age of the allograft is a strong independent predictor for the development of chronic allograft vasculopathy 53 â€” 55 and the largest single contributor to chronic graft loss Based on this knowledge, most centers in the US limit acceptance of donor organs. For example, heart allografts are generally not accepted from donors older than 60 years. Despite this established clinical phenotype, there is little experimental evidence that provides mechanistic insights into how aging within the donor enhances the development of allograft vasculopathy. A prior study in a rat kidney allograft model found that donor age up to 18 months synergized with donor ischemia time up to minutes in impairing allograft function defined as creatinine clearance and proteinuria However, other components of the allograft have not yet been examined as contributors of increased vasculopathy within the aging allograft. Clearly, aging enhances the development of atherosclerosis 15 , and atherosclerosis within an allograft is frequently a reason for not accepting an organ for transplantation. Moreover, even before the histological evidence of atherosclerosis, the vasculature exhibits low-grade increased inflammatory responses with aging 40 , 58 , These changes include the production of monocyte- and T cellâ€”attracting chemokines in the aging vasculature e. Hence, these alterations within the vasculature could increase T cell and monocyte recruitment into the vasculature of an older allograft to increase transplant vasculopathy. Determining the mechanistic basis for enhanced vascular inflammation may pave the way for novel therapeutic strategies that could be applied to the graft before implantation to reduce the immunogenicity of older organs while preventing the development of allograft vasculopathy after

implantation. The impact of aging on the adaptive T cell immune system Clinical studies show that aging affects various components of the immune response, which can lead to impaired host defense against tumors and infections as well as to defective vaccine responses and increased autoimmunity 60 , Most studies have focused on adaptive immunity â€" in particular, T cell function â€" with several reports showing that aging impairs T cell IL-2 production and Th1 immunity 62 â€" 64 , CD28 signaling 65 , and immune synapse formation Furthermore, aging reduces T cell thymic output as a result of thymic involution, leading to reduced numbers of naive T cells and Tregs. Aging also leads to an accumulation of memory T cells within the lymphoid system The above alterations reduce the size of the naive T cell receptor repertoire, leading to oligoclonality of the naive T cell pool Immune memory is a host defense mechanism that prevents reinfection and is the basis of vaccination therapies. Effects of aging on the recipient immune response to organ transplantation Clinical impact of recipient age. Regardless of the type of organ transplant, recipient age has a substantial impact on the outcome of organ transplantation. In addition to the complex changes occurring within the immune system, there are also increasing comorbidities with aging. Thus, the aging recipient is subject to the complex interaction of the senescent immune system, immunosuppression, and comorbid conditions. In all solid-organ transplants, older recipient age is an independent risk factor for post-transplant mortality. In addition to malignancies, infections also become more prevalent with increasing age These effects may be due to the synergistic effects of immune senescence and medical immune suppression Increasing recipient age is also associated with a decreased risk of rejection, although deaths related to rejection are more common in older adults Chronic graft dysfunction is also more prevalent in older adults, a condition that results not only from immunological factors but also from comorbid conditions, such as hypertension and diabetes, which increase with aging Of the few studies examining the impact of aging on the immune response to organ transplantation, most have focused on T cells. This reduction was associated with a delay in the tempo of fully MHC-mismatched skin allograft rejection in aged versus young transplant recipients In addition, an antiâ€"IL mAb delayed the tempo of skin allograft rejection in aged, but not young, recipients Aged mice 14â€"18 months resist the skin allograftâ€"promoting properties of anti-CD45Rb and anti-CD, which robustly enhance fully MHC-mismatched skin allografts in young murine recipients 78 , Aging and B cell responses after transplantation. B cells exhibit intrinsic alterations such as impaired immunoglobulin class switching with aging that impair antibody responses to vaccination B cells produce alloreactive antibodies against the transplant, leading to acute and chronic rejection 83 â€" However, until recently it was unknown how aging impacts B cell responses during organ transplantation. The B cell pool plays disparate roles depending on host age. In a skin allograft model in which anti-CD45Rb and anti-CD enhance graft survival in young mice, B cell depletion led to a faster tempo to skin allograft rejection in young mice In striking contrast, B cell depletion in aged mice 16â€"18 months of age led to a 7-day delay in skin allograft survival There was no alteration of regulatory B cell responses with aging; however, aged B cells exhibited enhanced priming of alloreactive B cells as compared with young B cells A nonâ€"germinal zone, nonâ€"marginal zone B cell population, termed age-associated B cells ABCs 87 , within the aged B cell pool were responsible for the enhanced T cell alloimmune priming and impaired the ability of anti-CD45Rb and anti-CD to prolong skin allograft survival after adoptive transfer into young mice Thus, this study indicates that ABCs within the aged host may represent a barrier to immune modulation and could indicate that B cell depletion, currently used in the treatment of antibody-mediated rejection, may have disparate effects depending on host age.

Chapter 5 : Aging and Degeneration of the Innate Immune System â€“ Fight Aging!

Immune System in Aging. The aging of the immune system is the objective of active research, in order to devise strategies for immune "rejuvenation" that will ensure better reaction to infections, which are indeed the major cause of morbidity and mortality in the elderly and in developed countries [10].

The master gland of the immune system, our thymus, is a pink, flat, two-lobed gland located under the sternum. It weighs about 1. When we turn 40, it is only 10 to 15 per cent of the size that it was at age One obvious result of this shrinkage is a decline in the production of hormones that organize and direct the B-cells and T-cells. The thymus also becomes less effective in converting immature white blood cells into fully functioning T-cells, and as those all important T-cells are less able to do their job, the whole immune army is thrown out of step. Because the thymus deteriorates early, the power of the immune system peaks in adolescence and goes downhill after that stage. The number of white blood cells we possess at age 80 is about the same as when we were 20 years old, but these senile white blood cells are less effective in receiving and transmitting commands. They may also experience difficulty in reaching their proper destination. Now the entire immune system is compromised. B-cells and T-cells no longer coordinate their actions to destroy and remove invading organisms. This results in older people becoming more susceptible to infection. An increase in the rates of influenza, pneumonia, tuberculosis and other diseases in the elderly prove this point. Cancer incidences are of particular concern to us today. Scientists assume that our body produces cancer cells at a fairly consistent rate throughout life. Younger immune systems mostly through T-cells are more efficient in identifying and killing these malignant cells before they multiply and spread throughout the body. This is most undesirable, since its presence causes our body to literally attack itself. B-cells begin producing auto-antibodies targeted to the lining of our blood vessels, nerves, and other normal cells in response to the errors made by our aging immune system. Our own cells now become labeled as the enemy by the B-cells. Auto-antibodies can be found in the blood of nearly every older person, and researchers suspect they play a part in conditions ranging from heart disease and arthritis to neurological ailments. The T-cells actually cause this collapse of the normally highly efficient immune system. Researchers have found that people with higher concentrations of auto-antibodies in their blood tend to run increased risks of cancer and heart disease, and have a generally shorter lifespans. It is probably due to a decrease in the adrenal androgen DHEA. The following table lists diseases that result from the production of auto-antibodies:

Chapter 6 : JCI - Aging and the immune response to organ transplantation

Aging has dramatic effects on many body systems; almost every aspect of immune response is changed with aging including adaptive immune cells (T & B), spleen and lymph node micro-architecture, skin, gut microbiome and the respiratory system.

Find articles by Montecino-Rodriguez, E. Find articles by Berent-Maoz, B. Find articles by Dorshkind, K. First published March 1, - Version history Abstract The effects of aging on the immune system are manifest at multiple levels that include reduced production of B and T cells in bone marrow and thymus and diminished function of mature lymphocytes in secondary lymphoid tissues. As a result, elderly individuals do not respond to immune challenge as robustly as the young. An important goal of aging research is to define the cellular changes that occur in the immune system and the molecular events that underlie them. Considerable progress has been made in this regard, and this information has provided the rationale for clinical trials to rejuvenate the aging immune system. Introduction One of the most recognized consequences of aging is a decline in immune function. While elderly individuals are by no means immunodeficient, they often do not respond efficiently to novel or previously encountered antigens. This is illustrated by increased vulnerability of individuals 70 years of age and older to influenza 1 , a situation that is exacerbated by their poor response to vaccination 2 â€” 4. The effects of aging on the immune system are widespread and affect the rate at which naive B and T cells are produced as well as the composition and quality of the mature lymphocyte pool. The goal of this article is to review recent advances, with a focus on adaptive immunity, in the understanding of the cellular and molecular events underlying these age-induced alterations and discuss their implications for the design of strategies to rejuvenate the immune system in the elderly. Effects of aging on immune system development Following their production in the bone marrow and thymus, naive B and T cells migrate to secondary lymphoid tissues such as the spleen 5 â€” 7. This process is particularly robust in the young in order to generate a diverse immune repertoire and to fill peripheral lymphoid compartments. In contrast, primary lymphopoiesis in the elderly is significantly diminished, as exemplified by involution of the thymus 8 â€” The causes of this age-related reduction in lymphocyte development are multifactorial and include changes in HSCs and progenitor cells 11 , 12 as well as the local tissue and systemic environments 13 , HSCs exhibit multiple age-related changes that include impaired adherence to stromal cells and, in some strains of mice 15 , 16 and elderly humans 17 , an increase in number. From an immunologic perspective, the most profound effect of stem cell aging in both mice 11 , 18 and humans 17 is a decreased capacity to produce lymphocytes and an increase in myeloid potential. This shift has been correlated with increased expression of myeloid lineage genes and downregulation of those specifying a lymphoid lineage fate 11 , The ability to identify, at least in mice, distinct HSC subsets that are lymphoid biased or myeloid biased, or that exhibit balanced lympho-myeloid potential has provided new insights into how aging affects the stem cell pool Figure 1 and refs. The age-related increase in expression of myeloid lineage genes in the studies noted above 11 , 17 likely resulted from the accumulation of myeloid-biased HSCs, as these analyses were performed on unseparated pools of HSCs. Despite the increase in their number, myeloid-biased stem cells are not as robust as their young counterparts 24 , which in turn could underlie the numerous age-related deficiencies observed in mature myeloid cells such as neutrophils and macrophages 25 , Figure 1 Effects of aging on HSCs and lymphocyte progenitors. Lymphopoiesis in the young left is characterized by robust B and T cell production in the bone marrow and thymus. The pool of HSCs includes a relatively high number of lymphoid-biased stem cells that efficiently generate lymphoid progenitors with high proliferative potential. However, with increasing age right , the number of lymphoid-biased HSCs declines and myeloid-biased stem cells predominate, contributing to the reduced numbers of lymphoid progenitors. In addition, B cell progenitors in the bone marrow and T cell progenitors in the thymus exhibit reduced rates of proliferation and higher levels of apoptosis compared with their young counterparts. The decline in primary lymphopoiesis in turn results in a reduced number of naive cells that migrate to secondary lymphoid tissues such as the spleen. Lymphoid-biased HSCs in old mice also appear to accumulate deficiencies that, as discussed below, may compromise their self-renewal potential and

contribute to the decline of this population In view of this, it is not surprising that the number of B cell 28 â€” 31 and T cell 32 , 33 progenitors in bone marrow and thymus is markedly reduced with age. In addition, the poor quality of the lymphoid progenitors that are generated in the aged further exacerbates the decline in lymphopoiesis 29 , 32 , For example, common lymphoid progenitors, preâ€”pro-B cells, and pro-B cells from old mice do not proliferate as extensively as do young cells, and they exhibit significantly higher rates of apoptosis. Similar to B cell progenitors, ETPs and DN cells from old mice also exhibit age-related defects in proliferation and high rates of apoptosis ref. Why aging results in a decline in the number of lymphoid-biased HSCs and reduced quality of lymphoid progenitors is not fully understood. On the one hand, intrinsically programmed events in stem and progenitor cells may be operative, which would presume that these cells have some sort of internal clock that regulates their function and longevity. However, accumulating evidence suggests that declines in lymphopoiesis are influenced by age-related changes in the environment. Declines in the bone marrow microenvironment, possibly as a result of decreased IL-7 secretion by stromal cells, have been implicated in B cell lineage aging 36 , Age-related microenvironmental changes also have a major impact in the thymus, where T cell development is dependent upon an intact thymic milieu composed of fibroblasts, macrophages, dendritic cells, and thymic epithelial cells. It is clear that the number of thymic epithelial cells declines over time and that they are not replaced, as a result of impaired proliferation In addition, the production of inflammatory mediators that may be thymocytotoxic also increases with age The thymus, particularly in humans, is increasingly infiltrated with adipocytes, the byproducts of which may be toxic to developing thymocytes and to the remaining stromal cell populations A similar fatty deterioration of the bone marrow microenvironment occurs 41 , but the role of adipocyte-derived factors in suppression of B lymphopoiesis is not well understood. Systemic changes that occur during aging may also affect lymphocyte production 14 and thymopoiesis in particular. For example, numerous reports have demonstrated that growth hormone GH and IGF-1 can stimulate thymopoiesis 13 , Because the production of these hormones declines with age 43 , this has led to the conclusion that age-related changes in the endocrine system contribute to declines in lymphopoiesis. This view has formed the rationale for clinical trials using GH, which we discuss below. Aging and the decline of immune function Although the number of naive B and T cells that migrate from primary to secondary lymphoid organs is reduced by aging, B and T cell development does not cease entirely. Indeed, some functional thymic tissue remains even in elderly humans The continued production of lymphocytes, albeit limited, and the presence of relatively normal numbers of lymphocytes in organs such as the spleen raises the question of why functional immunity declines in the elderly. The answer is that the composition and quality of the mature lymphocyte pool is profoundly altered by aging. For example, an increase in the number of memory T cells is now a well-recognized feature of aging. These cells, which are generated following the initial encounter with antigen, persist long after the initial challenge has cleared and provide a source of effectors that can respond rapidly upon antigen re-exposure. Exposure to multiple pathogens over time results in a diverse immune repertoire that includes an increased pool of protective memory cells. However, chronic stimulation with persistent viral infections such as CMV can exhaust the naive pool of cells and result in an oligoclonal memory cell expansion. The immune risk profile also includes B cells with impaired function. B cell number in mice is unchanged by aging, but in human peripheral blood their absolute number is reduced Human and murine B cells also exhibit impaired class switch recombination, which has been attributed to decreased induction of activation-induced cytidine deaminase AID enzyme Multiple B cell subpopulations have been defined, and additional study is required to determine how aging affects them. Thus, humoral immunity to influenza virus occurs in T cellâ€”independent and T cellâ€”dependent waves that may involve B1, marginal zone, and follicular B cells It was recently reported that marginal zone B cell number is reduced in old mice 60 , but whether and how this affects production of antibodies to specific antigens is unknown. Although present at a low frequency 61 , B1 B cells play a critical role in the response to S. However, very little is known about the effects of aging on their function. Inflammaging 64 , a condition in which there is an accumulation of inflammatory mediators in tissues, has been associated with aging. The source of these inflammatory factors has been proposed to be cells that have acquired a senescence-associated secretory phenotype SASP The SASP could be acquired by cells once they

have aged, or it may occur gradually in various populations over time as they acquire DNA lesions that in turn trigger the increased production of inflammatory mediators such as IL-6 66 , Regardless of how the shift occurs from a salutary to an inflammatory milieu, the end result may be a negative effect on the ability of naive lymphocytes from the bone marrow or thymus to lodge in an organ such as the spleen as well as the function of mature lymphocytes already resident in that tissue. The precise source of the various inflammatory mediators may vary between individuals. In one scenario, age-related changes in microenvironmental elements such as stromal cells or dendritic cells 72 would result in a shift from a salutary to an inflammatory environment. However, it is equally plausible that changes occurring in aging B and T cells or innate effectors 26 may alter microenvironmental elements. The development of Th17 cells is dependent on the basic leucine zipper transcription factor ATF-like BATF transcription factor 74 , but why its expression might increase with age is not clear. The specific cells and the order in which age-related changes occur in them may vary between individuals as a result of differences in genetic background and environmental exposure. However, once the effects of aging are manifest in one or more target populations, a vicious cycle may initiate that leads to a downward spiral of increasingly compromised immune function Figure 2. Figure 2 The strength of the immune response declines with age. Multiple age-related changes can affect the composition and function of lymphocytes in secondary lymphoid tissues. The number of B cells that respond to influenza is reduced, and antibody avidity in response to carbohydrate antigens is diminished. In addition, the tissue environment includes an increased concentration of inflammatory cytokines, which may be produced by stromal elements, dendritic cells, or aging B and T cells. The increased number of memory cells that occupy tissue niches and the inflammatory milieu in turn may compromise the ability of naive B and T cells migrating from the bone marrow and thymus to lodge in the tissue. Together, these changes result in diminished immune function in the elderly. Intracellular changes in developing and mature lymphocytes The analysis of stem and progenitor cells from various tissues has revealed that aging often results in the dysregulation of similar molecular pathways For example, alterations in the PI3K pathway are frequently exhibited by aging cells. Increased expression of tumor suppressor proteins such as p16Ink4a and ARF also occurs in aging cells from multiple tissues 79 , We have had a particular interest in understanding why the quality of lymphoid progenitors is reduced with age, and recent studies have shown that both Ink4a and Arf expression increases in pro-B cells from old mice and that inhibiting their expression can partially reverse the effects of aging Other age-associated changes may be more specific to the hematopoietic system. For example, altered expression of various B lineage transcription factors has been proposed to underlie declines in B lymphopoiesis Recent interest has focused on BATF, the expression of which is highest in the hematopoietic system, in the decline of lymphoid-biased HSCs during aging. This is a particularly interesting finding, because it provides a molecular mechanism for the age-related decline in the number of lymphoid-biased HSCs discussed above. Although there has been considerable focus on stem and progenitor cells, aging also affects patterns of gene expression in mature B and T cells. As previously discussed, class switch recombination is impaired in aging murine and human B cells due to decreased expression of enzymes such as AID 53 , Aberrant T cell signaling has also been associated with aging 48 , 85 , and the list of dysregulated genes continues to grow, as indicated by several recent reports 86 â€” 88 , two of which focused on altered expression of dual specific phosphatases DUSPs. DUSPs deactivate target kinases, including those in the MAPK pathway whose activity is critical for T cell activation, differentiation, and cytokine production. These signaling abnormalities in HSCs, lymphoid progenitors, and mature B and T cells may occur, at least in part, as a result of the age-related alterations in the systemic and local tissue environments discussed above. For example, over time exposure to an inflammatory milieu might induce epigenetic modifications that affect the expression of genes required for growth, survival, or differentiation 89 , In this regard, loss of DNMT3a impairs differentiation of HSCs while their number increases in the bone marrow 91 , and mice with hypomorphic expression of DNMT1 exhibit relatively normal myeloerythroid potential but show a significant block in lymphoid development Nevertheless, cell-autonomous events might also contribute to aging. Thus, repeated cell division may result in progressive telomere shortening that in turn results in DNA damage that can no longer be repaired efficiently due to age-related defects in DNA repair mechanisms It is interesting that telomere dysfunction has been associated

with changes in mitochondrial metabolism 93 , in view of a study linking compromised mitochondrial function and depressed thymopoiesis Rejuvenating the aging immune system The ultimate goal of research in immune system aging is to use the information to develop strategies to stimulate immunity in the elderly summarized in Table 1. As discussed above, a number of molecules have been identified whose aberrant expression contributes to aging, and targeting these molecules may potentially slow or reverse the aging process. For example, pharmacologic inhibition of Cdc42, a small Rho GTPase whose increased expression has been linked to murine HSC aging, with a selective Cdc42 activity inhibitor rejuvenated HSCs 95 , and other studies have shown the potential of antioxidants to improve the function of old HSCs 76 ,

Chapter 7 : Causes, consequences, and reversal of immune system aging

July 17, â€" (Bronx, NY) â€" Researchers at Albert Einstein College of Medicine of Yeshiva University have uncovered one of the mechanisms by which aging may compromise the ability of the immune system to fight infections and respond to vaccines. The study, conducted in aging mice, shows that.

URL of this page: Examples are bacteria, viruses, toxins, cancer cells, and blood or tissues from another person. The immune system makes cells and antibodies that destroy these harmful substances. The following immune system changes may occur: The immune system becomes slower to respond. This increases your risk of getting sick. Flu shots or other vaccines may not work as well or protect you for as long as expected. An autoimmune disorder may develop. This is a disease in which the immune system mistakenly attacks and destroys healthy body tissues. Your body may heal more slowly. There are fewer immune cells in the body to bring about healing. This can result in an increased risk of cancer. Get the flu and pneumonia vaccines, and any other vaccines your health care provider recommends. Get plenty of exercise. Exercise helps boost your immune system. Good nutrition keeps your immune system strong. Smoking weakens your immune system. Limit your intake of alcohol. Ask your provider how much alcohol is safe for you. Look into safety measures to prevent falls and injuries. A weak immune system can slow healing.

Chapter 8 : Aging and the Skin Immune System | JAMA Dermatology | JAMA Network

How Aging Affects Your Immune System. Over time, stress may lessen your immune response. "When you're constantly worried about something, it takes a toll on your body," Wolf-Klein says.

Chapter 9 : Effects of Aging on The Immune System: 50 Expert Sources - Del Immune

Aging impairs the immune system's response to the flu virus in multiple ways, weakening resistance in older adults, according to a Yale study. The research reveals why older people are at increased risk of illness and death from flu, the researchers said.