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Review

A review of the equine age-related changes in the immune system: Comparisons between human and equine aging, with focus on lung-specific immune-aging

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ABSTRACT

The equine aging process involves many changes to the immune system that may be related to genetics, the level of nutrition, the environment and/or an underlying subclinical disease. Geriatric horses defined as horses above the age of 20, exhibit a decline in body condition, muscle tone and general well-being. It is not known whether these changes contribute to decreased immune function or are the result of declining immune function. Geriatric years are characterized by increased susceptibility to infections and a reduced antibody response to vaccination as a result of changes in the immune system. Humans and horses share many of these age-related changes, with only a few differences. Thus, inflamm-aging and immunosenescence are well-described phenomena in both human and equine research, particularly in relation to the peripheral blood and especially the T-cell compartment. However, the lung is faced with unique challenges because of its constant interaction with the external environment and thus may not share similarities to peripheral blood when considering age-related changes in immune function. Indeed, recent studies have shown discrepancies in cytokine mRNA and protein expression between the peripheral blood and bronchoalveolar lavage immune cells. These results provide important evidence that age-related immune changes or 'dys-functions' are organ-specific.

Contents

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1. Introduction

Both the human elderly[1] population and the geriatric[2] horse population are increasing. In the year 2000, approximately 20% of the Danish and 16% of the U.S. human population were above the age of 60, and it is estimated that these percentages by the year 2050 will be 32% of the Danish and 27% of the U.S. population (UN Report, 2002). Likewise, it has been estimated that 7.6% of the U.S. equine population (Anon, 2005) and 13% of the UK equine population (Ireland et al., 2011) are above 20 years of age. In addition to demographic parallels, the horse is an ideal model for studying aging because of its many physiological similarities with humans. For example, the horse is a relatively long-living species with a maximum lifespan of 40 years, the longest of any domestic animal, and thus comparable to the human lifespan (Mauderly and Hahn, 1982; McFarlane et al., 2001). Also, it is common for geriatric horses to continue both as athletes and for reproduction purposes (Malinowski et al., 1997). As in humans, old age in horses is associated with decreased muscle tone and body condition (Austin et al., 1995; Pamplona et al., 1998; Ralston et al., 1988), along with an increased risk of aging-related diseases (Paradis, 2002). Also it is recognized that geriatric horses, like elderly humans, are susceptible to infections despite having existing antibody titers (Adams et al., 2011) as well as demonstrating hypo-responsiveness to most vaccines (Goto et al., 1982; Horohov et al., 1999).

A growing body of information indicates an overall reduction of immune function (immunosenescence) in geriatric horses. In addition to immunosenescence, geriatric horses also share with humans a propensity to exhibit increased or over-exaggered inflammatory responses, the phenomenon known as inflamm-aging (Franceschi et al., 2000). Since inflamm-aging is thought to lead to increased morbidity and mortality in the human elderly population, then a similar outcome is expected for geriatric horses. Nevertheless, the population of geriatric horses and elderly humans are increasing, then a better understanding of the underlying processes involved in immunosenescence and inflamm-aging is needed for a better understanding of how to manage age-associated changes of the immune system in both species.

2. Immunosenescence

Immunosenescence was first described by Walford (1964), and referred to as the age-associated deteriorations in immunity, characterized by a diminished reaction toward host pathogens. Immunosenescence is presumed to be one of the major contributors to the concept of age-related increased susceptibility to infectious diseases and decreased response, as well as the short-lasting effect of vaccination (Effros et al., 2003).

[1] Defined as humans greater than 65 years of age.

[2] Defined as horses greater than 20 years of age. Ralston, 1990. Clinical nutrition of adult horses. The Veterinary clinics of North America. Equine practice 6, 339-354.

2.1. Immunosenescence of the innate immune system in humans

An overview of systemic immunosenescence for both humans and horses are provided in Table 1. The immune system consists of two interacting components, the innate and adaptive immune system. Although it is widely accepted that immunosenescence affects primarily the adaptive immune system, evidence is emerging of effects on the innate immune system. The innate immune system includes various immune cells (*e.g.* neutrophils, macrophages, dendritic cells and natural killer cells), non-immune cells (*e.g.* epithelial cells) and non-cellular components such as the alternate complement pathway and antimicrobial molecules (*e.g.* nitric oxide, defensins and collectins). Innate immune cells respond in a non-specific manner to a broad range of exogenous stimuli (*e.g.* lipopolysaccharide [LPS], lipoteichoic acids, mannans, peptidoglycan, glucans and bacterial DNA) in terms of pathogen-associated-molecular-patterns (PAMP) *via* pathogen recognition receptors (PRR) (*e.g.* toll-like receptor [TLR]) as well as the subsequent production of cytokines and co-stimulatory molecules. Neutrophils are the most represented cell type in the peripheral blood. Although their cell numbers do not decrease with age (Fulop et al., 1985), several of their functions are affected by age, among those an increase in apoptosis (Fulop et al., 1997), a decrease in phagocytosis and the production of intracellular reactive oxygen species (ROS) (Fulop et al., 2004; Wenisch et al., 2000). Monocytes/macrophages numbers in the peripheral blood are not affected by age, although age-related changes in monocyte subsets are found (Nyugen et al., 2010). For example, with increasing age, macrophages exhibit decreased capabilities for phagocytosis, the production of superoxide anion (in rats) as well as the secretion of chemokines and cytokines *in vitro* (Alvarez et al., 1996; Boehmer et al., 2004; Fietta et al., 1993; Tasat et al., 2003). Also macrophages exhibit an age-related increase in the production of prostaglandin E2 (PGE_2), which leads to a decreased expression of MHC class II molecules and a decrease in antigen presentation, thus affecting the activation of the adaptive immune system (Villanueva et al., 1990; Wu and Meydani, 2008). Age-related changes in TLRs on monocytes/macrophages and other cell types includes a decrease or defect in TLR-1/2-induced production of TNF-α and IL-6 (van Duin et al., 2007), a decrease in TLR-8-induced IL-6 production and a decrease in surface expression of TLR-4. No changes in LPS-induced cytokine production have been noted (Nyugen et al., 2010).

2.2. Immunosenescence of the adaptive immune system in humans

The adaptive immune system responds to specific antigens with a memory component, which allows for a more rapid secondary response to the same antigen. T-cell antigen specificity is determined by the T-cell receptor, while the B-cell antigen-specific receptor includes both surface-bound and secreted antibodies.

Aging of the cellular immune system includes thymic involution with the consequences of a gradual decrease in naïve T-cells, including CD3+, CD4+ and CD8+ T-cells (Globerson, 1995). Another component of this immunosenescence is the presence of a pool of