Molecular Immunology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

The equine immune responses to infectious and allergic disease: A model for humans?☆

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ARTICLE INFO

Article history:
Received 15 August 2014
Received in revised form
23 September 2014
Accepted 29 September 2014
Available online xxx

Keywords:
Equine
Immunity
Allergy
Infectious disease

ABSTRACT

The modern horse, *Equus caballus* has historically made important contributions to the field of immunology, dating back to Emil von Behring's description of curative antibodies in equine serum over a century ago. While the horse continues to play an important role in human serotherapy, the mouse has replaced the horse as the predominant experimental animal in immunology research. Nevertheless, continuing efforts have led to an improved understanding of the equine immune response in a variety of infectious and non-infectious diseases. Based on this information, we can begin to identify specific situations where the horse may provide a unique immunological model for certain human diseases.

1. Introduction

The modern horse, *Equus caballus*, originated from a common ancestor of equids (horses, donkeys and zebras) some 4–4.5 million years ago (Orlando et al., 2013). The domestication of modern horses likely occurred some 5000 years ago in what is today Kazakhstan (Outram et al., 2009). Since then, horses have played an important role in the history of mankind. This contribution includes the field of immunology dating back to Emil von Behring's description of curative antibodies in equine serum over a century ago (Steinbach et al., 2002) and the horse continues to play an important role in human serotherapy (Nydegger et al., 2000). While mice are the predominant experimental animal in immunology research, efforts continue to characterize the immune response of horses and the role it plays in a variety of infectious and non-infectious diseases. As this knowledge base continues to expand, we can anticipate the translation of this basic information into practical application in the veterinary clinic. We can also begin to identify specific situations where the horse may provide a unique immunological model for human diseases.

2. Equine immune system

The equine immune system shares many similarities with humans, but also some notable differences. The equine major histocompatibility (MHC) genes, also called the Equine Lymphocyte Antigen (ELA), are similar in organization and function to those of humans, with adjacent class I, II and III regions (Gustafson et al., 2003; Yao et al., 2012). Despite these similarities, the genomic organization of the ELA differs from the MHC of other species. *In situ* hybridization studies have localized the ELA to chromosome 20q14–q22 (Maklad et al., 1994), except for a single class II homologue (DQA) which was localized to chromosome 5 (Fraser and Bailey, 1998). Overall, the equine class II locus also has greater allelic variation than most other species (Kamath and Getz, 2011). The functional significance of these observed differences in ELA genes remains unexplained. While there are a limited number of serological reagents to identify ELA antigens, microsatellite repeats in the ELA region can be used to identify ELA haplotypes (Brinkmeyer-Langford et al., 2013; Tseng et al., 2010). This approach has been used to examine specific ELA haplotype expression with disease susceptibility (Andersson et al., 2012; Kalemkerian et al., 2012). Such information regarding disease associations would be useful both in equine medicine, but could also provide new insights into similar diseases in other species.

Horses also have a typical, though distinct, distribution of immunoglobulin classes. While horses have the five major immunoglobulin classes (IgM, IgD, IgG, IgA, IgE), they also express

☆ This article belongs to Special Issue on Non-rodent animal models.

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http://dx.doi.org/10.1016/j.molimm.2014.09.020
0161-5890/

seven different IgG subclasses designated as IgG1–IgG7, each of which are encoded by separate genes for the constant heavy chain regions (Keggan et al., 2013). Similar to humans and mice, specific IgG subclass expression is associated with certain infections. Thus, IgG4, IgG7 and IgG1 are produced in response to intracellular infections, while IgG3 and/or IgG5 are produced mainly in response to extracellular pathogens (Keggan et al., 2013). As in other mammals, IgA plays a key role in mucosal immune defenses in the horse (Morton, 2005). Comparisons of transcriptional regulatory sequences of equine IgA indicate that horse and human pIgR expression is controlled through common regulatory mechanisms (Lewis et al., 2010). Also typical for other species, IgE is a minor immunoglobulin class present in equine serum and is involved in type I hypersensitivity reactions and parasite immunity in horses (Schaffartzik et al., 2012; Wagner, 2009). Horses, unlike rodents and primates, develop their antibody repertoire from a relatively small number of VH (variable heavy) genes of one or several families and extensive use of lambda-light chains over kappa (Ford et al., 1994). As horses do not transfer antibodies across the placenta to the fetus, colostrum is a critical source of immunity and failure of passive transfer leads to significant health problems in the foal (Chavatte-Palmer et al., 2001). This also provides the opportunity to determine the contribution of passively acquired antibodies in foal resistance to specific infections by depriving foals of colostrum (Chong et al., 1991; Tsujimura et al., 2009).

The white blood cells, or leukocytes, are found in the blood of horses and these include neutrophils, eosinophils, basophils, monocytes, and lymphocytes. Neutrophils are predominant amongst the circulating leukocytes compromising up to 90% of the total white blood cell population, though this can be affected by multiple factors (Holbrook et al., 2012; McTaggart et al., 2005; Raidal et al., 2000; Wichtel et al., 1991). As discussed below, neutrophils play a central role in the pathogenesis of airway inflammatory diseases in horses (Brazil et al., 2005; Franchini et al., 1998; Robinson et al., 1996), though other cells may also contribute to the pathology (Aharonson-Raz et al., 2012; van der Haegen et al., 2005). While mast cells, basophils and eosinophils that have been stimulated by IgE and some IgG subclasses are involved in Type I immediate hypersensitivity reactions in horses (Wagner, 2009; Wagner et al., 2006) and play a definitive role in insect bite hypersensitivity (IBH) (Vychodilova et al., 2013), their role in airway inflammation remains uncertain (as discussed below). Approximately 4% of the peripheral blood monocytes are $CD16^+$ and the rest $CD16^-$ negative (Noronha et al., 2012). In humans, the $CD16^-$ classical monocytes are in the majority (90%) while the $CD16^+$ pro-inflammatory cells account for about 10% of all monocytes under normal physiological conditions, though this number can increase or decrease under various conditions (Ziegler-Heitbrock, 2014). While the functional significance of $CD16^+$ monocytes in the horse is unknown, a similar pro-inflammatory function likely occurs. Both B and T lymphocytes are found in the circulation of horses with B cells being less frequent. No identification of B-1 or B-2 cells in the horse has been reported. In contrast, there is a considerable amount of information available on equine T cell subsets. T-cell receptor (TcR) alpha, beta, gamma, and delta chain genes have been identified in the horse (Schrenzel and Ferrick, 1995; Schrenzel et al., 1994). While TcR gamma/delta cells can be identified in a variety of equine tissues (Tschetter et al., 1998), their overall frequency is low and likely to predominate mucosal surfaces (Kabelitz et al., 2005). The majority of T cells in the equine circulation are alpha/beta cells which are further divided into $CD4^+$ and $CD8^+$ subsets, though both double negative and double positive cells are found (Grunig et al., 1994; Lunn et al., 1991).

In terms of the $CD4^+$ T cell population, the polarization of Th1 and Th2 responses of horses appear to be stronger than in humans, but less fixed than in rodents (Aggarwal and Holmes, 1999; Horohov et al., 1998; Wagner et al., 2010). There is also evidence of Treg (Hamza et al., 2011; Heimann et al., 2011) and Th17 (Regan et al., 2011) function in the horse. There have been numerous reports of MHC restricted killing by equine $CD8^+$ T lymphocytes in a variety of equine infectious diseases (Allen et al., 1995; Hammond et al., 1998; Harris et al., 2010; McGuire et al., 2004). Both natural killer and lymphokine-activated killer cells have been also been described in the horse (Hormanski et al., 1992; Viveiros and Antczak, 1999). A number of primary immunodeficiencies have been identified in horses (Perryman, 2000) and these have provided new insights into the underlying molecular basis for these diseases. Perhaps the best example of this was the identification that the underlying molecular basis of severe combined immunodeficiency in Arabian horses was distinct from that seen in SCID mice (Leber et al., 1998; Shin et al., 2000).

While equine immunology research trails humans and mice in terms of the number of reagents available, effort continues to be expended toward developing methods and reagents for characterizing equine immune responses (Bai et al., 2008; Burton et al., 2009; Giguere and Prescott, 1999; Gold et al., 2007; Hagen et al., 2012; Leutenegger et al., 1999; Sanchez-Matamoros et al., 2013; Swiderski et al., 1999; Wagner et al., 2010). Similar efforts have identified an ever growing list of antibodies and other reagents for cell surface antigens (Ibrahim et al., 2007; Kabithe et al., 2010; Keggan et al., 2013; Noronha et al., 2012). The commercial availability of many of these reagents has provided access to equine researchers across the globe. Likewise, the continuing application of next generation sequencing to the equine genome (Mienaltowski et al., 2009; Webbon, 2012) should yield additional information on the role of genetic variants in immune-related genes involved in various disease processes (Gerber et al., 2014; Horin et al., 2004, 2008).

3. Equine models for immune responses to infectious diseases

The close association of the horse with human economic and military activities over the millennia contributed to our awareness of equine infectious diseases. However, it is only within the past century that our understanding and control of these disease has been realized (Slater, 2013). Indeed, the history of equine infectious disease research and discovery parallels that of human medicine. This includes the recent advances in molecular biology and genomics that have led to a better understanding of the pathogenesis and immunology of infectious diseases of the horse.

3.1. Equine influenza virus

Equine influenza virus remains a major cause of respiratory disease in horse populations (Chambers, 2014). While equine influenza virus was first isolated in 1956, reports of influenzal disease in horses date back to the Greco-Roman period (Morens and Taubenberger, 2010). Equine influenza viruses share many similarities with human influenza viruses in terms of genomic structure, pathogenicity, and immunology; though they differ in their sialic acid targeting specificity such that equine influenza viruses cannot infect humans (Ito and Kawaoka, 2000), though they can infect dogs (Yamanaka et al., 2009). In horse populations, the only known circulating influenza A virus subtype is H3N8, first isolated in the United States in 1963 and now worldwide in distribution (Daly et al., 2011). Over the past several decades, equine influenza viruses have diverged into two evolutionary lineages, which were initially designated 'American' and 'Eurasian' on the basis of the geographic origin of the strains (van Maanen and Cullinane, 2002), but more

Please cite this article in press as: Horohov, D.W., The equine immune responses to infectious and allergic disease: A model for humans? Mol. Immunol. (2014), http://dx.doi.org/10.1016/j.molimm.2014.09.020