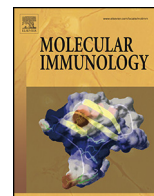




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Review

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

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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.

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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

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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 plgR 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 comprising 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) (Vyehodilova 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

recently as Clades 1 and 2 (Bryant et al., 2009). Influenza disease in the horse is characterized by an acute onset of clinical signs including pyrexia, anorexia, tachycardia, limb edema and nasal discharge (van Maanen and Cullinane, 2002). Clinical disease in both humans and horses is associated with the expression of pro-inflammatory cytokines (Quinlivan et al., 2007; Tisoncik et al., 2012). Secondary bacterial infections are not uncommon as the virus causes dequamation and denudation of respiratory epithelial cells resulting in an impairment of tracheal clearance (Willoughby et al., 1992). In previously exposed (immune) horses, symptoms are milder and often undetected following infection (van Maanen and Cullinane, 2002). Immunity to equine influenza, similar to human influenza viruses, involves both cellular and humoral components (Hannant and Mumford, 1989; Hannant et al., 1988). Vaccination against equine influenza is directed toward the induction of hemagglutination inhibiting antibodies, as it is for human influenza vaccines, and evidence of cell-mediated immunity (Paillot et al., 2006). Toward this end, a number of novel vaccines have been developed using a variety of adjuvant and delivery systems (Minke et al., 2007; Paillot et al., 2008; Van de Walle et al., 2010) including a modified live vaccine (Lunn et al., 2001). Also similar to humans, aged horses are susceptible to influenza infection and respond poorly to vaccination (Adams et al., 2011; Fermaglich and Horohov, 2002). As such, the horse provides a model for studying the pathogenesis and immunology of influenza virus in a natural host.

3.2. Equine infectious anemia

Swamp fever or equine infectious anemia was recognized as a clinical disease in 1843 and the causative agent was identified as a filterable virus in 1904 (Ishii, 1963). Equine infectious anemia virus (EIAV) is a lentivirus with the prototypical retroviral genomic organization of the major genes gag, pol and env bounded at both ends by long terminal repeats (LTR), thus sharing structural and genomic characteristics with human immunodeficiency virus. Clinical EIA manifests in three basic phases: acute, chronic, and inapparent (Craig and Montelaro, 2013). Waves of viremia accompany acute and chronic disease episodes, which are defined clinically by signs such as fever, anemia, thrombocytopenia, edema, and lethargy (Cook et al., 2013). Antigenic variation in the envelope protein of newly arising virus during these episodes is responsible for the evasion of pre-existing neutralizing antibodies (Craig et al., 2013). Ultimate control of viral replication leading to the chronic, persistently infected state is associated with the development of a cell-mediated immune response to the virus (Craig et al., 2013). The host cell-mediated immune response to EIAV consists of both CD4 and CD8 MHC-restricted, EIAV-specific cytotoxic T-lymphocyte (CTL) activity whose appearance within three to four weeks post-infection correlates with the resolution of the primary viremia (Craig and Montelaro, 2013). The majority of the protective CTL responses appear to be directed toward Gag epitopes, although Env sequences have been loosely correlated with protective immunity (Hammond et al., 1997; Lonning et al., 1999; McGuire et al., 2004). The majority of EIAV-infected horses ultimately control viral replication leading to the inapparent carrier state where immunosuppressive treatment can lead to new episodes of viremia and clinical disease (Craig et al., 2002). This ability of horses to immunologically control their infection is unusual and provides a unique opportunity to identify protective immune responses to these viruses (Craig and Montelaro, 2013). Current efforts are focused on the maturation of the cellular immune response to this virus as it shifts from immunodominant variable epitopes to immunorecessive conserved ones (Liu et al., 2014), a pattern similar to that seen in HIV (McMichael and Koff, 2014).

3.3. *Rhodococcus equi*

R. equi is an important cause of bacterial pneumonia in young foals (Prescott, 1991; Takai et al., 2003) and immunocompromised humans (Marchiori et al., 2005; Torres-Tortosa et al., 2003). While adult horses are typically resistant to *R. equi* infection (Hines et al., 2003), older horses with underlying immunological deficits are also susceptible to infection (Morrese and Walldridge, 2010; Vengust et al., 2002). Clearance of virulent strains of *R. equi* from the lungs of adult horses is associated with the production of IFN- γ by CD4⁺ and CD8⁺ T cells (Hines et al., 2003; Patton et al., 2004). While these results indicate cell-mediated immunity plays a critical role in resistance to *R. equi* (Giguere et al., 1999; Hines et al., 2003; Kohler et al., 2003; Patton et al., 2004), what remain unclear are the host factors that determine foal susceptibility to this bacterium (Chaffin et al., 2003, 2004; Cohen et al., 2005). The fact that adult horses and foals older than 6 months of age are resistant to *R. equi* infections indicates an age-dependent susceptibility of foals to this bacterium (Giguere and Prescott, 1997; Jacks et al., 2007). Indeed, epidemiologic and experimental data have shown that foals less than 1 month of age are at greatest risk for infection (Horowitz et al., 2001; Martens et al., 1982; Sanz et al., 2013). In general, the ability of the neonatal immune system to confer protection against viral, bacterial, and fungal infection is inadequate when compared to adults (Adkins et al., 2004; Flaminio et al., 2000; Schelonka and Infante, 1998). A lack of pre-existing memory T- and B-cells and diminished T-cell responses are contributors to the state of immune deficiency (Gold et al., 2006). In this regard, neonatal T cells have been shown to be functionally different from those of adults in that they make little interleukin (IL)-2 or IFN- γ , but high levels of IL-4 in response to primary stimulation *in vitro* (Adkins et al., 2002; Adkins and Du, 1998; Adkins and Hamilton, 1992). The reasons for this bias are unclear, but deficiencies in innate cellular immunity of neonates include decreased production of interferons, IL-12/IL-23, and IL-18 (Marodi, 2006). Dendritic cells (DC) from equine neonates appear phenotypically less mature than adult DCs, though their expression of IL-12, IL-15 and IL-18 mRNA was not different (Merant et al., 2009). However, increased expression of IL-10 has been reported for foal antigen presenting cells and over-expression of this anti-inflammatory cytokine could negatively impact IFN- γ production (Sponseller et al., 2009). Neonatal foals exhibit decreased production of IFN- γ both in the lung and in the peripheral blood coincidental during the known period of their age-related susceptibility to *R. equi* pneumonia (Breathnach et al., 2006; Prescott, 1991). Recent analysis of gene expression in PBMC from young foals stimulated with *R. equi* demonstrated a reduced repertoire of chemokines and lowered expression of other genes in response to this pathogen highlighting diminished immunity during the early life of foals (Kachroo et al., 2013). These results suggest age-dependent deficiencies in immune responses are an underlying factor contributing to susceptibility of foals to *R. equi*. The decreased production of IFN- γ is the result of epigenetic modification of the promoter region of this gene (Sun et al., 2013) and this can be modified by extrinsic signals (Sun et al., 2012). As such, the equine rhodococcosis provides an opportunity to examine the neonatal development of innate immune mechanism in a relevant infectious model.

3.4. Equine herpesviruses

The horse is host to a number of herpesviruses, some of which are important causes of respiratory, reproductive, and neurological disease. Equine herpesvirus (EHV) 1 & 4 are members of the subfamily of alphaherpesvirinae and commonly associated with respiratory disease in both young and older horses (Ma et al., 2013). In addition to respiratory infections, EHV-1 is also an important

cause of equine abortions and neurological disease (Dunowska, 2014). The incidences of equine herpesvirus myeloencephalopathy (EHM), caused by EHV-1, have increased in recent years, perhaps due to the emergence of neuropathogenic variants (Pusterla et al., 2009). The neuropathology of EHM remains ill-defined, though the likely mechanism involves EHV-1 infected peripheral blood mononuclear cells transporting virus to the central nervous system vasculature causing endothelial cell infection (Goehring et al., 2011) leading to an inflammatory response that causes ischemic thrombosis (Cardwell et al., 2003). The pathogenic potential of the other equine herpesviruses are less well understood. Thus, EHV-2 and EHV-5 are often isolated from horses with respiratory disease, though their role is unclear (Bell et al., 2006; Fu et al., 1986). As both viruses are members of the subfamily gammaherpesvirinae, it is speculated that they have immune modulating activities (Fu et al., 1986; Jensen-Waern et al., 1998). EHV-3, which is closely related to EHV-1, is the causative agent of equine coital exanthema (Allen et al., 1977; Barrandeguy et al., 2012). As is the case for human herpesviruses, immunity to these viruses is incomplete (Kydd et al., 2006; Slater and Hannant, 2000) as horses become latently infected with the virus and recrudescence of disease can occur (Pusterla et al., 2010). Thus, the horse provides interesting opportunities to examine the host and herpesvirus interactions in a variety of clinical presentations.

4. Equine models for allergic diseases

Ideally, animal models for allergic diseases should entail the same sensitization route as the natural exposure route of human subjects (Dearman and Kimber, 2009). Horses, like humans, suffer from a variety of allergic diseases (Fadok, 2013). Two common allergic conditions in horses, recurrent airway obstruction (RAO) and insect bite hypersensitivity (IBH) bear some similarity to human allergic diseases.

4.1. Recurrent airway obstruction

Equine recurrent airway obstruction (RAO), also known as heaves, is a recurring pulmonary disease of horses, characterized by chronic airway inflammation, airway hyperresponsiveness, and episodes of bronchoconstriction that may improve in response to β_2 -adrenergic agonists and corticosteroids (Herszberg et al., 2006). While there are reports that horses with RAO have elevated levels of IgE in bronchoalveolar lavage and serum (Eder et al., 2000; Halliwell et al., 1993; Schmollenbach et al., 1998) and increased production of Th2 cytokines (Cordeau et al., 2004; Lavoie et al., 2001), some cases of equine RAO more closely resemble hypersensitivity pneumonitis (Ainsworth et al., 2002; Beadle et al., 2002; Bogaert et al., 2009). While these disparate results could be due to different etiologies, more likely it is due to temporal differences as this is a chronic condition found in older horses (Horohov et al., 2005; Kleiber et al., 2005). In general, RAO in horses more closely resembles type II bronchial asthma in adults rather than childhood asthma (Choi et al., 2012; Tanizaki et al., 1993) as the primary cellular infiltrate in equine RAO is neutrophilic (Bureau et al., 2000) and the pathophysiological changes in the airway are quite similar (Herszberg et al., 2006). A dysregulation of neutrophils and bronchial expression of IL-17 are also key features of equine RAO (Debrue et al., 2005) and human asthma (Laan and Linden, 2008).

4.2. Insect bite hypersensitivity

Insect bite hypersensitivity (IBH) is a common condition in horses resulting from an immediate hypersensitivity reaction to feeding by biting flies and midges (*Culicoides*) (Cunningham and Dunkel, 2008; Schaffartzik et al., 2010). The response is due to the

production of IgE antibodies to salivary components of the insects (Schaffartzik et al., 2011). While a Th2 cytokine response is detected at the reaction site, a dysregulation of T regulatory cell functions has also been identified (Schaffartzik et al., 2012). Icelandic horses born in Iceland and transported to either Europe or the United States have a particularly high incidence of IBH (Hellberg et al., 2006), however, Icelandic horses born in Europe or the United States have a similar incidence of IBH compared to other breeds (Marti et al., 2008). This is likely the result of the absence of exposure of horses in Iceland to *Culicoides* (Schurink et al., 2014). A possible role of helminth infections in modulating IL-4 mediated production of IgE has also been proposed to explain the unique susceptibility of imported Icelandic horses to IBH (Hamza et al., 2010). This interaction between allergy development and exposure to parasites is reminiscent of the hygiene hypothesis developed to explain increased incidences of allergic and asthmatic diseases in human populations (Strachan, 2000). The immunomodulatory effect of helminth infections in this process is also of interest (Finlay et al., 2014). Horses thus provide an opportune model for further examination of these relationships between allergen sensitization and immunomodulation by parasites.

5. Other equine immunological models

The effect of aging on the equine immune systems has many parallels with humans. In particular, horses exhibit signs of both immunosenescence (Horohov et al., 2010; Katepalli et al., 2008; Muirhead et al., 2010) and inflamm-aging (Adams et al., 2009; Dakin et al., 2012) similar to that described for aged humans (Franceschi et al., 2000; Fulop et al., 2014). The effect of obesity on inflammatory responses in young and aged horses is also similar to that seen in humans (Adams et al., 2009; Florez and Troen, 2008). The horse has also been used as a model for the immunology of pregnancy (Noronha and Antczak, 2010). There has been considerable interest in the use of stem cells in the horse (De Schauwer et al., 2013; Spencer et al., 2011), with recent emphasis on the immunomodulatory function of stem cells (Carrade Holt et al., 2014; Ferris et al., 2014).

6. Limitations of the equine model and possible solutions

The major limitations to using the horse as a model for immunological research include its size, cost and lack of necessary reagents. Because of their size, the management and handling of horses, and ponies, requires specific facilities and experienced personnel. Such facilities are available at most veterinary schools and some colleges of agriculture. There are also a number of equine research centers in the United States and abroad which offer opportunities for collaborative research. Additionally, several groups have begun to develop equine tissue banks that provide high quality samples of various equine tissues to interested researchers. Likewise, the continuing development of immunological reagents will allow for more detailed studies of equine immune responses in the future. While the horse will never replace the mouse as the immunological model, it can offer opportunities that are not otherwise available as a disease model.

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