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Review Article

A Review of Candidate Genes for Development of Equine Recurrent Uveitis

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ABSTRACT

Equine recurrent uveitis (ERU) is a serious eye disease and the most common cause of blindness in horses. Until now, the cause of ERU is not fully understood. Persistent infections of pathogenic leptospires have been discussed. Chronic recurrent remitting episodes of inflammations and the positive therapeutic effects of corticosteroids have led to the hypothesis that ERU is an autoimmune disorder. The reason for a dysregulated autoimmune response may be linked to genetic factors. ERU shows similarities to human autoimmune uveitis with a genetic background. An association of the equine leukocyte antigen serological haplotype A9 with ERU in warmblood horses indicated that major histocompatibility complex I (MHCI) influences the development of ERU. The different types of human autoimmune and genetic uveitis, like Behçet's disease, systemic sarcoidosis, Vogt-Koyanagi-Harada syndrome, birdshot retinochoroidopathy, sympathetic ophthalmia, and acute recurrent anterior uveitis, had been associated with the human leukocyte antigen complex and genetic variants of the MHC. Furthermore non-MHC genes with a possible role in autoimmunity may also play a role in ERU-affected horses. The genes presented herein may be of interest for genome-wide association analyses of ERU-affected horses.

1. Introduction

Equine recurrent uveitis (ERU) is a common and serious eye disease among horses and in many cases the cause of blindness [1-3]. ERU shows similarities with human autoimmune uveitis, and there are no other mammalian species that spontaneously develop a similar disease [4-6]. An association of uveitis with the human leukocyte antigen (HLA) system [7] encoded by genes within the major histocompatibility complex (MHC) [8] has been found in humans. As uveitis in humans has a genetic component and shares many similarities with ERU, the aim of the present review was to discuss ERU-related candidate genes and proteins for horses based on previous studies performed in horses and humans.

2. Equine Recurrent Uveitis

The syndrome of ERU must be differentiated from primary uveitis. Any cause of damage to the uveal tract and subsequent compromise of the blood-aqueous barrier may result in primary uveitis. ERU, also known as moon blindness, recurrent iridocyclitis, or periodic ophthalmia, is characterized by recurrent-remitting episodes of inflammations in the eye at unpredictable intervals, followed by clinically quiescent stages [1-3]. Three main clinical syndromes can be distinguished: classic ERU, insidious ERU, and posterior ERU [1-12]. The acute phase of classic ERU involves inflammations of the iris, ciliary body, choroid, and anterior chamber. The repeated episodes of inflammation result in vision loss in many horses. Most

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horses are affected by classic ERU. However, Appaloosa and draught horses predominantly show insidious ERU, characterized by low-grade, persistent, and destructive inflammation of intraocular structures without outwardly painful episodes [2]. Cases of posterior uveitis develop inflammation of the choroid, retina, and vitreous body as well as mild anterior uveitis. This form of ERU seems to be most common in warmblood, draught breeds, and horses imported from Europe to the United States [2]. In Europe, most affected horses exhibit clinical signs of anterior uveitis consistent with classic ERU, and only a few patients develop posterior uveitis with inflammation of the choroid, retina, and vitreous body [3]. Frequently, panuveitis, affecting all structures of the uvea, can occur, particularly at later stages [9-12]. Long-term consequences of ERU are synechiae, pigment deposition on the anterior lens capsule, phthisis bulbi, retinal detachment, cataract of the lens, and lens luxation [1,9,13]. These damages can cause blindness or amblyopia, which results in high economic loss for the owners as blind horses must be euthanized. The diagnosis of ERU is based on characteristic clinical signs and on recurrent or persistent inflammation of the eye [14]. Differential diagnoses include nonrecurrent uveitis due to blunt or sharp trauma or due to septicemia [12]. Other masquerading syndromes can be keratitis, corneal ulcers, stromal abscesses, neoplasia, or glaucoma [1]. In horses with ERU, both eyes are nearly equally susceptible, and in approximately 37% of all cases, both eyes are involved simultaneously [1,14-16]. The prevalence of ERU in western Europe ranges from 3%-10% [15-17]. Geldings more often present among ERU-affected horses than mares and stallions [15,16,18]. This corresponds to the general distribution of sexes in European horse populations and does not reflect a sex-specific disposition to ERU. The disease can occur in horses of all ages. Nevertheless, Szemes and Gerhards [16] observed that 25%-33% of horses older than 15 years were affected with ERU. Another study identified the fact that horses older than 4 years show signs of ERU significantly more often than horses younger than 4 years [18]. With exception of one study [19], no significant relationships between ERU and different coat colors have been found [1,15,16,18].

At present, the cause of ERU is not fully understood. In previous reports, toxoplasmosis and vermination [15], hepatic dysfunction [20], vitamin B2 deficiency [21], and several bacterial and viral infections [1-3,21] have been discussed. Bacterial infections considered include infections with *Escherichia coli*, *Rhodococcus equi*, *Borellia burgdorferi*, and *Streptococcus equi*. Viral infections which were suspected to cause ERU are equine influenzavirus, equine herpesvirus 4, equine arteritis virus, and equine anemia virus [22]. Today, persistent infections with pathogenic leptospires or antibodies against leptospires in the eyes are discussed [23,24]. Due to the chronic recurrent nature of the inflammation, autoimmunity seems likely to be the primary cause of ERU [4,25]. While leptospiral infection and autoimmunity causes of ERU have been subjects of study for several decades, very few genetic studies have been conducted, so that hereditary predisposing factors are still largely unknown. The association between the A9 haplotype of the equine leukocyte antigen (ELA) and ERU in German warmblood horses could be the first evidence that the MHC region genetically influences ERU [26,27].

2.1. Autoimmune-Mediated Processes in Equine Recurrent Uveitis

Due to relapses of inflammation, response to corticosteroid therapy, insufficient therapeutic success of antibiotics, and the similarity to human autoimmune uveitis, it can be assumed that ERU is an autoimmune-mediated disease [14,28,29]. The predominant presence of $CD4^+$ T cells, an increased transcription of interleukin 2 (IL-2), and interferon-γ (IFNG) and low IL-4 mRNA expression in ERU-affected eyes suggest that ERU is a Th1-like lymphocyte-mediated autoimmune disease [25,29-32]. Furthermore, immunoreactivity for IL-6, IL-17, and IL-23 in conjunction with T lymphocytes as predominating inflammatory cells suggests that IL-17-secreting helper T cells play a role in pathogenesis of ERU [33]. Th1 and Th17 cells work together in a complex relationship to induce autoimmune reaction [33]. The gene encoding IFNG is located on horse chromosome (ECA) 6, IL-6 on ECA4, IL-17A and IL-17F on ECA20, and IL-23 on ECA6. IL-23 and IL-17 are important for the differentiation and maintenance of Th17 cells. An increased expression of chemokines such as regulated upon activation normal T-cell expressed and secreted (RANTES) mRNA, playing a role in the recruitment of T lymphocytes in the eyes of horses with ERU, were observed in the ciliary body of eyes with recurrent uveitis compared to normal eyes [34]. IL-6 plays an indirect role in the recruitment and differentiation of Th17 cells via RANTES and directly via macrophage signaling. In horses, RANTES (also known as chemokine ligand 5) is encoded by the *CCL5* gene located on ECA11. ERU-affected eyes were positive for CD3 T cells [33]. Furthermore, high concentrations of immunoglobulin G (IgG) were measured in eyes with uveitis [6]. Intraocular fluids of ERU-diseased eyes contain autoantibodies against the retinal autoantigens S-antigen and interphotoreceptor retinoid-binding protein (IRBP), as well as vitreal lymphocytes reacting with these autoantigens [6]. Proteome analysis showed downregulation of osteopontin [35], fibronectin 1 [35], pigment epithelium-derived factor [36,37], SFRP2, and DKK3 in vitreous samples of ERU-affected horses [38]. Most overrepresented protein pathways were linked to retinal Müller glial (RMG) cells [38,39]. Pathway enrichment analysis for differentially expressed proteins in vitreous samples of ERU-affected horses in comparison to controls and immunohistochemistry confirmed RMG cells as the primary responders to autoimmune triggers [38]. Protein expression patterns in peripheral leukocytes indicated a downregulation of talin 1 and, thus, pointed to a significant role of the innate immune system [40]. Following activation, most talin 1 undergoes proteolysis through calpain-like proteases, which leads to the release of $ß_2$ integrins [41]. The leukocytes become activated through $ß_2$ integrin and are then able to transmigrate the blood-retinal barrier and to attack retinal proteins, causing ocular inflammation [40,42]. Infiltration of the inner eye with granulocytes in specific clinical states of ERU cases seems to be caused by this dysregulation of the innate immune system.