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Review Article

Our current understanding of the pathophysiology of equine endometritis with an emphasis on breeding-induced endometritis☆

Mats H.T. Troedsson [a,*], Elizabeth M. Woodward [b]

[a] Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, KY 40546-009, USA
[b] Department of Clinical Studies, New Bolton Center, School of Veterinary Medicine, University of Pennsylvania, 382 West Street Road, Kennett Square, PA 19348, USA

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ABSTRACT

Equine endometritis is characterized by the expression of pro- and anti- inflammatory cytokines and an influx of polymorphonuclear neutrophils (PMNs) into the uterus. Mares resistant to persistent endometritis clear the inflammation within 24–36 h after exposure to microorganisms or semen. These mares have a rapid increase of pro-inflammatory cytokines and an upregulation of inflammatory modulating cytokines within 6 h after exposure to inflammatory challenge. In conjunction with effective uterine contractions, these events are believed to be responsible for the transient nature of the inflammation. In contrast, mares that are susceptible to persistent endometritis fail to clear the inflammation in a timely fashion. They have an imbalanced endometrial mRNA expression of pro- and anti-inflammatory cytokines, and have also been shown to suffer from an accumulation of intraluminal nitric oxide, which may be related to impaired myoelectrical activity and delayed uterine clearance. As a consequence, these mares establish a chronic inflammation, which interferes with the establishment of pregnancy. Recent studies on endometrial cytokine expression in resistant and susceptible mares have revealed information that suggest an underlying immunologic basis for susceptibility to persistent endometritis. However, the inflammatory pathways have yet not been fully studied, and a relationship between cytokine expression, nitric oxide, and myometrial contractions has not been established. In addition, seminal plasma has been shown to modulate breeding induced inflammation, but the molecular basis of the modulation is not understood. A holistic approach appears to be needed to better understand the characteristics of inflammatory pathways and ultimately the pathophysiology of the disease.

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* *Corresponding author*. Tel.: +1 8592574757.
E-mail address: M.Troedsson@uky.edu (Mats H.T. Troedsson).

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1. Introduction

Equine endometritis is one of the most common causes of infertility in the horse. While local components of uterine defense mechanisms ensure an effective and rapid clearance of an inflammation in mares with natural resistance to persistent endometritis, mares that fail to clear the uterus from an inflammation in a timely fashion are classified as susceptible to persistent endometritis [1]. In the past, the condition was believed to exclusively be the result of bacterial contamination of the uterus. More recent research on uterine defense mechanisms has increased our understanding of the pathophysiology of equine endometritis. Additional causative agents have been identified, and we have learned to separate between uterine infections and a physiological breeding-induced endometritis resulting from uterine exposure to semen. Both conditions involve a rapid inflammatory response, characterized by the expression of pro- and anti-inflammatory cytokines and an influx of polymorphonuclear neutrophils (PMNs) into the uterus.

When equine spermatozoa or bacteria enter the uterus, they trigger a chemotactic signal, resulting in an influx of PMNs into the uterine lumen [2–4]. Activated PMNs bind to spermatozoa and bacteria by the extrusion of DNA from PMNs forming extracellular neutrophil traps (NETs), and a traditional ligand receptor binding [5]. Following binding, the spermatozoa and contaminating bacteria are phagocytosed by the PMNs. During the activation of PMNs, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is released from cell membranes through metabolism of arachidonic acid *via* the cycloxygenase pathway. In addition to being an inflammatory mediator, $PGF_{2\alpha}$ causes contraction of smooth muscle, including the myometrium [6]. Uterine contractions are believed to physically remove accumulated fluid and harmful inflammatory products from the uterus [4]. Once these products are removed from the uterine lumen, the inflammation subsides, and the uterine environment returns to its normal state. In susceptible mares, this mechanism appears to fail at several levels resulting in an accumulation of intraluminal fluid and inflammatory products that may be involved in the development of endometrial fibrosis [7].

2. Mechanisms of inflammation

The inflammatory response is a complex process involving multiple signaling pathways. Immunoglobulins were suggested to be involved with the development of persistent endometritis, and several studies have investigated the presence of immunoglobulins in the uteri of susceptible mares [8–10]. Taken together, the results from these studies suggest that susceptibility to persistent endometritis is primarily due to factors other than a dysfunction of the adaptive immune response.

Previous studies hypothesized that mares susceptible to persistent endometritis had defective uterine PMNs. However, uterine PMNs from susceptible mares have been found to be fully functional, while the opsonizing ability of uterine secretions from susceptible mares was found to be decreased when compared to resistant mares [10,11].

The recognition of antigens and recruitment of inflammatory cells to the site of inflammation is initiated by cytokines that are produced by a variety of cell types, including lymphocytes and macrophages, but also epithelial cells, fibroblasts and stromal cells [12,13]. Among these cytokines, the interleukin (IL) 1 family is critical in the development and control of inflammation. The pro-inflammatory cytokines IL1α and IL1β are released at the onset of inflammation, and trigger an upregulation in the transcription of other pro-inflammatory cytokines, leading to the activation and recruitment of inflammatory cells. Interferon gamma (IFNγ) is another important pro-inflammatory cytokine involved with both the innate and adaptive inflammatory response. It has antimicrobial properties and aids in the migration of inflammatory cells through vessel walls. Additionally, the release of IFNγ leads to the upregulation of inducible nitric oxide (iNOS), which may play an important role in the pathophysiology of persistent endometritis [14,15].

To control the inflammatory response, anti-inflammatory cytokines are released in response to inflammation, such as IL10 and IL1 receptor antagonist (RA) [16–18]. IL1 pro-inflammatory cytokines are mediated in part by IL1RA [16]. This anti-inflammatory cytokine binds to the IL1 receptor and prevents the binding of IL1α and IL1β. It is critical for the proper balance of the pro- and anti-inflammatory effects. Along with IL1RA, IL10 is produced to contribute to the inflammatory mediating response. Susceptible mares were found to have an increased mRNA expression of IL8 and lower expression of IL10 compared to resistant mares 24 h after insemination [19,20]. While these results are supportive of the idea that normal mares are no longer signaling for the recruitment of inflammatory cells, the same group found that both resistant and susceptible mares had an increase in endometrial mRNA expression of other pro-inflammatory cytokines IL1, IL6, and tumor necrosis factor alpha (TNFα) 24 h after insemination [19]. These discrepancies are difficult to explain, however, it is important to define what ''resistant'' *versus* ''susceptible'' is, in order to make conclusions on the same population of horses. Two recent studies investigated the uterine inflammation at multiple time points within the first hours after intrauterine challenge with spermatozoa or *Escherichia coli* [21,22]. Susceptibility was strictly defined and standardized among mares in both studies. There was a distinct pattern of cytokine response for all mares, however, differences were observed between susceptible and resistant mares. Susceptible mares had lower expression of the inflammatory modulating cytokines IL10, IL1RA, and IL6 (which acts as an inflammatory modulator in the initial stages of inflammation [23]) when compared to resistant mares at 6 h after insemination. Based on this data, the authors concluded that 6 h after breeding may be a critical time in the development of persistent breeding-induced endometritis [22]. In a similar study, using *E. coli* rather than semen to experimentally induce endometritis, susceptible mares had an increase in the pro-inflammatory cytokines IL8 and IL1β at 24 h, and IL1β at 72 h after infusion compared to resistant mares [21]. Resistant mares had an increase in IL6 and TNF compared to susceptible mares 3 h after infusion. In contrast to when mares were inseminated, the authors found that susceptible mares had an increase in IL1RA compared to resistant mares at multiple time points after inoculation with

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