



Immune response of the reproductive tract to infectious agents

Resposta imune do trato reprodutivo a agents infecciosos

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Infections of the uterus are more common in cows than other domestic animals, making understanding of the immune capability of the reproductive tract extremely important, particularly in dairy animals. The protection of the reproductive tract depends on physical as well as immune functions. Physically, the reproductive tract is protected by a series of barriers including the vulva, the vestibule-vaginal junction and the cervix. Microbial contamination of the reproductive tract decreases with each successive barrier.

An important component of the defense mechanisms of the reproductive tract is the mucus it produces. Several mucins have been identified in reproductive tract mucus. Many of these bind directly to pathogens. This process aids their expulsion from the reproductive tract. Some mucins may be directly bactericidal. The reproductive tract also produces several specific antimicrobial peptides, including lingual anti-microbial peptide (LAP), tracheal antimicrobial peptide (TAP) and β -defensin. These antimicrobial peptides vary in concentration with stage of cycle and play an important role in reproductive tract defense.

The innate immune system is extremely important and plays a primary role in your uterine defense. Toll-like receptors (TLR) and NOD-like receptors (NLR) identify conserved molecular patterns characteristic of pathogens, and serve to initiate inflammatory responses. To date, epithelial cells and stromal cells of the uterus of cows have been shown to express Toll-like receptors 1 through 10 and NOD-like receptors 1 and 2. Stimulation of these receptors by microbial molecules initiates a signal transduction sequence culminating in release of cytokines. This, in turn, serves to attract leukocytes to the reproductive tract. These leukocytes may amplify the inflammatory response directly, phagocytose and kill pathogens, and also provide a link between the innate and acquired immune systems.

Acquired immune responses also play a role in reproductive tract defense. These include humoral and cytotoxic immunity. In contrast with other mucosal sites, the uterus is characterized by a greater IgG than IGA response. Antibody responses in the uterus are affected by stage of cycle and tend to be greatest under estrogenic stimulation. In some animal models vaginal or nasal application of antigens has resulted in optimal uterine response, but this has not been established for cattle.

The role of estradiol and progesterone in mediating immune responses of the uterus is not fully understood. However, it is clear that these hormones play a critical role. They modulate mucus production, epithelial integrity, cytokine production, leukocyte invasion, antimicrobial peptide production, and antibody migration. It is known that both lymphocyte and neutrophil function are impaired in the peri-parturient cow. This impairment is particularly pronounced in cows suffering severe negative energy balance. Impaired immune response, particularly impaired neutrophil activity, has been associated with retention of fetal membranes. It is now clear that severe impairment of the pro-inflammatory cytokine cascade in the immediate postpartum period subverts the uterine defense against bacteria, allowing bacterial pathogens to gain a foothold in the uterus. Cattle with a sluggish postpartum invasion of neutrophils into the uterus suffer more bacterial infections in the postpartum period than those with a more pronounced and immediate neutrophil response. In fact, impaired recruitment of neutrophils to the bovine uterus in the first week postpartum is itself associated with infertility in that lactation. Cows with the most pronounced immediate postpartum recruitment of neutrophils to the uterus have the best subsequent fertility.

Optimal defense of the reproductive tract depends on functional and coordinated efficacy of physical and functional defense mechanisms. Understanding defense mechanisms may allow improved prevention and treatment of postpartum uterine disease in dairy cattle.

Keywords: cow, immune response, uterus.

Palavras-chave: *resposta imune, utero, vaca.*

Recommended references

Cheong SH, Nydam DV, Galvão KN, Crosier BM, Gilbert RO. Cow-level and herd-level risk factors for subclinical endometritis in lactating Holstein cows. *J Dairy Sci*, v.94, p.762-770, 2011.

Galvão KN, Felipe MJ, Brittin SB, Sper R, Fraga M, Galvao JS, Caixeta L, Guard CL, Ricci A, Gilbert RO. Evaluation of cytokine expression by blood monocytes of lactating Holstein cows with or without postpartum uterine disease. *Theriogenology*, v.77, p.356-372, 2012.



- Galvão KN, Flaminio MJ, Brittin SB, Sper R, Fraga M, Caixeta L, Ricci A, Guard CL, Butler WR, Gilbert RO.** Association between uterine disease and indicators of neutrophil and systemic energy status in lactating Holstein cows. *J Dairy Sci*, v.93, p.2926-2937, 2010.
- Galvão KN, Santos NR, Galvao JS, Gilbert RO.** Association between endometritis and endometrial cytokine expression in postpartum Holstein cows. *Theriogenology*, v.76, p.290-299, 2011.
- Gilbert RO.** The effect of thawing temperature on post-thaw longevity of frozen bovine semen. *J South Afr Vet Assoc*, v.55, p.117-118, 1984.
- Herath S, Lilly ST, Santos NR, Gilbert RO, Goetze L, Bryant CE, White JO, Cronin J, Sheldon IM.** Expression of genes associated with immunity in the endometrium of cattle with disparate postpartum uterine disease and fertility. *Reprod Biol Endocrinol*, v.7, p.55, 2009.
- Hickey DK, Patel MV, Fahey JV, Wira CR.** Innate and adaptive immunity at mucosal surfaces of the female reproductive tract: stratification and integration of immune protection against the transmission of sexually transmitted infections. *J Reprod Immunol*, v.88, p.185-194, 2011.
- Sheldon IM, Bromfield JJ.** Innate immunity in the human endometrium and ovary. *Am J Reprod Immunol*, v.66 suppl.1, p.63-71, 2011.
- Sheldon IM, Cronin J, Goetze L, Donofrio G, Schuberth HJ.** Defining postpartum uterine disease and the mechanisms of infection and immunity in the female reproductive tract in cattle. *Biol Reprod*, v.81, p.1025-1032, 2009.
- Wira CR, Grant-Tschudy KS, Crane-Godreau MA.** Epithelial cells in the female reproductive tract: a central role as sentinels of immune protection. *American journal of reproductive immunology : AJRI : official journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction*, v.53, p.65-76, 2005.
- Wira CR, Patel MV, Ghosh M, Mukura L, Fahey JV.** Innate immunity in the human female reproductive tract: endocrine regulation of endogenous antimicrobial protection against HIV and other sexually transmitted infections. *Am J Reprod Immunol*, v.65, p.196-211, 2011.
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