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Mucosal immunity of the postpartum bovine genital tract

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ABSTRACT

In this review, mucosal immune defense mechanisms used to control infections in the bovine genital tract (vestibule, vagina, cervix, uterus and oviduct) during the postpartum period are reviewed. Knowledge gaps are highlighted to emphasize the need for further investigations. Physical barriers to the entry of microbes include vulvar sealing, vestibule-vaginal constriction, a narrow cervical opening and the mucosal epithelium along with the overlying mucus layer. Genital tract mucosal epithelial cells recognize damage-associated molecular patterns and pathogen-associated molecular patterns and respond by secreting antimicrobial peptides and cytokines to recruit and activate immune cells. Neutrophils and macrophages represent the first line of innate immune defenses recruited by cytokines to the site of inflammation. Macrophages, endometrial epithelial cells and dendritic cells interact with T-cells to elicit cellular responses and regulate antibody responses. Immune regulatory components such as M2-macrophages and regulatory T-cells, although less studied, may work in conjunction with epithelial cell regeneration to coordinate involution of the postpartum uterus and prepare the genital tract for the next pregnancy. A role for the vaginal and uterine microbiome in modulating uterine inflammation is an emerging research focus and further studies are required to integrate information on the nutritional and metabolic status of cows with innate immune responses and host-microbiome interactions. A greater understanding of these complex interactions is critical for developing more effective therapies for the prevention and treatment of uterine inflammation.

1. Introduction

The bovine female genital tubular system is functionally adapted to facilitate oocyte fertilization, nurture embryonic/fetal development, deliver a calf, and ensure a timely return to a pregravid state. Immunologically, the female genital system exhibits a large degree of flexibility from what is believed to be an immunotolerant state during pregnancy to the ability to mount active immune responses when encountering genital pathogens. The mechanisms of immunosuppression during bovine pregnancy have been extensively reviewed [1–3] and will not be covered in the present report. The current review will focus on knowledge of innate and acquired mucosal immune responses and their regulation during the postpartum period (up to 60 days in milk) in cattle.

The female genital tubular tract has several known physical barriers to minimize bacterial entry and colonization. These include vulvar sealing, vestibule-vaginal constriction, the cervix, cervicovaginal mucus secretion, and the epithelial barrier, but until recently an in depth understanding of these and other protective mechanisms at a cellular and molecular level was lacking. Classically, mucosal sites such as the intestine, respiratory tract, and ocular mucosa are associated with organized sub-mucosal lymphoid tissue, collectively referred to as mucosal-associated lymphoid tissues (MALT), that is populated by both T- and B-lymphocytes [4]. The MALT constitutes a crucial inductive site for both antibody-dependent humoral (mainly immunoglobulin (Ig) A) and cellular immune responses against potential antigens. Isolated lymphoid aggregates (follicles) and isolated lymphoid infiltrations have been observed in the vestibule and throughout the rest of female genital tract of cattle, respectively [5]. Lymph fluid from the bovine uterus drains primarily to the internal iliac and sacral lymph nodes, which also function as important immune induction sites [6].

The following sections will focus on mucosal defense

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mechanisms of the bovine tubular genital tract during the postpartum period. Integration of epithelial cell function and immune mechanisms is crucial for maintaining the integrity of the mucosal barrier and this interaction will be emphasized. Where necessary, information from other species is incorporated to provide a comparative analysis of immune function and to highlight knowledge deficits that need to be addressed to better understand the function of the bovine postpartum uterus.

2. Genital tract inflammation during the postpartum period

Following delivery of a calf, the bovine genital tract undergoes an active inflammatory process to clear cellular debris from the placenta and respond to bacterial contamination. In healthy cows, uterine inflammation subsides by the fourth to fifth wk postpartum, however, genital tract (mainly uterus) reparation is not complete until the sixth to eighth wk postpartum [7]. Some cows will, however, exhibit either a systemic inflammatory response during the first two wk postpartum or will experience a more prolonged genital tract inflammation. Factors that influence the development of a systemic inflammatory response or sustained uterine inflammation in the postpartum cow have been reviewed elsewhere [7,8]. Genital tract inflammatory conditions encountered in the postpartum period are often identified based on the anatomical location involved, such as the vagina (purulent vaginal discharge), cervix (cervicitis) and uterus (metritis/endometritis/pyometra). Detailed definitions of the infectious and inflammatory conditions affecting the bovine genital tract during the postpartum period exist in the literature [7–12]. Briefly, purulent vaginal discharge is associated with endometritis and cervicitis reflects persistent inflammation of the cervix. Metritis and endometritis are distinct diseases: metritis is inflammation affecting the endometrium and deeper tissue layers of the uterus, whereas endometritis is inflammation limited to the endometrium [7–11]. Metritis is commonly encountered during the first two to three wk postpartum while endometritis occurs primarily beyond three wk postpartum [7–11]. Owing to the continuous nature of the female genital tract, vaginal discharge, typically purulent or mucopurulent in these cases, has also been associated with endometritis. The vagina may serve as drainage route, or may be inflamed secondarily [8]. Collectively, these genital tract inflammatory conditions indicate a failure of physical barriers as well as innate and acquired immune defense mechanisms that normally limit microbial entry and colonization.

3. Uterine defense mechanisms

3.1. Epithelial cells

The mucosal epithelial lining of the genital tract offers a physical defense mechanism against microbial attachment and invasion. The type of mucosal epithelium and the thickness of this layer varies with the anatomical location, responding to differing physiological needs (Fig. 1). A multilayered squamous epithelium in the vestibule and vagina [5] is important as these sites are the first to be challenged by bacteria from fecal, uterine and environmental origins. Extensive folding of the cervical mucosa adds another physical impediment to microbial entry into the uterus (Fig. 1) but in contrast to the vestibule and vagina, the epithelium is limited to a single cell layer in the cervix, uterus [13,14] and oviduct [15] (Fig. 1). A glycocalyx layer present on the luminal surface of the uterus [16] and the oviductal epithelium [17] likely acts as an additional physical barrier at these sites, an aspect that needs to be studied in greater detail.

Maintaining the integrity of the epithelial barrier is a key component of uterine involution during the postpartum period. As part of the uterine involution process, uterine caruncles undergo necrosis soon after calving with villous areas being completely sloughed by 12–14 d postpartum [18]. Lack of an intact epithelium protecting caruncles during the first two weeks postpartum may contribute to an increased susceptibility to infection (metritis) during this period. As a result, epithelial regeneration at caruncular regions is a critical component of maintaining the epithelial barrier. Regeneration of the uterine epithelium appears first at the edges of the caruncular regions and then completely covers each of the caruncles by 30 d postpartum [18]. Our knowledge of the processes and potential factors regulating endometrial regeneration during the postpartum period in cattle is limited. In mice, potential progenitor cells of epithelial and stromal origin contribute to epithelial regeneration and thus maintain epithelial integrity during the postpartum period. Specialized epithelial cells in the genital tract also contribute to genital tract defense mechanisms by secreting mucus that facilitates physical clearance of microbial contaminants [19].

Bovine genital tract epithelial cells, similar to immune cells, have the capacity to recognize pathogen-associated molecular pattern molecules (PAMPs) as well as damage-associated molecular patterns (DAMPs) through a variety of pattern recognition receptors (PRRs) (Fig. 2a). Most studies analyzing responses to PAMPs and DAMPs in the genital tract have focused primarily on the uterus but some information is available for the oviduct. Bovine endometrial epithelial cells express transcripts for Toll-like receptor (TLR)-1 to 7 and 9 genes, while endometrial stromal cells expressed

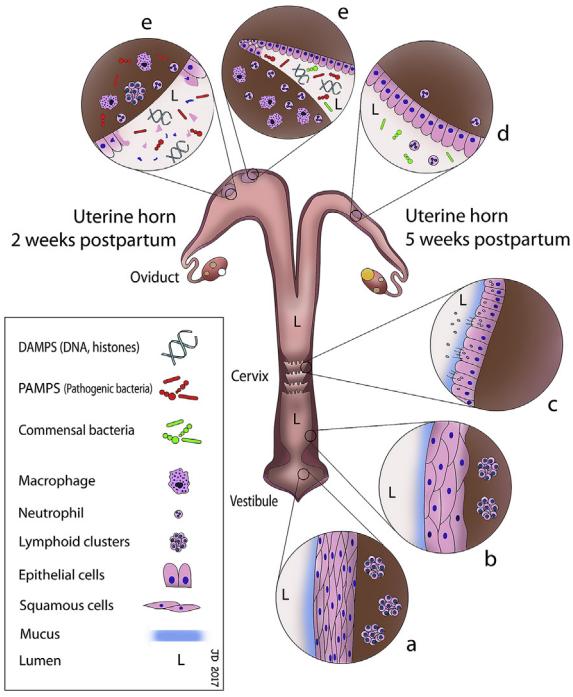

Fig. 1. Physical components of the immune defense mechanism in the bovine postpartum genital tract. The vulvar opening acts as the portal for entry as well as clearance of microbial contaminants. Multiple epithelial layers in the vestibule (a) and vagina (b) prevent bacterial entry at these anatomical sites unless they have been breached due to laceration during delivery. The cervix (c), although still dilated after calving, provides another barrier to the entry of microbes into the uterus due to epithelial folding and secretion of mucus that flows outward to the vagina. Around the second wk postpartum (e), the simple columnar uterine epithelial barrier is breached at the caruncles due to death of epithelial cells. For the next three weeks, the uterus responds to microbial contamination and colonization while re-establishing the integrity of the epithelial barrier (d).