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Analysis of endometrial myeloid and lymphoid dendritic cells during mouse estrous cycle

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Abstract

This study was performed to evaluate the frequency and localization of endometrial myeloid ($CD11c^+$ $CD11b^+$) and lymphoid ($CD11c^+$ $CD8\alpha^+$) dendritic cells (DCs) at different stages of murine estrous cycle. To address the systemic effect of ovarian hormones fluctuations during estrous cycle, the same variables were studied in splenic DCs as well. Stages of the estrous cycle of Balb/c mice were determined by examination of vaginal smears. Frozen sections of uterus and spleen at each stage of estrous cycle were stained for CD11c and MHC-II. Two-color immunohistochemistry was also carried out using anti-CD11c with one of the antibodies against CD11b, CD8α, CD86, and DEC-205. The average density of DCs and relative percentage of myeloid and lymphoid DCs (MDCs and LDCs) were determined at each stage of estrous cycle by morphometric analysis. Our results showed that DCs were present throughout the estrous cycle in mice endometrium, but their frequency was highest at estrus and lowest at proestrus ($P < 0.005$). The lymphoid subset of DCs was more prominent at estrus relative to those at other stages ($P < 0.005$). Conversely, the relative percentage of myeloid DCs at estrus was significantly lower compared to other stages ($P < 0.005$). Nearly all endometrial and splenic DCs expressed CD86 and MHC-II. At proestrus, and particularly at estrus, DCs were more

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concentrated subadjacent to the luminal and glandular epithelial layers with some scattered throughout the stroma whereas, at metestrus and diestrus, DCs were randomly distributed in stroma and around the glandular and luminal epithelial layers. The number and immunophenotype of splenic DCs were not statistically different between stages of estrous cycle. Our results suggest that endometrial but not splenic myeloid and lymphoid DCs are influenced by steroid hormones during estrous cycle.

Keywords: Dendritic cells; Estrous cycle; Mouse; Uterus; Spleen

1. Introduction

Within the female reproductive tract, the mucosal immune system plays a protective role against potential pathogens without compromising fetal survival (Wira and Stern, 1992). The female may be exposed to allogenic sperm or to a semiallogenic feto-placental unit that is immunologically foreign. To meet these diverse challenges, the mucosal immune system within the uterus, cervix and vagina is precisely controlled by female sex hormones and cytokines to optimize both maternal and fetal survival (Wira and Sandoe, 1997; Schumacher, 1980). Depending on the analyzed site and the reproductive state (endocrine balance), immunocompetency of the female reproductive tract may be either enhanced or suppressed to meet maternal and fetal needs (Wira and Stern, 1992). The uterus is a part of the mucosal immune system, sharing structural and functional similarities and common lymphocyte trafficking networks with the other mucosal tissues. It is supplied with abundant lymphatic drainage and contains the full range of lymphohematopoietic cells and mediators required to mount adaptive immunity (for review, see Robertson, 2000). In the uterus, both humoral and cell-mediated immunity can be induced after infection or immunization (Wira et al., 1999).

In the uterus, the magnitude and quality of an immune response to foreign antigens, besides the nature of antigen and other key factors in eliciting an immune response, is also influenced by ovarian steroid hormones (Wira et al., 1999). Thus the outcome of the immune response within the uterus can be markedly influenced by the stage of the estrous cycle at which priming or infection takes place (Gockel et al., 2003; Parr and Parr, 1999). It is well recognized that immune cells are present in the female reproductive tract and are involved in complex interactions with other resident cells (epithelial, stromal and endothelial) of the uterus and vagina. Immune cells including macrophages, major histocompatibility complex (MHC) class II-positive cells, T lymphocytes of both CD4 and CD8 type, and natural killer cells have been reported in the fallopian tubes, uterus and vagina of a number of species including mice, rats and humans (Head and Gaede, 1986; Kamat and Isaacson, 1987; King et al., 1989; Laguens et al., 1990; Parr and Parr, 1991; Nandi and Allison, 1993; Hunt, 1994). Depending on the species, these cells may either vary with the stage of estrous cycle or remain constant.

Among different immunocompetent cells present in the female reproductive tract, antigen-presenting cells are key players in induction of immune responses. Macrophages (Hunt and Robertson, 1996; Kaushic et al., 1998) and vaginal and uterine epithelial cells (Wira et al., 1999, 2002) are well-studied antigen-presenting cells in the female reproduc-