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Macrophage density in the pregnant rat uterine cervix is modulated by mast cell degranulation

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Abstract

The uterine cervix at term undergoes histomorphological changes that resemble an inflammatory process. The aim of this study was to better characterize these changes, describing the temporal and spatial pattern of macrophages and mast cells (MC) distribution in the uterine cervix and assessing whether both cells exert a coordinated action on angiogenesis. Macrophages and MC were identified by immunohistochemistry in cervical tissue from cycling, pregnant and postpartum rats. In order to inhibit MC degranulation, pregnant rats were injected with disodium cromoglycate. The expression of vascular endothelial growth factor (VEGF) by macrophages was also evaluated. Results showed that macrophage density increased towards parturition and declined at postpartum, whereas MC density showed an inverse pattern. Interestingly, disodium cromoglycate-treated rats showed an increased number of macrophages. VEGF expression in macrophages was detected neither in control nor in treated animals; however, a coordinated action between MC and macrophages on angiogenesis could not be excluded. The present study provides a detailed mapping of macrophage and MC densities and distribution in the rat uterine cervix. Moreover, an association between macrophages and MC along pregnancy is shown, and evidence that macrophage density in the rat cervix is modulated by MC degranulation is presented.

Keywords: Uterine cervix; Macrophages; Mast cells; Angiogenesis; Vascular endothelial growth factor

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1. Introduction

Almost three decades ago, Liggins et al. (1977) suggested that histomorphological and vascular changes characteristics of the uterus and cervix at term resemble an inflammatory reaction. Changes in the distribution of immunocompetent cells, such as granulocytes, lymphocytes, mast cells (MC) and macrophages, have been described in the uterine horns and cervical tissue along pregnancy, parturition and postpartum (PP) (Padykula and Tansey, 1979; Junqueira et al., 1980; Mitchell, 1984; Luque and Montes, 1989; Luque et al., 1996; Ramos et al., 2000; Salamonsen and Lathbury, 2000; Yellon et al., 2003; Varayoud et al., 2004).

Macrophage numbers in the mouse uterine cervix varied with respect to stage of pregnancy. Increased numbers of macrophages were found in cervices harvested at the end of pregnancy (day 18) and remained elevated in the postpartum within 12 h of birth (Mackler et al., 1999). Moreover, enhanced concentrations of macrophage cytokines in the uterine cervix at term have been associated with human cervical softening and dilation (Sennström et al., 1997, 2000; Kelly, 2002; Young et al., 2002). Whether the elevated production of these cytokines in the peripartum cervix is the consequence of either increased number of resident macrophages or an up-regulation of their secretion needs to be established.

Angiogenesis is an important component of the inflammatory process and also in the adaptation of the reproductive tract to different physiological conditions (Norrby, 1997; Griffioen and Molema, 2000; Reynolds et al., 2002). Macrophages are not angiogenic per se but, when they received an adequate stimulation, they could exert angiogenic activity by modifying the expression patterns of their secretory products (Polverini et al., 1977; Sunderkötter et al., 1994). In vitro studies showed that hypoxia induces macrophage activation, stimulating the release of angiogenic cytokines and growth factors (i.e. vascular endothelial growth factor, VEGF), along with proteolytic enzymes, which might play a role in the promotion of neovessel formation (Crowther et al., 2001). While many of these molecules have been identified as positive regulators of angiogenesis, VEGF dependent signals often represent a critical rate-limiting step in physiological angiogenesis (Ferrara et al., 2003). Recently, we showed that inhibition of MC degranulation during pregnancy diminished the angiogenesis process in the rat uterine cervix, suggesting that a hypoxic microenvironment may have been generated in this tissue (Varayoud et al., 2004).

The aim of the present study was to better characterize rat uterine cervix changes in the estrous cycle, along pregnancy and postpartum by: (1) describing the temporal and spatial pattern of macrophage distribution, (2) establishing a possible association between macrophages and MC, and if present, (3) assessing whether the inhibition of MC degranulation induces changes in macrophage VEGF expression.

2. Materials and methods

2.1. Animals

Female adult rats (200–250 g of body weight (bw)) of a Wistar-derived strain bred at the Department of Human Physiology (Santa Fe, Argentina) were used. Animals were