Endometriosis: Immune Cells and Their Products

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Endometriosis, defined as the occurrence of functioning endometrial tissue in ectopic (outside of the uterus) locations, is among the most enigmatic and problematic diseases affecting the reproductive health of women. Endometriosis is associated with pelvic pain and is believed to be the cause of infertility in up to 20% of subfertile women. Approximately 4 per 1000 women aged 15 to 64 are hospitalized with endometriosis each year (1). Endometriosis-related costs in terms of health care expenditures and time away from work of afflicted women are enormous, while the costs in terms of pain and suffering cannot be estimated.

Despite nearly 50 years of research, the pathophysiologic mechanisms responsible for the establishment and progression of endometriosis and endometriosis-associated reproductive failure have not been fully defined. There is a general consensus that endometriosis most probably develops as a result of retrograde menstruation (2), although extrapelvic cases of endometriosis (reviewed in 3) certainly cannot be explained by this mechanism. Retrograde menstruation appears to be a common occurrence. It has been observed in approximately 90% of women having a diagnostic laparoscopy performed while menstruating (4) and in up to 75% of women having laparoscopic sterilization during their menses (5). Endometrial tissue has been histologically observed in women with (19%) and without (11%) endometriosis who were experiencing retrograde menstruation at the time of laparoscopy (6). It can never be determined whether these observations were confounded by the surgical procedure necessitating anesthesia and paralytic medication, which could potentially facilitate retrograde menstruation. However, retrograde menstruation may be an important cause of pelvic endometriosis in susceptible individuals. What defines this susceptibility is still largely unknown, although accumulating evidence suggests that inflammatory/immunologic
factors may play an important role in the development of endometriosis and endometriosis-associated reproductive failure.

**Inflammatory Aspects of Endometriosis**

Inflammation is a localized protective response to tissue injury that can destroy both the injurious agent and the injured tissue. The inflammatory and immune responses are intimately connected through cytokine and antibody-mediating mechanisms. Peritoneal fluid lysozyme levels indicate that localized intraperitoneal inflammation occurs in women with active endometriosis (7). Macrophage numbers and concentrations are abundant in the peritoneal fluid of women with active endometriosis (8–11). In addition to being increased, peritoneal macrophages in women with active endometriosis also have altered maturational characteristics (12) and increased capping ability for major histocompatibility complex (MHC) class II antigens, unlike peritoneal macrophages from women without endometriosis (13). Increased macrophage activation in response to endometriosis causes secretion of growth factors and cytokines that can influence ectopic endometrial growth and further recruitment of the immune/inflammatory cells initiating the cytokine cascade. Fibroblast- and macrophage-secreted growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), have been shown to stimulate endometrial stromal cells in vitro (14) and may influence the growth of endometriosis through paracrine mechanisms via EGF receptors on endometriotic implants (15). The peritoneal environment is also immunostimulatory (16), suggesting that in the presence of antigenic stimulation caused by active endometriosis, proliferation and activation of recruited leukocytes could be enhanced.

The concept that ectopic endometrium is antigenic in some but not all women was proposed over 20 years ago following the observation that complement's biologically active fragment, C3, was present around ectopic endometrial glands (17). Other investigators have not demonstrated a difference in the specific deposition of complement in ectopic as compared to eutopic endometrial glands (18). Earlier, other investigators (19), using immunofluorescence techniques, reported no difference in the presence of either C3 or C4 in eutopic endometrium, regardless of menstrual cycle phase or surgical diagnosis (endometriosis, pelvic inflammatory disease, and normal pelvis).

Tissue implants of endometriosis have been demonstrated to be able to produce and secrete C3 in vitro (20). Proliferative endometrial biopsies from women with minimal (stage I) endometriosis (21) have also been shown to produce significantly greater amounts of C3 in vitro than biopsies from women with either no endometriosis or women with severe (stage IV) endometriosis (22). The propensity to secrete biologically