Journal of Reproductive Immunology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

Review

The immune system in the normal endometrium and implications for endometrial cancer development

A. Vanderstraeten [a], S. Tuyaerts [a,*], F. Amant [a,b]

[a] KU Leuven – University of Leuven, Department of Oncology, Gynecologic Oncology, B-3000 Leuven, Belgium
[b] University Hospitals Leuven, Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 9 July 2014
Accepted 22 December 2014

Keywords:
Endometrium
Immune system
Endometrial cancer
Immunotherapy

ABSTRACT

Although described for the first time some decades ago, the contribution of the immune system to the establishment of tumors has not been extensively pursued for a long time. Over the last decade, however, more and more evidence has been accumulating concerning the role the immune system plays in tumor development and progression and its possible role in patient prognosis. In addition, interest is growing in preclinical and clinical research concerning the use of the immune system in the treatment of cancer. Immunotherapy for gynecological cancers in general, and for endometrial cancer in particular, is still in its infancy. Only a small number of studies, with varying success rates, have been published. Here, we provide a concise overview of the literature available on the role of the immune system in the normal endometrium and in endometrial cancer, in addition to the possible implications for future immunotherapeutic studies.

1. Introduction

Many risk factors involved in the etiology of endometrial cancer have been described. Obesity and physical inactivity are two significant risk factors for the development of uterine tumors, along with elevated blood pressure, high energy intake, high serum glucose levels and increased exposure to estrogens (Amant et al., 2005). For some of these risk factors, the effects on and interactions with the immune system have been reported. Hormonal fluctuations during the menstrual cycle have been described to modulate immune functions, as reviewed by Wira et al. (2010). Hormonal fluctuations and interactions with immune cells result in a protective environment against invading pathogens, while creating a favorable environment for embryonic implantation and fetal development. Obesity, which is related to an increased risk of developing endometrial cancer, is considered to be a chronic inflammatory state, causing increased release of pro-inflammatory cytokines such as IL-6 and CRP (Visser et al., 1999).

In addition to the effect of the risk factors described on the immune system, the vast majority of endometrial cancer cases are diagnosed in post-menopausal women and often in elderly patients. Age has an important influence on the immune system, the so-called immunosenescence, which parallels hormonal changes that occur with increasing age (Pfister and Savino, 2008). Aging causes an overall

Abbreviations: BMI, body mass index; COX-2, cyclo-oxygenase 2; CRP, C-reactive protein; CTL, cytotoxic T lymphocyte; DC, dendritic cells; HLA-G, human leukocyte antigen G; IDO, indoleamine 2,3-dioxygenase; MALT, mucosa-associated lymphoid tissue; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, prostaglandin E2; TDLN, tumor-draining lymph nodes; TAM, tumor-associated macrophages; Treg, regulatory T cells.

* Corresponding author at: Department of Oncology, Division of Gynecologic Oncology, KU Leuven, Herestraat 49 Box 611, 3000 Leuven, Belgium. Tel.: +32 16 342905; Fax: +32 16 346215.
E-mail address: sandra.tuyaerts@uzleuven.be (S. Tuyaerts).

http://dx.doi.org/10.1016/j.jri.2014.12.006
0165-0378/

decrease in immune-related functions and results in a latent pro-inflammatory state.

Taken together, these data indicate that risk factors associated with the occurrence of endometrial cancer have an important influence on the immune system. In the current review, we provide an overview of the role the immune system plays in the normal non-pregnant uterus and how changes in the immune system may play a role in the development of uterine tumors and the possible clinical outcome. This knowledge is important for successful further development of immunotherapeutic strategies for uterine cancer.

2. The uterine immune system under physiological conditions and in cancer

The immune system in the normal uterus serves a dual purpose. On the one hand, it plays a role in protection against pathogens, while on the other hand, it has the ability to adapt to an immunosuppressive state in order to create feto-maternal tolerance toward a semi-allogeneic fetus. These separate functions involve the complex interplay of the hormonal fluctuations of the menstrual cycle and the immune system. Normal endometrium is naturally under strict hormonal control. It is under constant control of the variations in estradiol and progesterone during the menstrual cycle. Both the innate and adaptive arms of the immune system are influenced by these hormonal changes. Several risk factors have been described for endometrial cancer, which may be linked to increased inflammation of the endometrial tissue, as reviewed by Modugno et al. (2005). Increased exposure to estrogens has been shown to be associated with endometrial cancer development, owing to the mitogenic effect of estrogens (Austin et al., 1991; Potischman et al., 1996; Zeleniuch-Jacquotte et al., 2001). Consequently, estrogen-related carcinogenesis may be related to inflammatory events. Chronic inflammation has been linked to cancer development (Hanahan and Weinberg, 2011). Several inflammation pathways are involved in carcinogenesis. Many of these pathways are initialized by, among others, activation of STAT 3 or NF-κB (Elinav et al., 2013). The detailed role these pathways and their downstream mediators play in carcinogenesis is beyond the scope of this review and is briefly summarized in Fig. 1. This interplay is discussed and further elaborated on by Elinav et al. (2013).

2.1. Immune functions of normal and malignant endometrial cells

The endometrial epithelium serves as the primary line of defense against viruses and other pathogens entering the uterus. The epithelial cells form an integral part of the mucosal immune system. Next to forming a physical barrier, the epithelial cells have several direct immune-related functions, one of which is the secretion of defensins (Wira et al., 2005b). Defensins form a part of the innate immune system, considering their immediate antimicrobial function and their ability to activate the adaptive immune system. For example, defensins have been shown to attract T cells and immature dendritic cells (DC) in response to binding to the C-C chemokine receptor type 6 (CCR6) (Yang et al., 1999). Other secreted molecules include macrophage inflammatory protein (MIP)3α, also a ligand for CCR6, and secretory leukocyte protease inhibitor (SLPI) (Fahey and Wira, 2002; Fahey et al., 2006a). In contrast, uterine epithelial cells secrete unidentified, soluble immune mediators that confer a tolerogenic phenotype to DC (Ochiel et al., 2010).

Obesity and diabetes have also been shown to be associated with increased release of pro-inflammatory molecules, such as IL-6, TNF-α, CRP, leptin, and macrophage migration inhibitory factor (Dandona et al., 2004; Visser et al., 1999). Two studies evaluating the serum levels of IL-6, TNF-α, and CRP, and the risk of developing endometrial cancer, have shown that elevated levels of CRP are associated with endometrial cancer risk (Friedenreich et al., 2013; Wang et al., 2011). Wang et al. (2011) found this correlation after correcting for BMI and age. Friedenreich et al. (2013), in addition, found that CRP and endometrial cancer risk were associated with high BMI, and that serum IL-6 and endometrial cancer risk were associated with low BMI.

Indoleamine 2,3-dioxygenase (IDO), which is responsible for T cell suppression through the deprivation of the crucial metabolite tryptophan, is up-regulated in secretory *versus* proliferative endometrium. The presence of the enzyme may play a dual protective role: it functions as an anti-bacterial agent and induces suppression of T cells. The latter creates an immunosuppressive state to allow embryonic implantation (Lobo et al., 2004). IDO is also expressed by endometrial carcinoma cells (de Jong et al., 2012; Ino et al., 2008; Vanderstraeten et al., 2014), and was proven to be associated with myometrial invasion, lymph node metastases and lymphovascular space involvement (Ino et al., 2008). In addition, high IDO expression correlated with decreased $CD8^+$ TIL and NK cell involvement and was associated with poor survival (de Jong et al., 2012). Thus, in both normal and malignant endometrium, the primary function of IDO seems to be the induction of immunosuppression in order to allow embryonic implantation or tumor growth.

Endometrial epithelial cells are also potent antigen-presenting cells. Ferguson et al. found expression of major histocompatibility complex (MHC) class I in endometrial glands and in stromal cells and endothelial cells. MHC class II, on the contrary, was found to be expressed in the endometrial glands in approximately 50% of normal endometrium samples (Ferguson et al., 1985). Fahey et al. have shown that cultured epithelial cells express CD40 and CD1d and that epithelial cells in addition to stromal endometrial cells can elicit tetanus toxoid-specific T cell responses (Fahey et al., 2006b; Wallace et al., 2001). In endometrial tumors, classical MHC class I was down-regulated in 48.5% of 520 tumors, which is associated with worse disease prognosis (Bijen et al., 2010). In addition, the non-classical MHC class I molecule, human leukocyte antigen G (HLA-G) was up-regulated in 39.8% of samples, corroborating the results of Barrier et al., who found expression of HLA-G in 55% of samples (Barrier et al., 2006). Although requiring further investigation, the up-regulation of HLA-G molecules in endometrial tumors

Please cite this article in press as: Vanderstraeten, A., et al., The immune system in the normal endometrium and implications for endometrial cancer development. J. Reprod. Immunol. (2015), http://dx.doi.org/10.1016/j.jri.2014.12.006