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ENDOMETRIOSIS: A REVIEW OF ITS PATHOGENESIS

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1. ABTRACT

Although peritoneal endometriosis was recognized in 1860, its pathogenesis still remains unclear. Several theories attempt to explain the pathogenesis of this condition. From these, the implantation theory maintains that peritoneal endometriosis is the result of implantation and subsequent growth of retrogradely shed viable endometrial cells. Based on a second theory, the peritoneal mesothelium transforms to an endometrium-like tissue under the influence of products of regurgitated endometrium (induction). Cell adhesion molecules could be functionally involved in the binding of the endometrial cells to the peritoneal lining. In peritoneal endometriosis, a delicate equilibrium seems to exist between attacking forces (retrograde menstruation) and the defense mechanisms. On one hand, the amount and the nature of the regurgitated menstrual debris seems important to the development of the disease. On the other hand, the active intra-abdominal milieu may be involved. This milieu probably converts the regurgitated endometrial tissue into single cells via loss of functional cell adhesion properties. Endometriosis may result form the impairment of the function of the peritoneal milieu in disposing of the regurgitated cells. Alternatively, the endometriosis may occur if the number of regurgitated cells is too large. An intact peritoneal lining may be an important additional line of defense in preventing the binding of the endometrial cells. Endometriosis is likely to develop if such defense mechanisms fail. . Here, the scientific basis of the endometriosis theories is discussed.

2. INTRODUCTION

At least three different forms of endometriosis must be discriminated (1). These three forms are: peritoneal, ovarian and rectovaginal. The first histological description of a lesion consistent with endometriosis was described by Von Rokitansky in 1860 (2). It was Cullen (3, 4) who, in 1896, suggested that endometriomas, or adenomyomas as he called these lesions, resembled the mucous membrane of the uterus. However to this date, the pathogenesis of this enigmatic disease is still poorly understood and remains controversial. The theories dealing with the pathogenesis of endometriosis, in particular of peritoneal endometriosis, can be divided into three main concepts. The oldest concept is that endometriosis develops *in situ* from the remnants of the Wolffian or Müllerian ducts, or alternatively from metaplasia of the peritoneal or ovarian tissues (5, 6).

A second concept is based on the assumption that endometriosis results from differentation of mesenchymal cells, activated (induced) by substances released by degenerating endometrium arriving in the abdominal cavity (the induction theory) (7, 8).

A third concept is based on the transplantation and subsequent implantation of endometrial tissue on the peritoneal surface (9, 10). This would include transportation of viable endometrial cells during menstruation via the fallopian tubes into the abdominal cavity, implantation of these cells onto the peritoneum and the development of these cells into the endometriotic tissue (the transplantation or implantation theory). In the following section each of these concepts is discussed.

3. MAIN CONCEPTS

3.1 *In-situ* development theory

The theories considering the development of endometriosis from either the Wolffian duct or knob or from Müllerian tissue have been met with a lot of opposition over the years and for the most part have been disregarded. The finding of endometriosis on the serosal surface of the colon and the small intestines made a purely embryonic derivation too restrictive. The theory of coelomic metaplasia has still some support, because it can explain the origin of

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endometriosis, regardless of the sites or the conditions of its occurrence (11). The theory does not explain why endometriosis occurs exclusively in women, typically during the reproductive years, or why endometriosis mainly affects the pelvic organs, or why it only occurs in women with a functioning endometrium. Proof of this theory is lacking, either experimentally or clinically. There is only some circumstantial evidence, in case reports, of endometriosis occurring in young girls, even before menarche, and in reports of endometriosis at rare locations, such as pleura or diaphragma (12, 13).

3.2 Induction theory

In 1955, Levander and Normann introduced the induction theory (7). This theory is based on the assumption that specific substances which are released by the degenerating endometrium induce endometriosis from omnipotent blastema, present in connective tissues. This theory was proposed since, in experiments in rabbits, cell-free endometrial products were capable of inducing endometrial metaplasia (8). These changes, however, do not meet the criteria for the diagnosis of endometriosis, since no endometrial stroma was found in these experiments. Lauchlan introduced the term "secondary Müllerian system", referring to all Müllerian type epithelium located outside the course of the original Müllerian ducts (6). This layer of cells could then, particularly on the surface of the ovary, through metaplasia develop into four cell types, serous (tubal), mucinous (endocervical), Brenner epithelium, and endometrial. This could occur before or after invagination, particularly of the ovary. The fact that both serous and mucinous epithelium can be found in or around endometriotic lesions is an argument in favor of this concept (6).

3.3 Implantation theory

The implantation theory is based on the principle that viable endometrium implants on the peritoneal surface. Therefore this theory requires three steps. First, retrograde menstruation has to occur. Secondly, retrograde menstruation should contain viable endometrial cells, and, thirdly, adhesion to the peritoneum has to occur with subsequent implantation and proliferation. The implantation theory was originally neglected for a long time, because menstrual effluent was considered to contain only non-viable endometrial tissue and retrograde menstruation was thought to be a rare phenomenon (14, 15, 16, 17).

Retrograde menstruation and peritoneal adhesion of endometrial tissue is an essential element in the pathogenesis of endometriosis according to the Sampson theory (9, 10, 18). Menstruation is almost unique to human beings and a few other primates. Only recently, menstruation and menstrual shedding has been associated with disorgainzation of the site-specific distribution of desmoplakin I/II, E-cadherin, and alpha- and beta catenins (19). Menstrual effluent is composed of blood elements, endometrial cells and extracellular fluid. Menstrual effluent does contain viable endometrial cells as shown in the classical study of Keettel and Stein in 1951 (20). Cron and Gey tried earlier to prove the viability of the cast-off menstrual endometrium in culture However, they curetted the endometrium to obtain tissue for their experiments (21). Geist suggested that desquamation of endometrium was not due to necrosis, since menstrual effluent contained viable endometrial cells, that remained alive for at least one hour (22). Ridley and Edwards demonstrated, in 1958, that endometrial cells obtained from the menstrual effluent could be implanted into the abdominal wall fascia (23). However, only in one of 8 cases they succeeded in finding endometriosis developing at the site of injection.
The prerequisites for the implantation theory are discussed in further detail in the following section.

4. PREREQUISITE PROCESSES FOR THE IMPLANTATION THEORY

4.1 Retrograde menstruation

Initially Watkins reported the occurrence of blood dripping from one or both fallopian tubes, when a laparotomy was performed during menstruation (24). Subsequently, the presence of blood in the peritoneal fluid during menstruation was visualy documented in healthy women, in women undergoing peritoneal dialysis, and in women with endometriosis (25, 26). It was also shown that tubal flushing leads to retrograde seeding of the endometrium (27). It was shown that in up to 59% of patients with and without endometriosis at various stages of the menstrual cycle the peritoneal fluid contains viable endometrial tissue (28-32). Kruitwagen and coworkers reported presence of viable endometrial cells in peritoneal fluid, most likely epithelial cells that could be cultured (30). It was suggested that the demonstration of blood in the pouch of Douglas at laparoscopy was inadequate to support retrograde menstruation, since only a weak correlation was found between blood staining of peritoneal fluid and the presence of endometrial cells (34). On the other hand, endometrial glands were reported in the peritoneal cavity after dilatation and curettage and after uterotubal irrigation (27, 28, 35, 36). Most studies demonstrated the presence of endometrial cells in peritoneal fluid, using Papanicolaou staining (31, 32, 34). This has the disadvantage that only rather large clusters of cells, resembling endometrial glandular and stromal tissue, can be used for recognition of endometrial tissue. Van der Linden and coworkers demonstrated presence of endometrial cells in peritoneal fluid using immunohistochemistry (37). They have compared the immunohistochemical staining properties of these cells to the cells present in endometrium, menstrual effluent, peritoneum and endometriotic lesions. Using epithelial markers, it was found that the staining characteristics of cells from menstrual effluent, endometrium, peritoneal fluid, and endometriotic lesions were remarkably similar. In women with patent tubes, peritoneal fluid contained single epithelial cells, rather than endometrial tissue fragments. However, these findings do not provide supporting evidence for the implantation theory. Furthermore, the anatomic distribution of endometriosis correlates very well with this theory (33). Taken together these data support the concept of retrograde menstruation.

4.2 Adhesion

If retrograde menstruation is important in the pathogenesis of endometriosis, then at some point in time, endometrial tissue, either glands or stroma, should adhere to the peritoneum. In particular, *in vivo* studies showing the initial contact between just one or a couple of endometrial

cells and the peritoneal lining are still lacking. In theory, either the glandular epithelial cells or stromal cells or both cell types are directly involved in the contact with the mesothelium of the peritoneum. Alternatively, both cell types are mutually influencing each other to allow this first contact. Another possibility could be direct contact of endometrial cells with the extracellular matrix. Both implantation of viable endometrial tissue fragments and induction of coelomic metaplasia by these fragments will require adhesion of endometrial cells to the peritoneal lining.

Members of the integrin and cadherin family of proteins are expressed in endometriotic lesions and in cells and tissues that are potentially involved in the development of endometriosis (38, 39). Integrins $alpha_2beta_1$, $alpha_3beta_1$, $alpha_4beta_1$, $alpha_5beta_1$, and $alpha_6beta_1$ and E-cadherin were demonstrated to be expressed in endometriotic lesions as well as in cells and tissues that are potentially involved in the development of endometriosis (38). Regurgitated cells obtained from peritoneal fluid also expressed cell adhesion molecules, particularly E-cadherin and some $beta_1$-integrins, but to a lesser extent from that present in the native tissue (38, 39). The expression pattern of cell adhesion molecules suggests that the loss of cell adhesion properties could be involved in the shedding of endometrial tissue during menstruation and the attachment of endometrial tissue fragments to the peritoneum. Possibly, they are first lost, only to return after establishment of the endometriotic lesion. In an *in vitro* model to investigate the adhesion between endometrial fragments and cells to an ECM covered by an intact epithelium, intact amniotic membranes were used (40). No adhesion of fragments of normal endometrium to intact epithelium was found, whereas these fragments readily adhered to amniotic membranes which were denuded of their epithelium. Peritoneum and amniotic membrane show a great similarity in structure and in morphological and immunohistochemical features (40). It was therefore suggested that an intact peritoneal mesothelium prevents adhesion between endometrial cells shed into the peritoneal cavity and the peritoneum (40). On the other hand, carcinoma cell lines did show adhesion to intact epithelium. This suggests that the adhesive behavior of endometrial carcinoma cells in the process of metastasis is different from that of normally shed endometrial fragments. Disruption of the peritoneal lining seems to be a prerequisite for adhesion of endometrial cells to the peritoneal wall. This is in accordance with the fact that endometrial tissue growing on the peritoneal surface with intact mesothelium has never been described (41). The findings of these studies support the contention that, in endometriosis, in particular in peritoneal endometriosis, a delicate equilibrium exists between attacking forces (retrograde menstruation) and protective mechanisms. On one hand, the amount and the nature of the regurgitated menstrual debris is important to the development of the disease (42). On the other hand, an intact peritoneal lining may be an important first line of defense. Additional protection is afforded by the collagenase-like activity of the peritoneal fluid and the active intra-abdominal milieu, characterized by activated macrophages (43). This milieu probably reduces endometrial tissue into single cells, that, in addition, have lost their functional cell adhesion properties. If this active peritoneal fluid is impaired in disposing of the regurgitated cells, or if the number of regurgitated cells is too large, the surviving cells can adhere to the exposed extracellular matrix in damaged peritoneal lining. How an intact mesothelium gets damaged is a matter still open for debate. The derangement of a normal immune mechanism may include the cell-mediated and humoral responses, the macrophages and cytokine network, autoantibodies, and the complement components (44). If all defense mechanisms fail, endometriosis will develop. It is postulated that minimal endometriosis is a normal condition which occurs intermittently in normal women. In contrast, endometriotic disease occurs as deeply infiltrating endometriosis, and cystic ovarian endometriosis (45).

5. PERSPECTIVE

In conclusion, the implantation theory still remains the most widely accepted concept to explain the pathogenesis of endometriosis. Under normal conditions, the peritoneal defense system is capable of coping with the reflux of menstrual debris. The question that still remains is why, only in some women, this process leads to disabling complications.

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