

Review Article

Cell origin of endometriosis: contribution by the fallopian tube epithelium

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Received October 3, 2013; Accepted November 17, 2013; Epub December 7, 2013; Published December 15, 2013

Abstract: Endometriosis is one of the most enigmatic diseases in women. Extensive research has been carried out in the past since endometriosis has a significant impact in women's life. However, the pathogenesis of endometriosis remains unclear. In this review, we briefly summarized four main theories associated with the cell origin of endometriosis including retrograde menstruation, coelomic metaplasia from ovarian or peritoneal surface, embryonic rests from Müllerian tissue, and endometrioid tissue induction by hematopoietic stem cells. In addition, we have added our recently proposed theory of tubal origin of ovarian endometriosis based on our clinicopathological observations and recent experimental results. It would be interesting to know if the tubal contribution in the genesis of ovarian endometriosis can be truly accepted in future after additional in depth studies in various clinical, pathological, and molecular levels.

Keywords: Endometriosis, ovarian endometriosis, fallopian tube

Introduction

Endometriosis is one of the most enigmatic female diseases, which is chiefly found in reproductive-aged women. Endometriosis varies in appearance from a few minimal lesions on otherwise intact pelvic organs to dense endometriotic cysts involving the ovaries and peritoneum as the most common sites. Many researchers have independently pioneered efforts to identify and study endometriosis. Pathologists as well as gynecologists have been interested in the phenomenon since its reliable description in the mid-1800s [1].

Existing theories on the cell origin of endometriosis

Endometriosis is dynamic and often progressive with periods of development, regression, and active remodeling between different types of lesions. Once the implants of endometriosis develop, a multi-step evolution of the disease takes place. Different factors contribute to this process, such as the ability to escape from the

immune system, adhesion and the growth of ectopic cells, response to steroid hormones, neovascularization and invasion. In this review, we focus on the cellular origin of endometriosis, rather than the molecular mechanisms leading to, or subsequent to, the formation of endometriosis.

Although the definitive pathogenesis of endometriosis remains unknown, several theories of pathogenesis have been proposed. These can be categorized as follows: retrograde transplantation theory, coelomic metaplasia theory, embryonic cell rests theory and induction/stem cell theory. Currently, there is no consensus concerning the cell origin of endometriosis.

Retrograde menstruation and implantation

A scientific approach to understanding the pathogenesis of endometriosis began with a private practitioner, Dr. John Albertson Sampson who is well known as the Father of Endometriosis. He coined the term "endometriosis" first in 1920s [2] although the condition

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had previously been recognized for many years. Our knowledge of the pathology and pathogenesis of endometriosis stems from his original hypothesis. Based on clinical experience, he proposed that viable endometrial cells [3] reflux through the fallopian tube during menstruation, with subsequent implantation and growth on and into peritoneum and the surrounding pelvic structures [2]. Fallopian tubes communicate freely between the peritoneal and uterine cavities. He proposed in the 1920s [2, 4] that regurgitation of menstrual debris through the oviducts was the likely source of these cells in the vast majority of patients. Since then, a large body of evidence has accumulated which strengthens this hypothesis. Laparoscopic studies show that during menstruation there is blood in the peritoneal cavity of most women supporting retrograde menstrual flow as a normal physiologic phenomenon [4]. Retrograde flow further explains the endometriotic implants in the ovaries and the uterosacral ligaments found in patients with endometriosis. Uterine hyperperistalsis and dysperistalsis have been noted in women with endometriosis and result in subsequent increased endometrial reflux [5]. Additionally, animal experiments confirm that endometriosis was induced by obstruction of antegrade menstruation, thus forcing retrograde menstruation to take place [6]. Transtubal dissemination appears to be the most common route of dissemination. Other routes of transportation and implantation include dissemination of endometrial debris through venous channels [7, 8] and lymphatics [8], and iatrogenic dissemination during abdominal or pelvic surgery [9]. These modes of dissemination provide an attractive explanation for the occurrence of endometriosis at locations far away from the pelvic organs, such as lymph nodes, or the abdominal incision. This model also supports findings of vascular metastasis of endometrial fragments [8]. In addition, research evaluating a group of patients with pelvic endometriosis showed that 42% had pelvic lymph nodes containing endometrial-like glands or stroma, or both [10].

It is widely accepted that no single theory of the pathogenesis of endometriosis can explain all cases of the disease. Sampson's theory of retrograde menstruation and implantation is believed to explain most cases of endometriosis because viable endometrial cells have been demonstrated in the menstrual effluent and,

further, endometrium can be implanted and grow within the peritoneal cavity. However, this model fails to explain the presence of endometriosis in areas outside the peritoneal cavity such as the lungs, skin, lymph node, and breasts. Nor can it explain the presence of lesions which have been described in premenarchal girls who cannot have experienced menses. Neither is the model specific as over 90% of women have some degree of retrograde menstruation [4] but only 6-10% have endometriosis [1]. However, the proposed modes of dissemination do provide a platform to justify the theories of lymphovascular metastasis, coelomic metaplasia, and differentiation or metaplasia of Müllerian embryonic rests.

Coelomic metaplasia

The first widely considered theory of endometriosis histogenesis was that of coelomic metaplasia, initially advocated by Dr. Robert Meyer at the turn of 20th century [11]. It suggests that the parietal peritoneum is a pluripotential tissue that can undergo metaplastic transformation into endometrial-like gland and stroma, changing their original character and even physiologic function under certain unspecified stimuli. Because the ovary and the progenitor of the endometrium, the Müllerian ducts, are both derived from coelomic epithelium, metaplasia may explain the development of ovarian endometriosis. In addition, the theory has been extended to include the peritoneum because of the proliferative and differentiation potential of the peritoneal mesothelium. This theory is attractive in instances of endometriosis in the absence of menstruation [12], such as in premenarche [13] and postmenopausal women [14-16], women with an absent or hypoplastic non-functioning uterus and the occasional presence of endometriosis in men [17, 18]. An in vitro model using human ovarian-surface epithelium cells reported that endometriotic lesions could arise from a process of metaplasia [19]. Although, the absence of endometriosis in other tissues derived from coelomic epithelium argues against his theory, Meyer did not intend the coelomic metaplasia theory to exclude consideration of other ideas.

Embryonic cell rests theory

Another theory speculates that embryonic cell rests could explain the presence of ectopic

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endometrium found in endometriosis. This theory assumes that the developing Müllerian duct system may leave behind small clusters or rests of Müllerian cells that have the potential to develop into functioning endometrial-like tissue, particularly in peritoneal pockets or defects at the base of the broad ligaments [20]. If the embryonic cell rest hypothesis were correct, one would anticipate finding the endometriosis immediately after menarche, when hormonal stimulation is initiated. In contrast, endometriosis has its greatest incidence in the fourth decade of life [21]. The embryonic distribution of the urogenital ridges is from the pelvis into the thoracic cavity. The distribution of ectopic endometrium would be expected to correspond to the distribution of the putative precursors, but no such type of the cell rests has been documented. On the basis of these considerations the likelihood that endometriosis has its origin in remnants of embryonic structures remains speculative.

Induction/stem cell theory

Proponents of the induction theory propose that exogenous or endogenous factors released from degenerating menstrual endometrium [22] may subsequently induce a metaplastic process in the serosal epithelium of ovaries and in the serosal cells of mesothelium, resulting in endometrial tissue [23]. For instance, in vitro studies have demonstrated the potential for ovarian surface epithelium, in response to estrogens, to undergo transformation to endometriotic lesions [19]. The induction theory is also supported by experiments performed on female rabbits [24]. In these experiments, Millipore filters containing myometrium, fat, or endometrium were implanted into the cul-de-sac, beneath the peritoneum, and subcutaneously in rabbits. Surrounding tissue was excised at varying intervals after implantation and examined histologically. Cysts lined with cells resembling endometrial epithelium and occasional gland-like structures were observed in tissues adjacent to diffusion chambers containing endometrium, but not next to those containing myometrium or fat. Endometrial glands were not apparent, however, and none of the surrounding tissue sections contained tissue resembling endometrial stroma [24]. Although many putative factors have been identified, their propensity to cause endometriosis in some women but not in others demonstrates

the still unidentified pathogenesis of this disease. Unfortunately, no direct evidence showing the formation of endometriosis stroma has been reported as a consequence of the metaplastic process of the serosal epithelium. A more recent proposal which could have validity, states that extrauterine stem/progenitor cells originating from bone marrow may differentiate into endometriotic tissue at a different anatomical site. Candidate cell lineages include bone marrow mesenchymal stem progenitors and endothelial progenitors, and this represents an active area of investigation. This hypothesis, of non-hematopoietic progenitor cells stemming from the bone marrow populating Müllerian structures is an area of active investigation [25-28].

Understanding the contribution of each of these hypotheses is difficult as there are few suitable in vivo models. The different locations, possible origins, appearances and hormonal responsiveness also make definitive conclusions elusive. To this end, it was suggested recently that peritoneal endometriosis, ovarian endometriosis and adenomyotic nodules of the retrovaginal septum are three different entities [29], each with a different pathogenesis.

The fallopian tube as a potential source of ovarian endometriosis

Physiologically, the fallopian tube has close contact with the ovary [30-34] and tubal mucosa is able to form endometrial-like tissue. For instance, endometrialization is commonly seen within the tubal lumen after tubal ligation [35-37]. Tubal epithelia shed viable cells onto ovarian surface forming endosalpingiosis or ovarian epithelial inclusions (OEI), a common finding seen within the ovary in approximately 30% of cases [30, 38]. Based on collective clinicopathological observations, we propose that ovarian endometriosis, at least partially, may be derived from the fallopian tube. This hypothesis of tubal origin of ovarian endometriosis is novel, which has not been previously proposed in the literature. The challenge in finding scientific supporting evidence that ovarian endometriosis can be derived from the fallopian tube and not only from the endometrium is in identifying unique markers which can link ovarian endometriosis and fallopian tube together in exclusion of the endometrium. Therefore, we identified a set of novel genes which are either highly expressed

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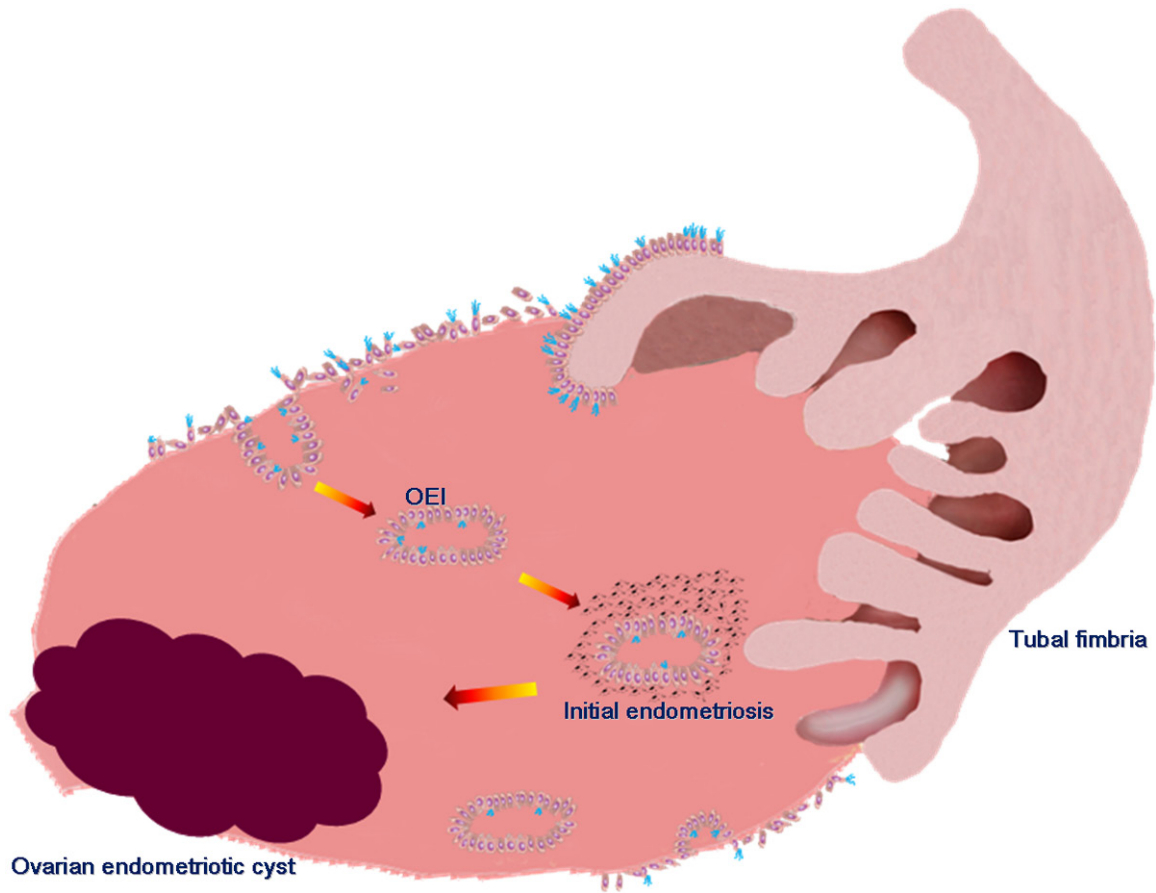


Figure 1. A schematic model of “the fallopian tube contributing to ovarian endometriosis”. When the tubal fimbriated end is in intimate contact with the ovary, some of normal tubal epithelial cells dislodge from the fimbria. They implant on the denuded surface of the ovary, resulting in the formation of an ovarian epithelial inclusion (OEI). OEIs are transformed into ovarian initial endometriosis probably by a metaplastic process via unknown factors, and then develop into an ovarian endometriotic cyst (endometrioma).

in the fallopian tube or in the endometrium through a gene differential array study. We further validated these unique genes and their corresponding protein expression in ovarian endometriosis by comparing their expression levels in the fallopian tube and the endometrium in paired patients. The findings suggest that approximately 60% of the ovarian endometriosis we studied is likely to be derived from the fallopian tube, while about 40% of the cases are more likely to be of endometrial origin (unpublished data). It is on the basis of this preliminary data, that we believe that the fallopian tube could be a source of ovarian endometriosis.

This hypothesis is thought provoking, although the mechanism remains unclear. Tubal epithelia are potentially able to form endometriosis. Endometrialization of the fallopian tube repre-

senting endometrium-like tissue within the proximal end of the tubal segment is commonly observed in patients who have undergone tubal ligation for undesired fertility. The easy detachment of normal tubal epithelia, which are usually not associated with stroma due to scanty stromal cells are present in the tubal fimbria, provides a practical route for the tubal epithelia to transfer to the ovarian surface. This common process has long been described as “endosalpingiosis” [39-41]. Epithelial inclusions found in the ovary are also called as ovarian cortical inclusions or ovarian epithelial inclusions [42, 43]. The question remains of how endosalpingiosis or ovarian epithelial inclusions are transformed into endometriosis (endometrial type cells in morphology).

One of our recent studies [30] regarding the cell origin of ovarian serous cancers has demon-

strated that ovarian epithelial inclusions are mainly derived from fallopian tube, supporting the terminology of endosalpingiosis. Additionally, the transformation from endosalpingiosis or ovarian epithelial inclusions can be explained by metaplasia, a process commonly seen in Müllerian system [44]. This interpretation is supported by our previous observation of ovarian initial endometriosis (IE) [45]. IE represents the earliest morphologic changes of ovarian endometriosis. The most characteristic morphologic features of IE include part of the endosalpingiosis glands with endometriotic stromal cells as well as prominent vascularization in the stroma, while the remaining part of the endosalpingiosis glands have normal looking spindle shaped ovarian stroma without appreciable vessels. The endometriotic stromal cells can be confirmed by CD10 immunohistochemical staining [45]. This phenomenon cannot be explained by the retrograde menstruation theory, whereas metaplasia via unidentified factors is likely applicable in this situation. Above all, the fallopian tube remains a likely contributor to the formation of ovarian endometriosis. A schematic model of our hypothesis is shown in **Figure 1**.

Perspective

Endometriosis is a multi-factorial disease with multifaceted features. The underlying mechanisms that lead to the development and maintenance of endometriosis are still an enigma. No single theory, at present, can fully explain the pathogenesis of endometriosis; each theory must be taken as complementary to one another. Our research is investigating new mechanisms and pathways which may contribute to the genesis of this mysterious and troublesome disease.

Acknowledgements

The work is supported in part by Better Than Ever Fund, NCI NIH P30 CA23074 from Arizona Cancer Center and Department of Pathology, University of Arizona Startup fund to WZ.

Disclosure of conflict of interest

None.

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