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Endometriosis: New concepts in the pathogenesis

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ABSTRACT

Endometriosis is a gynaecological disease defined by the histological presence of endometrial glands and stroma outside the uterine cavity. Though there are several theories, research scientists remain unsure as to the definitive cause(s) of endometriosis. Considering the relevant health problems caused by endometriosis, all new information on the pathogenesis of this disease, may have important clinical implications. Goal of this article is to summarize the latest advances in the pathogenesis of endometriosis, with particular emphasis on the embryological theory, that has been recently re-proposed. The possible clinical implications of these findings will be discussed.

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1. Introduction

Endometriosis is classically defined as the growth of endometrial glands and stroma at extra-uterine sites, most commonly implanted over visceral and peritoneal surfaces within the female pelvis (Baldi et al., 2008; Giudice and Kao, 2004; Bulun, 2009). It is a prevalent gynaecological disorder that may be present in 10% of women of reproductive age. Deep infiltrating endometriosis is a particular form of endometriosis associated with pelvic pain symptoms, located under the peritoneal surface (Signorile et al., 2009a). Endometriosis is often accompanied by chronic pelvic pain, adhesion formation and infertility, and is responsible for more than 100,000 hysterectomies each year in the United States alone, with the annual health care costs attributable to this disease of over 1 billion dollars for the year 2002 (Missmer, 2009). Therefore, endometriosis could be considered a “social disease”, since it affects quality of life and reproducibility, causing not only costs for its diagnosis and treatment, but also for its socio-economic impact, such as the loss of economic performance of the patients. Moreover, the available treatments are surgery and/or medical therapies, but these are invasive or only symptomatic with the consequence that often such therapeutic strategies are associated with recurrence and unwanted side-effects.

2. Pathogenesis

2.1. The “classic” theories

Though endometriosis has been described for the first time in 1690 (Shroen, 1690) by the German physician, Daniel Shroen, researchers remain still unsure as to the definitive cause of this disease. Many theories have been proposed to explain the development and establishment of endometriosis. The most widely accepted theory for the pathogenesis of endometriosis, proposed in the 1920s by Sampson, is the retrograde menstruation/transplantation, that claims the adhesion and growth of endometrial fragments deposited into the peritoneal cavity via retrograde menstruation (Sampson, 1927). Endometriosis, would, therefore, represent simply an auto-transplant, in which normal endometrial tissue is transplanted to an ectopic location in the organism. However, this theory fails to explain the presence of endometriosis in such remote areas outside the peritoneal cavity, as the lungs, skin, lymph nodes, breasts (Bulun, 2009). Moreover, the presence of the disease in early puberty and exceptionally also in newborns (Ebert et al., 2009; Marsh and Laufer, 2005; Diez Garcia et al., 1996), as well as in women affected by the Mayer–Rokitansky–Küster–Hauser, a syndrome characterized by congenital aplasia of the uterus and the upper part of the vagina (Balci et al., 2008), and in male (Bulun, 2009) further contrasts the validity of the theory. Nevertheless, elegant observations by Redwine suggest that endometriotic tissue lacks characteristics of an auto-transplant (Redwine, 2002).

The coelomic metaplasia theory claims that formation of endometriomas in the ovary or recto-vaginal endometriosis is
caused by metaplasia of the coelomic epithelium, perhaps induced by environmental factors (Nisolle and Donnez, 1997). This theory would explain why most women have some degree of retrograde menstruation but only a little percentage have endometriosis, and the presence of the disease in absence of menses.

The theory of endometrial stem cells or transient amplifying progenitor cells claims that circulating stem cells originating from bone marrow or from basal layer of endometrium could differentiate into endometriotic tissue at different anatomical sites (Bulun, 2007). As a matter of fact, proving or disproving all these hypotheses is difficult, since there are no or few suitable in vitro or in vivo models.

2.2. A “new but old” theory

Interestingly enough, a different theory, formulated by pioneer scientists of this disease in the late 19th and 20th century, postulates that endometriosis is caused by small defects of organogenesis (Knapp, 1999; Benagiano and Brosens, 2006). Table 1 summarizes the most important observations supporting the embryological theory in chronological order, as clearly described by the work of Benagiano and Brosens (2006). Recently, our research group has demonstrated the presence of ectopic endometrium in a significant number of human female foetuses (4 in 36 cases) analyzed by autopsy (Signorile et al., 2009b). These structures were misallocated outside the uterine cavity and could not be ascribed to any normal anatomical formation. In particular, the locations of these endometrial structures were: in the recto-vaginal septum, in the proximity of the Douglas pouch, in the mesenchymal tissue close to the posterior wall of the uterus, in the rectal tube at the level of muscularis propria, and in the wall of the uterus. To note, these anatomical sites are common location for endometriosis in women (Baldi et al., 2008). In a successive work, we have analyzed at autopsy an additional series of 13 human female foetuses and we have described a case of foetal endometriosis in women (Baldi et al., 2008). In a successive work, we have analyzed at autopsy an additional series of 13 human female foetuses and we have described a case of foetal endometriosis in the wall of the uterus (Signorile et al., in press-a). The immunohistochemical characteristics of these organoid lesions have been analyzed: the glands expresses CA125, Cytokeratin 7 and oestrogen receptor in the epithelial component, while the stromal cells expressed both CD10 and the oestrogen receptor. Interestingly, the identical expression pattern for the molecular markers analyzed, was detected for the endometrium inside the uterine cavity of the foetus. Based on these observations, we have suggested that these structures must be ascribed to endometrial tissue, misplaced outside the uterine cavity during the earlier steps of organogenesis and displaying identical molecular phenotype to the endometrium present in the uterus. These observations have been the first direct and systematic demonstration of the theory of developmentally misplaced endometrial tissue as the cause of endometriosis. The exact anatomical distributions and the histological appearances of all the endometriosis-like structures found in the foetuses in these two works, are depicted in detail in Fig. 1.

Interestingly enough, the existence of choristoma composed of müllerian remains in adult has been codified and named müllerianosis, even if this phenomenon has been interpreted, but not demonstrated, as different from endometriosis (Batt et al., 2007). We speculate that this ectopic endometrium would remain quiescent and asymptomatic until puberty, when the hormonal inputs, like it happens to the normal endometrium, would cause its re-growth and, consequently, the onset of the symptoms of endometriosis.

Our data, indeed, sustain the embryological origin for endometriosis (Redwine, 1987), suggesting alterations in the fine
tuning of female genital structures organogenesis. The exact molecular mechanisms underlying this phenomenon must be elucidated. The proper function of the normal human endometrium relies on well-organized cell–cell interactions regulated locally by cytokines and growth factors under the direction of steroid hormones. The onset and progression of the disease processes of endometriosis may result from disruptions of this well-balanced cellular equilibrium, dominated by genetics and or epigenetics factors, that would cause the interruption of some organizational events associated with development of the neonatal uterine wall. This is also supported by the increment of incidence of the endometriosis in patients affected by uterine malformations (Baldi et al., 2008; Giudice and Kao, 2004; Bulun, 2009). It is possible that still unidentified internal or external accidents may affect the embryology of the uterus during highly sensitive windows of time (Selevan et al., 2000).

3. Conclusions

In conclusion, it is possible to claim that endometriosis is a multi-factorial disease with multifaceted features; therefore, all the theories on its pathogenesis must be taken complementary to one another and by no way are mutually exclusive. Nevertheless, when compared to the retrograde menstruation theory, the defects in embryogenesis theory is considered to have much minor importance in explaining this disease. The recent findings reviewed in this article seem to contrast this opinion. The demonstration of the presence of ectopic endometrium in the female foetus in same anatomical locations found in the adult patients affected by endometriosis and with a frequency very similar, makes the embryogenetic theory on endometriosis the only one scientifically proved and suggests that this pathogenetic mechanism is prevalent in the genesis of this disease. The clinical and therapeutic implications are straightforward. Endometriosis could still be regarded as a recurrent disease, nevertheless recurrence could not be ascribed to the retrograde menstruation, but to an incomplete surgical intervention, since it is demonstrated that endometriosis lesions could be also made up of microscopic foci. Therefore surgery, if complete can be considered curative. However, it must be underlined the fact that other pathogenetic mechanisms for the genesis of endometriosis cannot be completely ruled out by these observation, even if, to date, there are no direct evidence of their validity. Our research group is intensively working in order to clarify the real impact of embryological defects on the insurgence of endometriosis in adult life and to clarify the molecular mechanisms responsible of this phenomenon. In a very recent work, indeed, we have described an endometriosis-like phenotype in mice exposed in utero to the endocrine disruptor bisphenol (Signorile et al., in press-b). Such studies could shed new light on the pathogenesis of this disease and, possibly, suggest suitable therapeutic targets.

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