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Review

Endometriosis research: animal models for the study of a complex disease

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ABSTRACT

Endometriosis is a common gynaecological disease that is characterized and defined as the presence of endometrial tissue outside the uterus, causing painful periods and subfertility in approximately 10% of women. After more than 50 years of research, little is known about the mechanisms underlying the development and establishment of this condition. Animal models allow us to study the temporal sequence of events involved in disease establishment and progression. Also, because this disease occurs spontaneously only in humans and non-human primates and there are practical problems associated with studying the disease, animal models have been developed for the evaluation of endometriosis. This review describes the animal models for endometriosis that have been used to date, highlighting their importance for the investigation of disease mechanisms that would otherwise be more difficult to elucidate, and proposing new alternatives aimed at overcoming some of these limitations.

1. Introduction

Endometriosis is an estrogen-dependent disease characterized by the growth and survival of endometrial tissue at ectopic sites, leading to the development of lesions of different sizes and appearance containing endometrial glands and stroma. This condition may present as asymptomatic or associated with pelvic pain and/or infertility. Endometriosis constitutes probably the most frequent gynaecological disorder, affecting an estimated 10% of women in the reproductive age group (Eskenazi and Warner, 1997).

Even though endometriosis was first ackowledged more than 100 years ago, the pathogenic mechanisms underlying the development and maintenance of this condition remain far from being understood. A well supported and widely accepted mechanism involved in the pathogenesis of endometriosis is proposed by Sampson (1927), in which endometriotic lesions result from the attachment and growth of endometrial fragments deposited in the peritoneal cavity via retrograde menstruation. However, since such reflux of menstrual tissue occurs in almost all women of reproductive age (Halme et al., 1984), additional dysregulations must contribute to the establishment and survival of ectopic endometrium. Our lack of understanding of the pathophysiology of endometriosis arises mainly from the fact that women are rarely diagnosed in the early stages of the disease. Besides, ethical issues hinder the design of controlled experiments in large populations to assess cause and effect relationships. For example, endometriosis patients should ideally be compared with women with a normal pelvis (negative controls) and with patients suffering from other disorders that result in a sim-

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ilar symptomatology (positive controls). This would allow confirmation of the disorder (by comparing with negative controls), and also would help to define specific markers for endometriosis compared with other disorders (positive controls) associated with similar symptoms.

The above-mentioned limitations have prompted the design of different strategies to induce endometriosis-like lesions in laboratory animals, with the aim of establishing validated research models to allow the identification and elucidation of the mechanisms by which refluxed endometrial cells adhere, invade and persist at ectopic sites. Although none of the currently available animal models succeeds completely in mimicking all aspects of human disease, they have proven valuable tools for the design of controlled studies with the ultimate goal of developing better methods for early diagnosis as well as potential therapeutical interventions. The most commonly used models for endometriosis research have been established using either non-human primates or different inbred mouse strains. Some of these models will be introduced in the present review article, focusing on the discussion of their strengths and limitations as well as their relevance to the different scientific questions posed by this complex disease.

2. Primate models

According to Sampson's hypothesis, endometriotic lesions arise from endometrial cells refluxed through the fallopian tubes during menstruation. Therefore, the spontaneous development of endometriosis will only occur in species that undergo a menstrual cycle. The establishment of lesions resembling their human counterparts both in terms of morphology and location has been documented in several species of non-human primates (reviewed in Story and Kennedy, 2004) and has been suggested to result from increased exposure to retrograde menstruation due to controlled mating in captivity (D'Hooghe et al., 1996a). These studies on non-human primate species that spontaneously develop endometriosis have shed light into the natural progression of this condition. In baboons for instance, endometriosis has been characterized as a dynamic process undergoing phases of development, regression and remodeling (D'Hooghe et al., 1996b). Furthermore, through the analysis of autopsy records from a colony of rhesus monkeys, it was possible to identify elevated estradiol levels and genetic predisposition as significant risk factors for the development of endometriosis (Hadfield et al., 1997; Zondervan et al., 2004). For instance, over-expression of some oncogenes like c-myc, c-erbB-1 and c-erbB-2, or some apoptotic genes like bcl-2 (which is increased in the endometrial phase) have been associated with this condition (Bischoff and Simpsom, 2002).

Though spontaneous endometriosis in non-human primates probably constitutes the most suitable model to study the pathophysiology of this disease, its low incidence and slow progression have encouraged development of several methods to artificially induce the formation of lesions in these animals (reviewed in D'Hooghe and Debrock, 2002; Story and Kennedy, 2004). Pioneer studies date from 1950 when, in an attempt to simulate

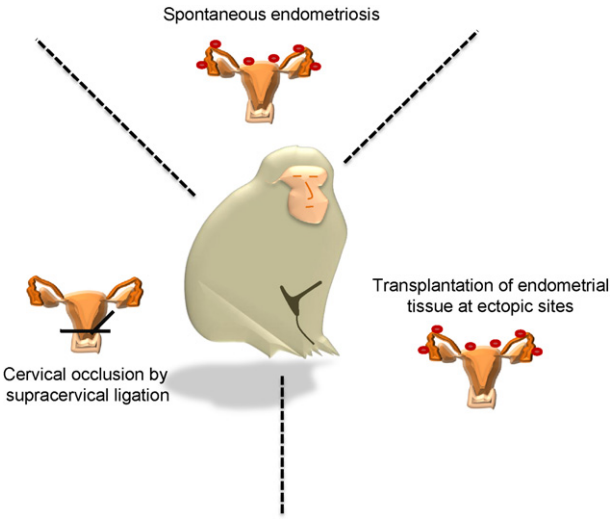

Fig. 1. Diagram illustrating the different non-human primate models for studying endometriosis.

retrograde menstruation, the cervix of female rhesus monkeys was surgically repositioned resulting in an increased reflux of menstrual tissue into the abdomen and development of endometriotic lesions (Te Linde and Scott, 1950). Subsequent experimental approaches included the use of different methods to occlude the uterine cervix (D'Hooghe et al., 1994) or the transplantation of homologous endometrial tissue at ectopic sites within the peritoneal cavity (Yang et al., 2000; Fazleabas et al., 2002). In baboons, intraperitoneal inoculation of endometrium results in lesions that develop similarly to those observed in the spontaneous disease (D'Hooghe et al., 1995a). Interestingly, menstrual endometrium (either surgically removed or collected using a pipelle) has proven to be more efficient for the induction of lesions than luteal phase tissue (Fig. 1).

Whether in the context of spontaneous or induced disease, non-human primate models are well-suited for the study of pathological mechanisms. As an example, the relationship between the immune system and the establishment and progression of endometriosis has been the focus of numerous studies based on these models. The immunological status of the animal seems to have a strong influence on disease progression, as demonstrated by studies in the baboon showing an increase in the number and size of spontaneously developed lesions upon treatment with immunosuppressants (i.e., methylprednisolone or azathioprine) (D'Hooghe et al., 1995b). However, a causal link seems to be precluded because baboons with a previously-documented normal pelvis did not develop endometriotic lesions as a result of the treatment.

Likewise, studies on non-human primates have improved our understanding of the link between endometriosis and increased peritoneal inflammation. Elevated local levels of inflammatory cytokines as well as cellular mediators (i.e., leukocytes and macrophages) are a hallmark of women with endometriosis (Kyama et al., 2003), but the study of cause–effect relationships in these patients is hindered by ethical considerations. In baboons,

experimental induction of endometriosis is associated with a transient intrapelvic inflammation (increased peritoneal fluid volume and local concentration of leukocytes and inflammatory cytokines) (D'Hooghe et al., 2001), which is no longer observable after 2–3 months from the induction. Additionally, the percentage of peripheral blood $CD4^+$ and interleukin 2 receptor $(CD25)^+$ cells has been shown to be increased in animals with long-term endometriosis (both spontaneous and induced) when compared to those with recent spontaneous endometriosis or a normal pelvis (D'Hooghe et al., 1996c). Thus, current evidence in non-human primates suggests that rather than being a cause, peritoneal inflammation appears as a consequence of the disease, which probably results from an exacerbated immune response to ectopic endometrial debris.

Primates also offer a relevant preclinical model to test drugs for the prevention or treatment of endometriosis in the context of a reproductive anatomy, endocrinology and physiology that are most similar to humans. Artificially-induced disease allows the evaluation of strategies aimed at preventing the attachment of endometrial tissue at ectopic sites. In this approach, the putative preventive drug is applied either systemically or locally (i.e., by incubating the endometrium used for injection) at or before the time of induction, and its efficiency is subsequently evaluated by monitoring the extent of induced endometriosis in treated animals compared to the appropriate negative controls (D'Hooghe et al., 2006). As an example; tumor necrosis factor alpha (TNFα) inhibition in baboons has a proven preventive effect similar to GnRH antagonists (Kyama et al., 2008), which is associated with decreased expression of transforming growth factor beta (TGFβ) in endometriotic lesions.

Studies to assess therapeutical effects can alternatively be performed in animals that have already established endometriosis (either spontaneous or induced). This strategy allows the performance of both paired (before and after treatment) and unpaired (treatment vs. positive and negative controls) comparisons. Using this approach, treatment with antiprogestins (i.e., RU486) and/or GnRH analogues was shown to decrease implant size in animals with induced disease (Grow et al., 1996). Interestingly, RU486 treatment – either alone or in combination with GnRH analogues – was associated with maintenance of estradiol secretion, suggesting that long-term therapeutic interventions that avoid the undesirable effects of hypoestrogenism are possible. More recently, the same approach has been applied in baboons to show that both neutralization of TNFα activity (Falconer et al., 2006) and selective immunomodulation with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (Lebovic et al., 2007), can be successful in the treatment of induced endometriosis.

The above-described features arguably make non-human primate models the most suitable for the study of endometriosis. However, these models pose the limitations of being ethically sensitive and high cost associated with their development and maintenance. Moreover, although the genomes of humans and primates are very close, small differences can influence the immune response and clinical manifestation of diverse diseases (Van Duyne et al., 2009). As a consequence, non-human primates often do not completely reproduce the pathophysiology of human diseases (Legrand et al., 2009).

3. Murine models

Animal models based on laboratory mice have been widely used for endometriosis research. Among other reasons, this is due to their low cost, the possibility of introducing endometrial tissue into recipients and performing different analyses in genetically similar animals, to study the endometrial lesions at different intervals of time and acquire knowledge about the effect of different drugs or treatments (Becker et al., 2006). However, despite being the most frequently applied models to study this disease, they also present several limitations. One of the major physiological differences between mice and humans is that mice lack menstruation and consequently do not develop spontaneous endometriosis. As a result, endometriotic lesions in murine models have to be induced surgically (Hirata et al., 2005) or by peritoneal injection of endometrial tissue (Somigliana et al., 1999; Fainaru et al., 2008). According to the origin of the tissue used for induction, murine models of endometriosis are classified in two types: homologous and heterologous models (Fig. 2).

3.1. Homologous models

Homologous models are based on the surgical transplantation of endometrial fragments from syngeneic animals in immunocompetent recipients. Such models have been successfully established in different rodent species commonly used for research including mice (Cummings and Metcalf, 1995), rats (Golan et al., 1984; Sharpe et al., 1991) and hamsters (Steinleitner et al., 1991). Most of these models are based on surgical implantation of endometrial tissue at different sites within the peritoneal cavity of recipient animals, resulting in lesion occurrence in the intestine, mesentery (Cummings and Metcalf, 1995) or abdominal wall (Becker et al., 2006). Other homologous models, like the one by Somigliana et al. (1999), induce the endometriotic lesions directly by intraperitoneal injection of endometrial fragments or cell suspensions. Recipient mice develop lesions on the peritoneum, perivesical adipose tissue and the intestinal or uterine surface (Hirata et al., 2005).

In these models, donor and recipient animals are ovariectomized and receive exogenous oestrogen treatment (100 μg/kg i.m.) in order to abrogate variation in the oestrous cycle. Oestrogen treatment additionally facilitates the growth and proliferation of the endometrial cells in donor mice, allowing endometrial tissue suitable for performing endometriosis induction to be obtained. However, oestrogen supplementation in the recipients is likely to influence the development and progression of endometriosis, since oestrogen is known to be involved in the pathophysiology of the disease. Despite this limitation, homologous models can still serve the study of steroid hormone effects on the ectopic lesions (Vernon and Wilson, 1985; Rossi et al., 2000). Because in these models autotransplanted uterine tissue is steroid hormone-responsive,

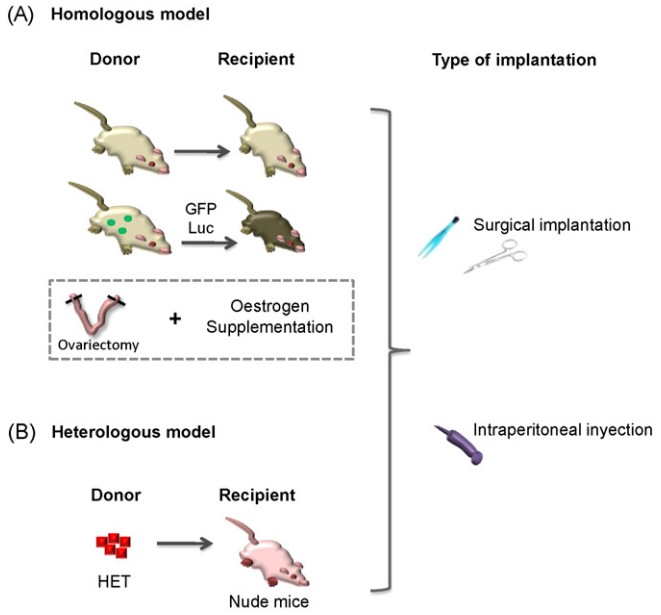

Fig. 2. Diagram illustrating the different murine models for studying endometriosis. (A) Summary of the homologous-murine models showing the non- and fluorescence models. GFP, green fluorescence protein; Luc, luciferasa. (B) Heterologous murine model. HET, human endometrial tissue.

it is possible to study hormone effects on the induced ectopic lesions in a situation resembling the hormone-dependence of human ectopic endometrial tissue.

One of the main problems found in mouse models is that endometrial lesions tend to be small and embedded in the murine tissue and are therefore difficult to identify. This has fostered the design of "fluorescent murine models", in which endometrial lesions can be more easily identified through the use of transgenic donor mouse strains expressing the green fluorescent protein (GFP; Hirata et al., 2005) or luciferase (Becker et al., 2006). The first of such studies assessed lesion establishment, location and size; and found that the fluorescence in estrogen-supplemented recipients was significantly higher compared to control mice, concomitant with the oestrogen-dependence of endometrial lesions. In the second model, introduced by Becker et al. (2006), donor mice are bioluminiscent due to expression of a luciferase transgene. In general, "fluorescent models" offer the advantage of monitoring endometrial ectopic lesion growth without having to sacrifice the recipient animals. In the first study, endometrial fragments are visualized 2 weeks after injection by illuminating the peritoneal cavity with a GFP-lighting system, allowing the acquisition of representative images for computer-based quantitative analysis. In the second study, Becker et al. (2006) imaged the mice and quantified bioluminescence of each luminescent lesion surgically induced.

3.2. Heterologous models

Heterologous murine models are based on the xenotransplantation of endometrial human tissue into immunodeficient mice by inoculation into the peritoneal cavity (Somigliana et al., 1999), by minilaparotomy (Nisolle et al., 2000) or subcutaneous administration (Zamah et al., 1984). It is known that some of the causes of endometriosis rely on the eutopic endometrial tissue itself and the design of heterologous models is meant to compensate for the numerous physiological differences between mouse endometrium and its human counterpart. Human endometrial tissue for these models can be obtained from the menstrual fluid, by biopsies taken at any time of the menstrual cycle (Story and Kennedy, 2004) and even from ovarian endometriomas (Zamah et al., 1984).

As an example, Nisolle et al. (2000) studied the progression of human menstrual endometrium transplantated into the peritoneal cavity at different periods of time, and reported a greater proliferative activity in glandular cells together with higher vascular endothelial growth factor (VEGF) expression, suggesting that the stromal cells are involved in the attachment process and glandular cells in lesion growth. In a similar approach, Wang et al. (2005) isolated human endometrial tissue from late secretory phase and transplanted it by laparotomy into nude mice and showed evidence of fusion between ectopic endometrium and murine tissue, followed by the establishment of a robust blood supply. More recently, the establishment and growth of heterologous endometrial tissue in immune deficient mice could be assessed for prolonged periods in a non-invasive, real-time, quantitative manner by using CBR-luciferase-transformed human endometrial cells, in a manner resembling the fluorescent homologous models (Masuda et al., 2007).

Like homologous models, heterologous models present both advantages and disadvantages. On the one hand, they are cheap and also they often show a reduced immunological response. This is due to a markedly reduced NK activity together with decreased numbers of functional T and B cells (Shultz et al., 2005), which diminishes the risk of graft vs. host disease and allows the preservation of implanted

human tissue (Awwad et al., 1999; Grümmer et al., 2001). On the other hand, these features make the mice more susceptible to murine pathogens, thereby reducing their life span. Additionally the mice are unable to replicate the immune changes which occur at the endometriosis implantation site in humans (Awwad et al., 1999; Bruner-Tran et al., 2002).

One of the major flaws of heterologous models is the fact that the transplanted human tissue has a limited lifespan, with human endometrium inoculated in nude mice being unable to persist beyond 4 weeks (Grümmer et al., 2001). However, their main potential resides in the use of human endometrium, which allows the performance of therapeutic studies to test different types of drugs with potential application in subsequent clinical trials. Additional benefits of the mouse–human system are that host and donor genes can be differentiated and studied independently. For instance, the use of species-restricted monoclonal antibodies allows the differentiation of molecules of donor and recipient origin that may contribute to disease mechanisms. More recently, advances on gene array technologies has allowed the study of transcripts in human (Borthwick et al., 2003) and mouse endometrium (Umezawa et al., 2009), leading to the identification of highly expressed endometrial genes that can be used as tissue-specific markers for this condition.

4. A homologous mouse model to study the progesterone resistance of ectopic endometrial tissue

One of the most common treatments to remove endometrial lesions is surgery. However, it often does not provide a definitive treatment, with 47% of the lesions appearing again (Evers et al., 1991). The treatment of endometriosis should be directed not only towards the removal of endometriotic tissue but also to prevention of recurrence, and several of the above-described models have proven valuable tools for the assessment of therapeutic strategies. (Somigliana et al., 1999; Hirata et al., 2005; Wang et al., 2005; Becker et al., 2006).

It has been reported that compared to eutopic endometrium, ectopic endometrial tissue shows a distinct progesterone resistance due to low expression of progesterone receptor-B (PR-B) (Attia et al., 2000). This leads to a defective expression of 17β-hydroxysteroid dehydrogenase-2 (17-β-HSD-2) which results in high levels of estradiol (E2)-induced endometrial cell proliferation. In turn, the estrogen receptor (ER)-β acts as a suppressor of ERα, the ER isoform that stimulates PR expression levels, in both endometrial and endometriotic stromal cells (Trukhacheva et al., 2009). It is also known that progesterone induces prolactin mRNA expression in endometriotic cells and that expression levels are lower compared with eutopic endometrial cells (Bulun et al., 2006). These findings, together with the impaired response often observed in endometriosis patients subjected to progestin treatment protocols (Winkel and Scialli, 2001), support the notion that endometriosis can be thought of as a progesterone-resistance disease.

The majority of murine models can provide insights on the aetiology and factors associated with endometriosis, but show limitations for the establishment of a therapeutic model aimed at preventing endometriosis. We are therefore interested in establishing a homologous model to investigate therapeutic interventions using PR-ablated mice, which would mimic the progesterone resistance observed in this disease. In consequence, due to low levels of 17β-hydroxysteroid dehydrogenase-2 (17-β-HSD-2), estradiol (E2) is not metabolized into estrogen (E1), thus E2-induced endometrial proliferation remains high.

The homologous-murine model will be developed based on the method described by Somigliana (Somigliana et al., 1999), using fragments of endometrial tissue harvested from donor mice differing in PR genotype (i.e. PR−/− mice and their wild type counterparts). This mouse model succeeds in reproducing important aspects of the disease, such as the low expression of PR in the ectopic human endometrium. This provides an appropriate basis to test novel and less-invasive therapies targeting well-established hallmarks of the disease, including its hormone-dependence, evasion of immune surveillance, and neo-vascularization of ectopic endometrium. These studies potentially constitute a crucial prerequisite for the development and optimization of therapeutical protocols in endometriosis patients. However, it is important to note that a remaining limitation of this model is that it does not fully represent the aetiology of the disease because it is not based on human endometrium. Thus, we can study different molecules or mechanisms that participate in this disease, but the potential for testing pharmacological and hormonal modulation of human endometriosis tissue is still limited.

5. Concluding remarks

It is known that 10% of gestational-age women suffer from endometriosis. Animal models, both murine and non-human primate, are largely used to study this disease. Murine models are the most frequently used because of their low cost and wide range of possible treatments, allowing the study of endometrial differentiation, physiology and pathophysiology. Despite this, it is important to recognise that murine models are limited in reproducing several aspects of this condition by the absence of spontaneous disease, the possibility of graft vs. host disease, and the differences between rodent and human physiology. Therefore mouse models do not reflect “real” endometriosis. This is one of the main disadvantages to overcome in endometriosis research.

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