

Endometriosis: where are we and where are we going?

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Abstract

Endometriosis currently affects ~5.5 million reproductive-aged women in the U.S. with symptoms such as painful periods (dysmenorrhea), chronic pelvic pain, pain with intercourse (dyspareunia), and infertility. It is defined as the presence of endometrial tissue outside the uterine cavity and is found predominately attached to sites within the peritoneal cavity. Diagnosis for endometriosis is solely made through surgery as no consistent biomarkers for disease diagnosis exist. There is no cure for endometriosis and treatments only target symptoms and not the underlying mechanism(s) of disease. The nature of individual predisposing factors or inherent defects in the endometrium, immune system, and/or peritoneal cavity of women with endometriosis remains unclear. The literature over the last 5 years (2010–2015) has advanced our critical knowledge related to hormones, hormone receptors, immune dysregulation, hormonal treatments, and the transformation of endometriosis to ovarian cancer. In this review, we cover the aforementioned topics with the goal of providing the reader an overview and related references for further study to highlight the progress made in endometriosis research, while concluding with critical areas of endometriosis research that are urgently needed.

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Introduction

Endometriosis is an estrogen-dependent gynecological condition characterized by the presence and growth of ectopic endometrial tissue, often associated with inflammation, severe and chronic pain, and infertility (Hickey *et al.* 2014). Lesions identified during laparoscopy are categorized as superficial peritoneal lesions, endometriomas, or deep infiltrating nodules, with high degree of individual variability in lesion color, size, and morphology. Histopathological analysis requires the presence of at least two features for a diagnosis of endometriosis, the features being endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-filled macrophages (Hsu *et al.* 2010). Retrograde menstruation, in which uterine epithelial and stromal cells are disseminated and implanted into the peritoneal cavity via the fallopian tubes, is the most accepted mechanism for the pathogenesis of endometriosis (Sampson 1927b, Ahn *et al.* 2015a). More than 90% of women undergo retrograde menstruation; however, the prevalence of endometriosis in the general population is 6–10% (Sampson 1927a, Syrop & Halme 1987). Such a discrepancy between these two values suggests that women who develop endometriosis are likely to have other genetic, biochemical, and

pathophysiological factors contributing to development of the disease (Ahn *et al.* 2015a).

The goal of this review is to provide a broad overview of the advancements in endometriosis research over the last 5 years (2010–2015). First, we delve into animal models often used in endometriosis research. After which, we cover critical areas of endometriosis study, including basic and clinical research, and the transformation of endometriosis into ovarian cancer. Within basic research, we focus on angiogenesis, cytokine/chemokine expression, and hormones and their receptors, and the significance they may play in the pathogenesis of endometriosis. This review is a synopsis of important findings for researchers to quickly find relevant sources of interest to his/her studies.

Animal research models

The use of animal models in the study of endometriosis allows for the control of numerous variables related to pathogenesis and disease progression, including angiogenesis, inflammation, and hormonal response. Nonhuman primate and rodent models are the most common animal models used, while the chicken chorioallantoic membrane model has limited use.

Nonhuman primate models

Nonhuman primates (baboons and rhesus macaques) are often used to study pathogenesis, progression, and treatment of endometriosis. While primates can spontaneously develop endometriosis at a low prevalence (D'hooghe *et al.* 1996, Zondervan *et al.* 2004, King *et al.* 2016), techniques have been developed to increase disease incidence. Cervical occlusion to promote retrograde menstruation (Scott *et al.* 1953, D'Hooghe *et al.* 1994) and a homologous model, in which endometrial tissue is excised from a donor primate and surgically transplanted or injected into a recipient primate, are used (Te Linde & Scott 1950, D'Hooghe *et al.* 1995, Sillem *et al.* 1996). Primate models, including advantages and disadvantages, have been described previously (Tirado-Gonzalez *et al.* 2010, Grummer 2012, King *et al.* 2016).

Rodent models

Rodents are often used in endometriosis research due to quick generation time, ability for genetic manipulation, and relatively low cost, especially in comparison to nonhuman primate models. Rodent models of endometriosis are divided into two main groups: heterologous or homologous/autologous models. Heterologous models use human tissue transplanted into immunocompromised mice, while homologous models involve transferring endometrial tissue from one animal to a syngeneic animal (Tirado-Gonzalez *et al.* 2010, King *et al.* 2016).

Heterologous models involve the transfer of human endometrial tissue into an immunocompromised rodent, such as athymic nude, severe combined immunodeficient (SCID), or *Rag2 γ (c)* mice, to prevent the rodent immune system from attacking the foreign tissue (Zamah *et al.* 1984, Aoki *et al.* 1994, Greenberg & Slayden 2004). Once human tissue is collected, it is disseminated via intraperitoneal or subcutaneous injection into the immunocompromised rodent. Heterologous rodent models with associated advantages and disadvantages have been described (Tirado-Gonzalez *et al.* 2010, Bruner-Tran *et al.* 2012, Grummer 2012, King *et al.* 2016).

Several homologous rodent models are utilized in endometriosis research, and the generation of these models involves several important considerations regarding the reproductive status of the donor and recipient, transplantation method, and potential genetic manipulation (King *et al.* 2016). Often, the recipient rodents are ovariectomized and treated with estrogens to promote lesion growth (Cummings & Metcalf 1995, Somigliana *et al.* 1999, Styer *et al.* 2008, Burns *et al.* 2012). Critically valuable for the study of endometriosis is that the homologous model maintains an intact immune system. A large difference between homologous models is the method of transplantation

and tissue dissemination. Various models exist for the development of ectopic lesions, including: (1) suturing uterine tissue into the peritoneal wall or intestinal mesentery; (2) injecting minced uterine tissue intraperitoneally to disperse freely and attach at sites within the peritoneal cavity; (3) using entire uterine tissue or endometrial tissue; and (4) using minced "menstruated" tissue for intraperitoneal injection (Vernon & Wilson 1985, Somigliana *et al.* 1999, Burns *et al.* 2012, Greaves *et al.* 2014). For models used to study endometriosis, it is critically important to remember the definition of and requirements for an endometriotic lesion. Discouragingly, some models inherently do not fulfill these criteria and are suboptimal for the study of endometriosis, ultimately occluding comprehensive comparison and interpretation of data in the scientific literature.

Chicken chorioallantoic membrane model

The chicken chorioallantoic membrane (CAM) assay is used to study molecular processes involved in adhesion, invasion, and angiogenesis of developing endometriotic lesions. This assay involves culturing human endometrial tissue on the CAM of fertilized chicken embryos (Maas *et al.* 2001). The CAM has a dense microvasculature, useful for examining angiogenesis and for experimentation with anti-angiogenic agents (Nap *et al.* 2005). This method has been used to study the impact of matrix metalloproteinase (MMP) expression and activity on adhesion and invasion (Nap *et al.* 2004, Juhasz-Boss *et al.* 2010). However, it is not suited for studying immunological or inflammatory aspects of lesion development or for potential effects of systemic treatments.

Pathogenesis and progression of endometriosis

Animal models and human samples are paramount in the study of pathogenesis and progression of endometriosis. They allow for in-depth analysis of factors involved in this disease, including inflammation, angiogenesis, cytokine/chemokine expression, and endocrine alterations such as steroid and steroid receptor expression. These components also form a complex, interacting system greatly impacting the development of endometriosis. While we understand that several other factors are involved in the pathogenesis and progression of this disease, including genetics and epigenetics, and significant advances in these components have been made, covering them in depth is beyond the scope of this review. For researchers interested in these topics, an elegant and comprehensive review by Bulun and coworkers (2015) recently addresses the molecular biology, genetics, and epigenetics of endometriosis and covers 25 years of research (1990–2015).

Inflammation – angiogenesis

Angiogenesis is the formation of new blood vessels, and subsequently, is a key process to form functional blood vessels to ectopic menstrual tissue for the establishment/maintenance of endometriotic lesions. Theorized is that women with endometriosis respond to retrograde menstrual tissue as a “wound” that must be healed and not as “self” that must be removed (Herington *et al.* 2011). Examining key players involved in angiogenesis, both in women with endometriosis and in animal models, similarities between angiogenesis in endometriotic lesions and angiogenesis in wound healing exist. A variety of growth factors and genes related to angiogenesis have been studied in endometriosis.

The VEGF protein family is well known for roles in angiogenesis, vasculogenesis, and lymphangiogenesis. Human peritoneal fluid (PF) from women with endometriosis show inconsistent protein levels of VEGF, but this may be due to sample size, dilution of PF, or true variability among women. For example, some studies show increased VEGF levels in the PF (Bourlev *et al.* 2010, Xu *et al.* 2013, Szubert *et al.* 2014); however, other studies show no increase in VEGF levels in women with endometriosis compared with healthy women (Barcz *et al.* 2012, Bersinger *et al.* 2012, Rathore *et al.* 2014). Interestingly, more consistency is found in animal models of endometriosis, most likely because of controlled onset of experimental conditions. A variety of rodent models of endometriosis show VEGF levels increase in endometriosis-like lesions (Machado *et al.* 2010, Ricci *et al.* 2011, Kumar *et al.* 2014, Lu *et al.* 2014a, Machado *et al.* 2014, Zhao *et al.* 2015). Data are inconsistent when attempting to target VEGF in the mouse to treat endometriosis (Xu *et al.* 2011, Novella-Maestre *et al.* 2012, Virani *et al.* 2013, Kumar *et al.* 2014); however, the data suggest that VEGF drives angiogenesis in endometriosis. Furthermore, these results from human and animal models demonstrate challenges of clearly deciphering VEGF as an appropriate marker for endometriosis.

Other angiogenic factors play important roles in the adhesion and maintenance of endometriosis lesions, including hypoxia factors (i.e. HIF1A), MMPs (i.e. MMP9), and microRNAs (miRNA). As mentioned, the peritoneal microenvironment of women with endometriosis is often different from healthy women. In a heterologous mouse model, hypoxic conditions promote angiogenesis and proliferation of endometriosis demonstrated by larger lesions, higher levels of VEGF, HIF1A, Ki67, and PECAM1 (Lu *et al.* 2014b). Concomitantly, the same group shows that lesion location affects adhesion and angiogenesis when comparing intraperitoneal versus subcutaneous endometriotic tissue injection (Lu *et al.* 2014a), suggesting that the microenvironment of the peritoneal cavity plays a crucial role in lesion adhesion and angiogenesis. MMPs are proteases required for reorganizing existing blood vessels during budding

angiogenesis (Page-McCaw *et al.* 2007). Recently, the role of MMPs in endometriosis were not studied in-depth, but MMPs play a known role in endometriosis (Machado *et al.* 2010). For example, *Mmp9*^{-/-} uterine tissue does not grow in a mouse suture endometriosis model (Han *et al.* 2012); however, this model does not account for actual tissue attachment. An emerging field in endometriosis is the function of miRNA in angiogenesis. Primary eutopic and ectopic endometrial stromal cells exposed to PF from women with endometriosis have downregulated miRNAs known to regulate VEGF expression compared with cells exposed to PF from control women (Braza-Boils *et al.* 2013, 2014, 2015). Future in-depth analysis of the interplay between inflammation and angiogenesis in the early stages of endometriosis development is needed to determine which molecules could potentially be targeted therapeutically.

Inflammation – cytokine and chemokine expression

Cytokines and chemokines are emerging as key players in endometriosis pathobiology. Cytokines are a broad group of secreted proteins important in cell signaling, while chemokines are a family of cytokines important in inducing chemotaxis in nearby cells. A complete overview of chemokines and cytokines in endometriosis is too exhaustive; however, these proteins are altered in PF, ectopic lesions, eutopic endometrium, and serum. To demonstrate the growing role of cytokine research in the study of endometriosis, Table 1 lists cytokines and chemokines that appear in more than two endometriosis research papers between 2010 and 2015. Additional to the dysregulation of cytokines/chemokines, altered levels of a large number of cytokines/chemokines are found in cyst fluid removed from endometriomas/chocolate cysts (Chen *et al.* 2013b). Before elucidating the interplay and implications of chemokines and cytokines in endometriosis, large-scale-controlled human studies or meta-analyses will need to be conducted to fully encompass cytokine dysregulation. Most likely, with the signaling complexity of the immune system and endometriosis as a disease, a single chemokine/cytokine will not diagnose disease, but instead, a disease profile of altered cytokines may be used to establish disease diagnosis. Furthermore, as nicely outlined by Fassbender and coworkers, international standardized methods for BioBanking endometriosis samples needs to be implemented (Fassbender *et al.* 2013).

Hormones and hormone receptors

Endometriosis is intimately associated with steroid metabolism and associated pathways, corresponding to the paramount roles estrogen receptors (ESRs) and progesterone receptors (PGRs) play in uterine biology. Both human and animal model studies show endometriosis

Table 1 Cytokine or chemokine alterations in endometriosis.

| Cytokine/chemokine | Model | Results | Reference |
|-----------------------|----------------|-------------------|---|
| CCL2 (MCP-1) | hPF | +, ++, +++ | (Mier-Cabrera <i>et al.</i> 2011, Margari <i>et al.</i> 2013), (Tao <i>et al.</i> 2011), (Bersinger <i>et al.</i> 2012) |
| CCL5 (RANTES) | hPF | NS, +, ++ | (Bersinger <i>et al.</i> 2012, Margari <i>et al.</i> 2013), (Mier-Cabrera <i>et al.</i> 2011), (Beste <i>et al.</i> 2014) |
| CCL11 (Eotaxin) | hEctopic | Qualitative +, ++ | (Wang <i>et al.</i> 2010), (Yang <i>et al.</i> 2013) |
| CXCL1 (GRO α) | hPF | ++, + | (Bersinger <i>et al.</i> 2012), (Mier-Cabrera <i>et al.</i> 2011) |
| CXCL8 (IL8) | hPF | Nearing | (Bersinger <i>et al.</i> 2012) |
| | hPF | NS, +, ++ | (Velasco <i>et al.</i> 2010, Bersinger <i>et al.</i> 2012), (Mier-Cabrera <i>et al.</i> 2011, Beste <i>et al.</i> 2014), (Milewski <i>et al.</i> 2011, Malhotra <i>et al.</i> 2012) |
| | hSerum | ++ | (Carmona <i>et al.</i> 2012) |
| | hEESCs | ++ | (Delbandi <i>et al.</i> 2013) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |
| CXCL10 (IP-10) | hLesion | NS trend – | (Bellelis <i>et al.</i> 2013) |
| | hPF | ++ | (Bersinger <i>et al.</i> 2012) |
| CXCL12 (SDF1) | hEctopic | + | (Bellelis <i>et al.</i> 2013) |
| | hPF | + | (Leconte <i>et al.</i> 2014) |
| IL1B | hPF | +, ++, +++ | (Mier-Cabrera <i>et al.</i> 2011, Beste <i>et al.</i> 2014), (Sikora <i>et al.</i> 2012) |
| | hEctopic | + | (Chen <i>et al.</i> 2013) |
| | hPF cells | NS | (Yeo <i>et al.</i> 2013) |
| IL4 | hPF | NS, ++ | (Mier-Cabrera <i>et al.</i> 2011, Wickiewicz <i>et al.</i> 2013), (Beste <i>et al.</i> 2014) |
| IL6 | hPF | NS, +, ++, +++ | (Rathore <i>et al.</i> 2014), (Mier-Cabrera <i>et al.</i> 2011, Khan <i>et al.</i> 2015), (Velasco <i>et al.</i> 2010, Kang <i>et al.</i> 2014), (Milewski <i>et al.</i> 2011, Bersinger <i>et al.</i> 2012, Podgaec <i>et al.</i> 2012, Wickiewicz <i>et al.</i> 2013) |
| | hSerum | +, ++, +++ | (Kinugasa <i>et al.</i> 2011), (Carmona <i>et al.</i> 2012), (Elgafor El Sharkwy 2013) |
| | hEESC | ++ | (Delbandi <i>et al.</i> 2013) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |
| IL10 | hSerum/PF | NS/NS | (Andreoli <i>et al.</i> 2011) |
| | hPF | NS, + | (Bersinger <i>et al.</i> 2012, Podgaec <i>et al.</i> 2012), (Mier-Cabrera <i>et al.</i> 2011, Wickiewicz <i>et al.</i> 2013) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |
| IL12 | hSerum/PF | NS/NS | (Andreoli <i>et al.</i> 2011) |
| | hPF | NS | (Mier-Cabrera <i>et al.</i> 2011) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |
| IL17A | hEndo, Serum | **/+ | (Ahn <i>et al.</i> 2015) |
| | hSerum/PF | NS/NS | (Andreoli <i>et al.</i> 2011) |
| | hPF | NS | (Podgaec <i>et al.</i> 2012) |
| | hFF/Serum | +++ / +++ | (Sabbaghi <i>et al.</i> 2014) |
| IL18 | hPF | +, --- | (Bersinger <i>et al.</i> 2012), (Sikora <i>et al.</i> 2012) |
| IL22 | hEctopic | ** | (Guo <i>et al.</i> 2013) |
| | hSerum | -- | (Santulli <i>et al.</i> 2013) |
| IFNG | hPF | NS, + | (Wickiewicz <i>et al.</i> 2013), (Mier-Cabrera <i>et al.</i> 2011) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |
| MIF | hPF | ++ | (Beste <i>et al.</i> 2014) |
| | hEctopic | ++ | (Lin <i>et al.</i> 2010) |
| TGFB | hPF | +++ | (Podgaec <i>et al.</i> 2012) |
| | mKO w/human | – size | (Hull <i>et al.</i> 2012) |
| TNFA | hPF | NS, +, ++ | (Tao <i>et al.</i> 2011, Wickiewicz <i>et al.</i> 2013), (Mier-Cabrera <i>et al.</i> 2011, Beste <i>et al.</i> 2014, Young <i>et al.</i> 2014a,b), (Khan <i>et al.</i> 2015) |
| | hEctopic cd56+ | + | (Chen <i>et al.</i> 2013) |
| | pfNKcell | + | (Funamizu <i>et al.</i> 2014) |
| | bEctopic | NS | (Ilad <i>et al.</i> 2010) |
| | hPF mRNA Cells | NS | (Yeo <i>et al.</i> 2013) |

Increased levels: + P <0.05, ++ P <0.01, +++ P <0.001, **qualitative IHC. Decreased levels: – P <0.05. NS, nonsignificant; h, human; b, baboon; Ectopic, ectopic endometriosis lesion; PF, peritoneal fluid; FF, follicular fluid; EESC, ectopic endometrial stromal cells.

is estrogen (E2) dependent and is regulated through the ERs alpha and beta (*ESR1* and *ESR2*) (Burns *et al.* 2012, Pellegrini *et al.* 2012, Wu *et al.* 2012, Han *et al.* 2015, Zhao *et al.* 2015). An increased ratio of *ESR2* to *ESR1* mRNA is observed in endometriomas compared with endometriosis implants and eutopic endometrium (Bukulmez *et al.* 2008). Knockout studies in mice show that lesion attachment, size, and proliferation are closely associated with the presence or absence of *Esr1* and *Esr2*

(Burns *et al.* 2012). The Bulun Laboratory has focused efforts on *ESR2* and demonstrates that *ESR2* expression is highly increased in endometriotic tissue due to hypomethylation of the promoter region (Dyson *et al.* 2014). They also identify RAS-like estrogen-regulated growth inhibitor (RERG) as a key enzymatic target of estradiol signaling through *ESR2*. This enzyme regulates numerous factors involved in the progression of endometriosis, including cell proliferation and apoptotic resistance

(Monsivais *et al.* 2014). Additionally, they have nicely detailed multiple studies on the role of ESR2 in endometriosis in a comprehensive review (Bulun *et al.* 2012). Use of estrogen receptor ligands, inhibitors, and agonists also support the role of ESRs in endometriosis (Colette *et al.* 2011, Kulak *et al.* 2011, Han *et al.* 2012, Chen *et al.* 2014, Naqvi *et al.* 2014, Zhao *et al.* 2015, Palmer *et al.* 2016). Specifically, selective estrogen receptor modulators (SERMs) are synthetic molecules which bind to ESRs and act as either antagonists or agonists. Two compounds, chloroindazole (CLI) and oxabicycloheptene sulfonate (OBHS), have strong ER-dependent anti-inflammatory effects on endometriosis lesions *in vivo* in a suture mouse model of endometriosis and *in vitro*, with primary human endometriotic stromal cells (Zhao *et al.* 2015). Their data suggest that both CLI and OBHS inhibit the establishment of new lesions and reduce the size of already established lesions; however, important next studies using these inhibitors will be to examine lesion attachment without a suture endometriosis model, as suturing alone creates an unnecessary inflammatory response similar to any reaction toward a foreign body (Carr *et al.* 2009) and, in some respects, negates the use of homologous tissue.

Progesterone (P4) and its receptor isoforms, PGR-A and -B, also have established roles in endometriosis. The endometrium of women with endometriosis demonstrates an attenuated response to P4 because PGR-responsive genes are not suppressed in the eutopic endometrium of women with endometriosis compared with healthy women in the early secretory phase of the menstrual cycle, suggesting the presence of a progesterone resistance phenotype in these women (Burney *et al.* 2007). A more recent study to discriminate between the PGR isoforms finds elevated levels of PGR-A in endometriosis lesions and eutopic endometrium from women with endometriosis and shows a PGR-A-dominant state, regardless of menstrual phase (Bedaiwy *et al.* 2015). While the data are from a small cohort of women, their findings suggest that a PGR-A-dominant menstrual efflux in the peritoneal cavity may mirror the growth and invasive properties known about cancers overexpressing PGR-A.

Aromatase is the enzyme responsible for the aromatization of androgens into estrogens. Aromatase protein level is increased in vaginal septum lesions and decreased in intestinal lesions in women with endometriosis (Goncalves *et al.* 2015). Ovarian endometriomas express higher levels of aromatase and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1A) than associated ectopic lesions and eutopic endometrium (Suganuma *et al.* 2014). Activation of peroxisome proliferator-activated receptor gamma (PPARG) inhibits the growth and survival of human endometriotic cells by suppressing E2 biosynthesis and prostaglandin E2 (PGE2) signaling (Lebovic *et al.* 2013). The use of AIs for the treatment

of endometriosis is becoming more common and is discussed below.

The last 5 years have expanded our knowledge of hormones, hormone receptors (HRs), and associated coregulators. These studies are important for integrating dysregulation found in ectopic lesions, but also have allowed for the design of more targeted areas to be studied. More in-depth studies with targeted HR uterine knockouts, coregulator knockouts, and/or with the recently synthesized SERMS will lead to greater understanding of the role of HR in disease. The results of these future experiments will allow for even more targeted experiments and hopefully development and use of more targeted therapeutic paradigms.

Interactions between inflammation and the endocrine system

Crosstalk between the immune/inflammatory and endocrine systems can significantly impact pathogenesis and progression of endometriosis. The sex hormone receptors can markedly alter the immune response in ectopic tissue. Both *ESR1* and *ESR2* have distinct roles in regulating the immune response, as discovered through the use of multiple animal models. Signaling of E2 through *ESR1* appears to have both an anti- and pro-inflammatory roles, as observed by increased mitogenesis and decreased *IFNG*, *TNF*, and *IL12* transcript expression (Burns *et al.* 2012). Overexpression of *ESR2* activates the inflammasome and modulates TNF-induced apoptosis, as observed with increases in *IL1B* and cleaved caspase-1 levels and decreases in cleaved caspase-8 levels in ectopic lesions (Han *et al.* 2015).

Hormones themselves also directly alter the immune system. Monocyte chemoattractant factor-1 (MCP1/CCL2) is an example of a chemokine significantly affected by sex hormones. In human endometrial endothelial cells from women with endometriosis, both E2 and P4 increase *MCP1* mRNA and protein expression; this effect is not observed in cells from healthy women (Luk *et al.* 2010). After treating monocytes with control peritoneal fluid (cPF) or endometriotic peritoneal fluid (ePF), the addition of E2 to the culture suppresses MCP1 release from cPF-treated monocytes. However, E2 does not suppress MCP1 release from ePF-treated monocytes (Lee *et al.* 2012). E2 promotes a pro-inflammatory environment by increasing the secretion of *IL6* and *TNF* from peritoneal macrophages from women with endometriosis compared with control women. This effect is further enhanced by co-treatment with lipopolysaccharide (Khan *et al.* 2015). Other chemokines, *CXCR4* and *CXCL12*, are downregulated by sex hormones in human epithelial endometrial cells and human endometrial stromal cells, respectively (Ruiz *et al.* 2010). All of these findings provide evidence that the immune environment and its response to sex hormones is altered in women

with endometriosis; however, a definitive mechanism for these differences is largely unknown and is a major area that future research needs to address.

A third aspect to the endocrine-immune crosstalk involves aromatase expression. Macrophage migration inhibitory factor (MIF) increases aromatase mRNA and protein expression in ectopic endometrial stromal cells via post-transcriptional stabilization (Veillat *et al.* 2012). Interestingly though, E2 treatment in the same cells increases *MIF* mRNA and protein expression, suggesting a positive feedback loop between the endocrine and immune systems in women with endometriosis (Veillat *et al.* 2012). Potential for a continuous positive-feedback loop between these systems is an area for further exploration to understand the dynamic and altered environment in women with endometriosis.

Clinical symptoms and diagnosis of endometriosis

Endometriosis is often characterized by pelvic pain that manifests in a variety of ways; most commonly, patients present with dysmenorrhea, noncyclical pelvic pain, and dyspareunia, but other common symptoms are dyschezia, dysuria, and infertility (Fritz MA 2011, Practice Committee of the American Society for Reproductive 2014). Definitive diagnosis of endometriosis is by visualization or excision of lesions via laparoscopy. The American Society for Reproductive Medicine (ASRM) grading system for endometriosis guides surgeons in determining the severity of disease (American Society for Reproductive Medicine 1997) and was created to help predict pregnancy with fertility treatment. The grading system does not correlate with pain level, and has limited reproducibility to predict pregnancy; however, it remains the best objective to communicate disease severity between physicians and surgeons.

Accuracy of visual diagnosis increases with disease severity (Fernando *et al.* 2013). While the European Society of Human Reproduction and Embryology (ESHRE) requirements suggest that surgical diagnosis by visualization alone is appropriate, ASRM stresses that biopsies be taken when diagnosis is unclear (Fernando *et al.* 2013). Importantly, poor correlation exists between clinical symptoms and disease burden (Dunselman *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Diagnosing endometriosis by pelvic pain alone is not sufficient, as pelvic pain is also a symptom of many other diseases, including pelvic adhesions, adenomyosis, and gastrointestinal urologic disorders (Bulun 2009, Practice Committee of the American Society for Reproductive 2014). This vast differential diagnosis for pelvic pain can complicate the diagnosis of endometriosis.

Treatments

Several different treatment modalities, including medical, surgical, and alternative, exist for endometriosis. First-line medical management includes options that have a favorable safety and cost profile, that are well tolerated by the patient, and that are effective in treatment (Zito *et al.* 2014). If medical therapy fails, surgical therapy to remove endometriotic lesions and endometriomas is performed. Finally, alternative therapies are being used to supplement conventional treatments.

Medical therapy

Combined oral contraceptive pills (OCPs), which include ethinyl estradiol (EE) and various progestins, are used to treat endometriosis, particularly in women not trying to conceive (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). Historically, OCPs have been first-line therapy, but most studies are decades old and the pills contained higher doses of EE. Based on a more recent randomized control trial (RCT) in 100 patients, low-dose OCPs decrease pain more significantly than placebo on the Visual Analog Scale (VAS) (Harada *et al.* 2008). Continuous OCPs decrease recurrence rates of dysmenorrhea after surgical therapy when compared with cyclic OCPs (Zorbas *et al.* 2015, Muzii *et al.* 2016). Of the progestins, the 19-nortestosterone derivatives are less androgenic and offer better side-effect profiles (Angioni *et al.* 2014). In an RCT, dienogest significantly decreases endometriosis-related pain similar to gonadotropin-releasing hormone agonists (GnRHa), both as initial and postoperative therapy, without the negative side-effect profile of GnRHa (Angioni *et al.* 2014, Andres Mde *et al.* 2015, Granese *et al.* 2015, Strowitzki *et al.* 2015). Levonorgestrel, delivered through an intrauterine system after conservative surgery, significantly decreases dysmenorrhea, dyspareunia, and noncyclic pelvic pain compared with expectant management in an RCT of 55 patients (Tanmahasamut *et al.* 2012, Imai *et al.* 2014).

Several therapies aim to create a hypoestrogenic state in women with endometriosis. Examples of these treatments include GnRHa, GnRH antagonists (GnRH-ant), synthetic androgens, and AIs. GnRHa therapy downregulates gonadotropin receptors and desensitizes the body to gonadotropins. It decreases pain and endometriotic nodules in comparison to placebo (Leone Roberti Maggiore *et al.* 2014, Brown & Farquhar 2015). A multicenter RCT comparing GnRHa to OCPs as postsurgical therapy reports that both groups increase quality of life scores (Granese *et al.* 2015). Although GnRHa is proven effective, a severe side effect is decreased bone mineral density (BMD); therefore, estrogens or progestins are given for bone protection (Leone Roberti Maggiore *et al.* 2014, Zito *et al.* 2014). In contrast, GnRH-ant inhibits gonadotropin receptors.

Elagolix improves dysmenorrhea and dyspareunia compared with placebo in a phase 2 RCT (Ezzati & Carr 2015, Munoz-Hernando *et al.* 2015), and comparing BMD profiles of elagolix with depot medroxyprogesterone acetate, both minimally impact BMD (Carr *et al.* 2014, Ezzati & Carr 2015).

Danazol, a synthetic androgen, inhibits the luteinizing hormone (LH) surge; however, it also increases free testosterone, causing undesired side effects including hirsutism, deepening of voice, weightgain, and acne. Danazol effectively decreases pelvic pain compared with placebo, and is as effective as other hormonal therapies, but the numerous side effects limit the use (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). AIs are currently a second-line treatment in women refractory to first-line treatments (Abu Hashim 2014). AIs such as letrozole decrease estrogen stimulation of endometriosis and, when used in combination with GnRHa, improve pelvic pain more than GnRHa alone. Additionally, letrozole with norethindrone acetate add-back has improved endometriosis symptoms, and high dose aromatase inhibition reduces ovarian endometrioma size (Agarwal *et al.* 2015). In contrast, a small RCT investigating postsurgical endometriosis pain comparing OCPs alone and in combination with letrozole reports similar pain scores, suggesting no benefit with letrozole addition (Almassinokiani *et al.* 2014).

Surgical therapy

Surgical therapy for endometriosis is typically necessary for intractable pelvic pain despite medical therapy. Several different surgical techniques are performed (Table 2), including excision/removal of endometriosis, uterosacral nerve ablation, presacral neurectomy, and hysterectomy with bilateral salpingo-oophorectomy (BSO) (Daniels *et al.* 2010, Healey *et al.* 2014, Posadzka *et al.* 2015), and some techniques provide better symptomatic control than others. For symptom improvement and preventing disease recurrence, endometrioma removal is superior to drainage (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Hysterectomy without BSO is less effective because of continued hormonal stimulation of microscopic endometriotic lesions. Hysterectomy with BSO leads to surgical menopause, which negatively impacts bone and cardiac health. Extreme surgical management is reserved for patients who fail conservative management (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014).

Alternative therapy

Given that endometriosis is such a difficult disease to treat, alternative therapies are welcomed in addition to conventional therapy. Comparing Chinese medicine (CM) to GnRHa as postsurgical treatment for endometriosis found no differences in recurrence rates on

Table 2 Endometriosis surgical treatments and associated efficacy.

| Surgical treatment | Surgical technique | Compared treatment | Efficacy |
|---|--|---|--|
| Laparoscopic ablation | Ablate, or apply heat, to lesion | CO ₂ laser vs electric cautery Diagnostic laparoscopy | Decreased pain with ablation (NRS 3) vs CO ₂ laser (NRS) (Posadzka <i>et al.</i> 2015) Decreased overall pain OR 5.63 (Duffy <i>et al.</i> 2014) |
| Laparoscopic excision | Remove lesion with scissor or laser | Ablation | No difference in overall pain, dyspareunia, or dyschezia at 1 year (Bulun 2009, Duffy <i>et al.</i> 2014) Excision decreased dyspareunia (VAS 3.2) vs ablation (VAS 6.0) at 5 years (Healey <i>et al.</i> 2014) Ablation required more medical treatment (31%) vs excision (20%) (Healey <i>et al.</i> 2014) |
| Conservative laparoscopy | Ablate or excise lesions, restore anatomy, adhesiolysis | Diagnostic laparoscopy | Decreased overall pain OR 6.58 (Duffy <i>et al.</i> 2014) |
| Laparoscopic uterosacral nerve ablation | Ablate nerve fibers responsible for pain pathway | Conservative laparoscopy | No difference in pain level (Daniels <i>et al.</i> 2010) |
| Endometrioma removal | Separate cyst wall from ovary and excise cyst | Cyst drainage | Decreased recurrence of cyst (Dunselman <i>et al.</i> 2014) Decreased recurrence of dysmenorrhea (OR 0.15) (Brown & Farquhar 2015) |
| Presacral neurectomy | Disrupts sympathetic innervation of uterus at level of superior hypogastric plexus | Conservative laparoscopy | 1 RCT: decrease midline dysmenorrhea (Practice Committee of the American Society for Reproductive 2014) (Dunselman <i>et al.</i> 2014) 1 RCT: no additional benefit (Practice Committee of the American Society for Reproductive 2014) |
| Hysterectomy+BSO | Debulking to place in surgical menopause | Hysterectomy without BSO | Improved symptoms (Practice Committee of the American Society for Reproductive 2014) (Dunselman <i>et al.</i> 2014) (Duffy <i>et al.</i> 2014) |

BSO, bilateral salpingo-oophorectomy; VAS, visual analog scale; NRS, numeric rating scale; OR, odds ratio.

follow-up (Weng *et al.* 2015). In contrast, Chinese herbal enemas decrease dysmenorrhea comparable to danazol (Kong *et al.* 2014), and CM and herbal enema combination is superior to danazol in decreasing pain symptoms (Flower *et al.* 2012). An acupuncture study in addition to conventional medical therapy significantly decreases pelvic pain by 5–6 points on the 10-point VAS (Rubi-Klein *et al.* 2010). Pelvic physical therapy includes internal manual treatment to stretch pelvic floor muscles, myofascial release, biofeedback, and trigger point release. In those with myofascial chronic pelvic pain, 63% report significant pain improvement after at least 6 sessions (Bedaiwy *et al.* 2013). Exercise can provide pain relief, based on questionnaire studies composed of 50–2730 women with endometriosis and 400–4000 control women; however, other survey studies correlate exercise with increased pelvic pain. Unfortunately, not all of these studies are controlled and all are from self-reporting (Bonocher *et al.* 2014). Large prospective cohort or case-control studies demonstrate increased risk of endometriosis with diets high in trans-fatty acids and decreased risk with diets containing high levels of long-chain omega 3 fatty acids (Hansen & Knudsen 2013). More high quality studies are needed in these areas, and importantly, a positive publication selection bias likely exists with alternative therapies, exaggerating true effectiveness (Kong *et al.* 2014).

Association between endometriosis and cancer

The potential association between endometriosis and cancer has been theorized for decades. This association is based upon observational case-control and cohort studies that propose malignant transformation occurs within endometriotic lesions, giving rise to cancer. Our molecular-genetic understanding of both endometriosis and ovarian cancer continues to rapidly evolve; yet, a definitive mechanism for malignant transformation remains elusive.

Risk and prognosis

The 10% prevalence of endometriosis, and an even higher prevalence for women with infertility or chronic pelvic pain, makes the establishment of an absolute

“cause-and-effect” relationship problematic. Lifetime risk of developing ovarian cancer in the general population is ~1.4%, with a median age of onset in the early 60s (Schorge *et al.* 2010). Epithelial ovarian cancer is no longer seen as a single disease, but rather a constellation of multiple diseases based upon histologic subtypes and unique molecular signatures (Galic *et al.* 2013). The risk of ovarian cancer increases for women who incur fewer pregnancies and/or suffer from infertility. The possibility of confounding when assessing associative risk between these two entities must be considered because infertility is related to both conditions.

Nonetheless, a number of epidemiologic and clinical features lead investigators to propose an association between endometriosis and cancer. The establishment of an association was reported 90 years ago (Sampson 1925) and was refined in 1953, proposing that benign endometriosis should be observed in close anatomic proximity to the arising endometriosis-associated cancer (Scott 1953). Chief among the observations are that both entities produce tissues that can metastasize, invade, and destroy normal surrounding tissues. Furthermore, cancers often are identified in endometriotic lesions or in tissues that are contiguous with endometriosis, and there are often findings of candidate precursor lesions exhibiting histologic atypia in these surrounding tissues (Wei *et al.* 2011). Finally, endometriosis in younger women, which persists into older age, creates a long window for malignant transformation.

Several retrospective studies initially document the increased rate of endometriosis in women with ovarian cancer. A Swedish study containing over 20,000 patients that cross-matched inpatient endometriosis diagnosis and any cancer diagnosis (Brinton *et al.* 1997) found a small increased risk of any cancer, but the risks were not confirmed upon long-term follow-up (Brinton *et al.* 1997). The risk of ovarian cancer, however, is significantly increased in both the initial and long-term analyses. In patients with a history of prolonged endometriosis, the statistical risk for the development of ovarian cancer is even higher.

A linkage analysis of over 99,000 women from Denmark shows that an endometriosis-related increase

Table 3 Summary of risks associated with endometriosis and cancer from registry studies by Brinton *et al.* (1997, 2005).

| Population | Risk | SIR* or RR | 95% CI |
|--|-----------------------------|------------|------------|
| History of endometriosis admission (HEA) | Any cancer | 1.2* | 1.1–1.3* |
| HEA | Ovarian cancer | 1.9* | 1.3–2.8* |
| HEA & prolonged endometriosis | Ovarian cancer | 4.2* | 2.0–7.7* |
| HEA | Endometrial cancer | 1.1* | 0.6–1.9* |
| HEA long-term F/U | Any cancer | | |
| HEA long-term F/U | Ovarian cancer | 1.43* | 1.19–1.71* |
| Long-term F/U & prolonged endometriosis | Ovarian cancer | 2.23* | 1.36–3.44* |
| HEA Denmark cohort | Clear cell ovarian cancer | 3.37 | 1.24–9.14 |
| HEA Denmark cohort | Endometrioid ovarian cancer | 2.53 | 1.19–5.38 |

HEA, history of endometriosis admission; SIR, standardized incidence ratio; RR, relative risk; CI, confidence interval; F/U, follow-up. *denotes SIR.

in ovarian cancer occurs in two histologic subtypes, clear cell and endometrioid (summarized in [Table 3](#)) ([Brinton et al. 2005](#)). Recent evidence also suggests a correlation between endometriosis and high-grade serous histologic type ovarian cancer ([Lee et al. 2016](#)). A large case-control study confirms an approximate three-fold increased risk of clear cell or endometrioid ovarian cancer in association with endometriosis ([Rossing et al. 2008](#)). Malignant transformation risk to ovarian cancer from ovarian endometriosis is reportedly 0.2–2.5% ([Gadducci et al. 2014](#)). Recent studies also show the association between endometriosis and different forms of ovarian cancer: serous, mucinous, clear cell, and endometrioid, with the predominant cell types being clear cell and endometrioid ([Table 4](#)).

A meta-analysis conducted by [Kim et al. \(2014\)](#) evaluates the risk and prognosis of ovarian cancer in ~445,000 women with or without endometriosis. Based on 35 studies, women with endometriosis are significantly at risk of developing ovarian cancer; however,

stage is more likely to be early and low-grade, suggesting that the cancer is slow growing and less invasive. Endometrioid and clear cell are common in women with endometriosis, with the serous subtype occurring less frequently and the mucinous subtype displaying no differences between control women and women with endometriosis ([Kim et al. 2014](#)). Endometriosis does not affect prognosis, and the overall survival in women with endometriosis-associated ovarian cancer (EAOC) and in women with non-EAOC are similar when accounting for histology, disease status, assessment of endometriosis, and potential confounding factors. Unfortunately, the effect of endometriosis on a successful debulking surgery is not analyzed ([Kim et al. 2014](#)), so it is unknown if there is a benefit in survival in women with EAOC.

Proposed mechanisms of malignant transformation

Complex hormonal, genetic, and immunologic interactions must be considered when assessing the interplay

Table 4 Ovarian cancer types arising from endometriosis transformation.

| Population (# patients EAOC/total in study) | Ovarian cancer type in EAOC | Age (mean ± s.d.) years | Reference |
|--|---|----------------------------------|--|
| Quebec, BC (41/2854) | Serous 19.51% Mucinous NR Clear cell 21.9% Endometrioid 24.4% | OC 53.9±11.4 EAOC 48.3±10.8 | (Aris 2010) |
| Belegrade, Serbia (23/210) | Serous 3.5% Mucinous NR Clear cell 36.8% Endometrioid 31.6% | NR | (Dzatic-Smiljkovic et al. 2011) |
| Michigan, USA (42/184) | Serous 55% Mucinous 10% Clear cell 21% Endometrioid 14% | OC 59 EAOC 52 | (Kumar et al. 2011) |
| Athens, Greece (17) | Serous 5.9% Mucinous NR Clear cell 58.8% Endometrioid 35.3% | EAOC 58 (27–76) | (Kondi-Pafiti et al. 2012) |
| Ovarian Cancer Association Consortium (738/7911) | Serous 7.1% Mucinous 6.0% Clear cell 20.2% Endometrioid 13.9% | OC 56.1 | (Pearce et al. 2012) |
| Ankara, Turkey (45/1086) | Serous 13.3% Mucinous 8.9% Clear cell 37.8% Endometrioid 33.3% | EAOC 56.3 EAOC 55 (35–77) | (Boyrac et al. 2013) |
| Massachusetts, USA (67/134) | Serous 0% Mucinous NR Clear cell 38.8% Endometrioid 61.2% | OC 56.6 EAOC 51.7 | (Davis et al. 2014) |
| Milano, Italy (27/73) | Serous NR Mucinous NR Clear cell 76.1% Endometrioid NR | OC 58.4±11.2 EAOC 51.4±10 | (Scarfone et al. 2014) |
| San Juan, Puerto Rico (20/192) | Serous 2.2% Mucinous 2.7% Clear cell 23% Endometrioid 50% | OC 56.1±14.9 EAOC 48.8±11.6 | (Acien et al. 2015) |
| Shiraz, Iran (28/110) | Serous 14.5% Mucinous 0% Clear cell 14.5% Endometrioid 39% | OC 50.18±12.8 EAOC 49.93±9.36 | (Akbarzadeh-Jahromi et al. 2015) |

OC, ovarian cancer; EAOC, endometriosis-associated ovarian cancer; NR, not reported.

between endometriosis in the development of epithelial primary peritoneal or ovarian carcinomas. Chronic inflammation, autocrine and paracrine effects, hormonal interactions, and microenvironmental alterations caused by endometriosis in the pelvic region could be relevant mechanisms for malignant transformation. Aberrant immune function, stimulated by estrogens, may create a positive-feedforward loop, enhancing growth and invasiveness of endometriosis and promoting malignant transformation (Ness 2003). Zanetta and coworkers report a role for a hyper-estrogenic state in stimulating endometriosis and promoting malignant transformation (Zanetta *et al.* 2000).

A permissive microenvironment and accumulation of genetic mutations is suggested to cause malignant change in endometriosis (Wei *et al.* 2011). Distinct molecular events may occur in early stages of tumorigenesis of endometriosis-associated carcinoma. Recent studies focus on genetic alterations such as phosphatase and tensin homolog (*PTEN*), tumor protein p53 (*TP53*), and B-cell lymphoma (*BCL*) gene mutations that lead to malignant changes in endometriosis (Nezhat *et al.* 2008, Munksgaard & Blaakaer 2012, Lai *et al.* 2013, McConechy *et al.* 2014). An interplay of genetics and oxidative stress, with decreased expression of interleukin 1 receptor type 2 (*IL1R2*), is a common signature between endometrioid ovarian cancer and endometriosis (Kobayashi *et al.* 2009, Keita *et al.* 2010, 2011). IL1 ligands are expressed by all endometriosis-associated ovarian cancer subtypes and endometrial cells. A decrease in IL1R1 levels, a protector against the tumorigenic effects of IL1, occurs in endometrioid carcinoma (Keita *et al.* 2010, 2011).

Multiple tumor-associated somatic mutations, detected by examining single gene or by whole genome sequencing, have revealed a signature of mutations. Mutations in catenin beta 1 (*CTNNB1*) are seen in 60% of ovarian endometrioid carcinomas (Matsumoto *et al.* 2015). Mutations in AT-Rich Interactive Domain 1A (*ARID1A*) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) appear most consistently in clear cell ovarian carcinomas (Gadducci *et al.* 2014, Anglesio *et al.* 2015, Matsumoto *et al.* 2015). Mutations in *ARID1A*, involved in chromatin remodeling, are present in both clear cell (15–75%) and endometrioid carcinomas (30–55%) (Wiegand *et al.* 2010, Gadducci *et al.* 2014). Associated with malignant transformation, mutations in *ARID1A* lead to the loss of its product, BAF250a, which correlates strongly with ovarian clear-cell carcinoma and endometrioid carcinoma subtypes, as well as with high-grade endometrial carcinomas (Wiegand *et al.* 2010, 2011, Ayhan *et al.* 2012, Lowery *et al.* 2012, Samartzis *et al.* 2012, Chene *et al.* 2015). *ARID1A* mutations and BAF250a loss are also observed in tumors and contiguous atypical endometriosis, but not in distant endometriotic lesions. The loss of *ARID1A* expression usually coexists with PI3K-Akt pathway

activation and/or zinc finger protein 217 (*ZNF217*) amplification in ovarian clear cell cancers and may indicate an early event in the malignant transformation of endometriosis into the various histotypes of ovarian cancer (Ayhan *et al.* 2012, Huang *et al.* 2014).

Loss of *PTEN* is observed in clear cell-associated endometriosis and cancers, including a significant increase in expression levels of X-ray repair cross-complementing protein 5 (*XRCC5*), patched 2 (*PTCH2*), elongation factor 1-alpha 2 (*EEF1A2*), and protein phosphatase 1 regulatory subunit 14B (*PPP1R14B*). However, these changes are not observed in benign endometriosis (Worley *et al.* 2015). *PTEN* loss is proposed as an early and permissive event in endometriosis development, while loss of *ESR1* and polycomb-mediated transcriptional factor cause ultimate malignant transformation (Worley *et al.* 2015).

Future research will clarify the likely complex interaction among genetic alterations, estrogen exposure, inflammatory cytokines, and the immunologic microenvironment in the transformation of endometriosis to endometrioid and clear cell ovarian and primary peritoneal cancers. Treatment of these cancers will hopefully improve with the use of targeted and immunologic therapies that address the underlying causes of malignant transformation.

Concluding remarks: where are we going?

While the studies reviewed from the last 5 years demonstrate a deeper understanding of endometriosis as dysregulations pertain to hormones, hormone receptors, immune function, and transformation to ovarian cancer, endometriosis still remains mysterious from many facets. Critically needed for this enigmatic disease are mechanistic understandings of disease initiation and perturbation that will hopefully lead to the development of noninvasive disease diagnosis and the development of treatments that do not negate hormonal cyclicality or have other undesired side-effect profiles and decrease the need for surgical extirpation. To allow for this to happen, the following areas of need are identified:

- Establish clear limits to animal models and clarify what the model may and may not reveal.
- Establish international standards for collection of patient information and samples as outlined by (Fassbender *et al.* 2013).
- Establish disease profile through clearer understanding of cytokines and the potential association with autoimmune disorders.
- Characterization of interplay between the hormonal milieu and immune system.
- Focus on lifetime exposures, acute and chronic, to endocrine disrupting chemicals that may interfere with uterine development, immune system regulation, and ultimately endometriosis development.

- Full recognition that this disease is truly multifaceted with pain, psychology, infertility, immunity, etc.
- Transformation of endometriosis to ovarian cancer through characterization of the lag between endometriosis found on the ovary to an ovarian cancer diagnosis.
- Determine if age, parity, weight, and hormonal regulators (oral contraceptives) contribute to transformation to cancer diagnosis.

Declaration of Interest

A D G, S A L, J A K, J M S-R, and K A B do not have any conflict of interests to disclose. T J H, in the last 2 years, has served on Advisory boards to: Roche/Genentech, AstraZeneca, Caris Life Sciences, Clovis Oncology, and Johnson & Johnson.

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