Editorial

What the Transcriptome of the Eutopic Endometrium from Women with Endometriosis tells us about the Disease Pathophysiology: A Brief Reflection

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Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity, usually represented by deep peritoneal, ovarian and/or infiltrative lesions[1,2] and, more rarely, in extrapelvic sites.[3] The estimated prevalence is of 5 to 10% of reproductive-age women,[4–6] despite the suggestion of an actual lower prevalence, of up to 1.8%, in a recently published study based on a population of two million individuals.[7] The incidence, in turn, is more difficult to be estimated, but seems to be between 1.3 to 1.6 cases per 1,000 women in this same age group.[8] Even considering this wide variation, if extrapolating to the Brazilian female population aged between 15 and 50 years estimated in the last census of 2010, there may be between 1 million and more than 5 million women with endometriosis, which is a very expressive number. Women with endometriosis may be asymptomatic or have varied symptoms, with the most frequent being pain (dysmenorrhea, dyskinesia, acyclic pain, dyspareunia) and infertility, followed by abnormal uterine bleeding and ovarian mass.[9,10] Despite these associations, there are no clinical symptoms or signs that are good predictors of the disease,[11,12] which culminates in the difficulty of an accurate clinical diagnosis.[13] Other important aspects are the absence of a correlation between the severity of symptoms and extent of the disease,[14] the presence of endometriosis in a reasonable number of asymptomatic women,[15] and the lack of knowledge about the events determining the natural evolution of the disease, be it spontaneous progression or regression.[16] Nonetheless, the disease is associated with a significant psychological and social impact, negative repercussions on the woman's quality of life[17] and productivity,[18] and relevant socioeconomic burden.[19,20]

Several theories have been proposed to explain the origin of the disease, among which are theories of retrograde menstruation (the most widespread and accepted), celomic metaplasia, lymphovascular metastasis, and, more recently, the theory of neonatal uterine bleeding.[21,22] Although reasonable, by themselves these theories do not explain the origin and evolution of the disease in all its nuances, and other factors need to be considered, such as: genetic, endocrine, immunological, inflammatory, and neuroangiogenic. Regardless of controversies, the eutopic endometrium in women with the disease definitely has peculiarities and a relevant role in the pathophysiological process of the disease.[23–25] If we added genetic susceptibility[26] and immune system dysfunction to this context, including autoimmunity and deficient immune surveillance,[27–29] we would already have a plausible explanation for the question of why only some women develop the disease. Still, there would be another question: what would be or what would lead to this initial alteration of the eutopic endometrium? A potential explanation would be the presence of somatic mutations in the epithelial and/or stromal endometrial components. Despite their relevance to ovarian lesions (endometriomas), they do not appear to be crucial or significant in components of the eutopic endometrium.[30] Another interesting element is the importance of endometrial progenitor cells, or endometrial stem cells in their broadest concept. However, although admittedly associated with the development of the lesion at ectopic sites,[31] primary constitutive changes in these cells, when isolated from the eutopic endometrium, are still controversial. In this scenario of uncertainties about the triggering event of the first changes in the eutopic endometrium of women with endometriosis, it is worth discussing an equally interesting, although less explored, hypothesis of microbiological contamination. Some authors defend intrauterine microbial colonization as the trigger for pathophysiological events that culminate in endometriosis.[32] Furthermore, infections can trigger cumulative genetic and epigenetic changes with the potential to trigger or maintain endometriosis.[33] Although recently published, the concept of an initial eutopic endometrial infection followed by sterile inflammation has been proposed before.[34] These propositions are

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supported by the association between endometriosis and endometritis,[13,35–39] by the microbial contamination observed in the uterine cavity and ectopic lesions,[40–42] and by dysbiosis in the microbiome of the intestine and genital tract of women with endometriosis.[43]

Concomitant to these findings, the modernization of molecular biology techniques in recent decades has allowed great advances in understanding the processes involved in the evolution of several diseases. Currently, these methodologies are more affordable, easy to execute, and have good reproducibility.[44,45] Transcriptome analysis, for example, is a direct reflection of gene expression in tissues. In this sense, the transcriptome analysis of the eutopic endometrium of women with endometriosis has an invaluable potential in contributing to understand local events associated with the condition. In fact, there are already relevant studies evaluating the transcriptome of the eutopic endometrium of women with and without endometriosis.[46–50] However, some limitations are inherent to these studies, such as: reduced casuistry size; heterogeneous sample regarding phenotypic characterization, mainly of the menstrual cycle phase, the extent of the lesions, and associated symptoms; inadequate selection of healthy controls; non-optimized evaluation by the bioinformatics tools available; and redundancy in the interpretation of biological pathways, among others.

To try to remedy these limitations, our group conducted a meta-analysis including raw eutopic endometrial transcriptome data available in international databases from healthy women and from women with endometriosis. We restricted the control group to women with no known disease and stratified women with endometriosis into those with stages I and II disease and those with stages III and IV disease. For both groups, we considered the phase of the menstrual cycle, since it can interfere with the expression of the tissue transcriptome.[51] By using some bioinformatics tools, we were able to predict the tissue microenvironment computationally, that is, we could infer the types of cells present in each sample. The method used can identify 64 cell types, including immune cells, stem cells, and stromal cells, among others. Thus, we observed that the eutopic endometrium of women with endometriosis in stages I and II has more proinflammatory characteristics than the endometrium of women in stages III and IV of the disease. Initial cases have a predominance of activated dendritic cells, effector memory CD4+ T-cells, eosinophils, type M1 macrophages and natural killer T-cells, which are typical of an inflammatory process induced by acute infections. In more advanced cases (stages III and IV), there is a predominance of M2 macrophages and natural killer T-cells. This last cell profile is characteristic of an antiinflammatory process, of tissue healing and repair[52] present in late stages of infectious diseases[53] that may be associated with the promotion of tumor growth.[54] As for biological pathways, in women with endometriosis there is a direct involvement of the processes related to immune surveillance, stem cell self-renewal, and epithelium-mesenchymal transition. These mechanisms are already reported in the literature, but we note that pathways related to greater permissiveness of the immune system to cells in ectopic environments and imbalance between cell growth and survival[55] are more evident in advanced disease. Anyway, the predominance of different cell types added to the interaction between genes and the predominant biological pathways in each condition, regardless of the phase of the menstrual cycle, indicates that the eutopic endometrium of women affected by endometriosis has peculiar characteristics of a tissue that suffered or has been suffering some harm, aggression, or stress caused by an external, potentially microbiological agent.

Based on what was briefly mentioned above, thinking about an initial endometrial aggression, possibly by a microbiological agent, sustained for a variable period of time, and followed by the induction of genetic and epigenetic changes in the tissue and consequent self-sustained inflammation (sterile or not), all occurring in a genetically susceptible woman, whose immune system behaves anomalously and is permissive to the presence of endometrial cells (especially stem cells) in ectopic environments, would be an at least plausible hypothesis and justify further investigations. However, studies must be conducted to resolve limitations that may skew the results obtained, especially a good phenotypic characterization of patients and a good selection of healthy controls.

Conflict of Interests

The authors have no conflict of interests to declare.

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