Do we need to separate initiation and growth to understand endometriosis?

A series of elegant experiments demonstrate that "epidermal growth factor (EGF) increases the expression of endometriosis-associated hyaluronan and its synthase hyaluronan synthase 2, both of which mediate EGF-induced stromal cell migration and invasion in women with endometriosis. These effects can be blocked by the pharmaceutical blocking of the EGF receptors. In addition serum EGF and hyaluronan levels are more elevated in women with endometriosis than in women without endometriosis, and the concentrations of hyaluronan correlate with EGF concentrations in all women" (1). The interpretation of these data to understand progression of endometriosis should be done carefully.

Interpretation of the data is hampered by the design of the study. The control group is composed of women with hydrosalpinx or unexplained infertility, both of which might have a predisposition to develop endometriosis. The stromal cell invasion was investigated only in women with endometriosis and without a control group. The study does not specify whether women with stage I-II endometriosis had subtle, typical, or even deep endometriosis. This might be important as these could be three different diseases.

The results of the article by Zhan et al. (1) needs to be understood in the framework of the existing knowledge. The stimulation of invasiveness and motility of endometrial and endometriosis stromal cells by EGF should be considered together with the many factors known to regulate this motility and the mesenchymal endothelial transition. In addition these mechanisms are not unique for endometriosis. They are fundamental in endometrial regeneration after menstruation, decidualization, implantation, placentation, and obstetric complications such as hypertension in pregnancy and small for birthweight babies. It is surprising that the increased invasiveness and migration of stromal cells from endometriosis and of the endometrium from women with endometriosis (2) was not addressed in this study, performed with the "aim to investigate progression of endometriosis." The results confirm that EGF concentrations are very variable but increase in women with endometriosis. That EGF stimulates hyaluronan synthase 2 and hyaluronan expression adds to our knowledge that EGF up-regulates matrix metalloproteinase and ovarian endometriosis progression (2). However, hyaluronic acid production or degradation enzymes (3) were reported to be similar and standard CD44 expression does not differ in eutopic menstrual endometrial cells (3) in women with and without endometriosis. This prior knowledge would benefit from improved discussion with less selective focus on hyaluran and endometrial cancer invasion.

It is unclear how these data add to our understanding of the pathophysiology of endometriosis, which was the aim of the study. The implantation theory includes dissemination, the histologic differences between endometrium and endometriosis, and the transition from typical endometrial tissue to endometriotic tissue with fibroblastic changes. Implantation seems supported by the motility and invasion of endometrial stromal cells (1), which is, in addition, enhanced by peritoneal mesothelial cells and by an inflammatory reaction in the peritoneal cavity (2). However, invasiveness of endometrial stromal cells does not explain why not all women develop progressive endometriosis given the universal aspect of retrograde menstruation. To explain the absence of progression in most women and with observations, such as the clonal aspect of endometriotic lesions, the genetic-epigenetic (G-E) theory (4) postulates that the onset of the disease/invasion requires that the cumulative set of G-E incidents has reached a certain threshold. The polygenetic inheritance determines the susceptibility of developing the disease when additional G-E incidents occur because of mutagenic substances, the oxidative stress of (retrograde) menstruation and infection/microbiota in the peritoneum or upper genital tract (5). Although inflammation fits in the model of endometrial stromal cell invasion, this study cannot differentiate whether the initial invading cells causing endometriosis are G-E normal or abnormal. It is also unclear how the data on EGF stimulated hyaluran expression add to our understanding of the subsequent growth and development of endometriosis lesions. Growth may vary with their set of G-E incidents, by the endocrine and immunologic environment that varies from ovarian, peritoneal, or other tissues and by bleeding and microtrauma in the lesions.

The observations on EGF, hyaluran, and endometrial stromal cell invasion, do not help to understand the pathophysiology of endometriosis with three major problems. First, most endometriosis-associated changes, such as infertility, immunologic changes, and changes in the endometrium can be explained either as an endometriosis prone constitution (i.e., signaling inherited incidents) or as a consequence of endometriosis. In addition this question became more complicated by the observation that stromal cells from endometriotic lesions can migrate to the endometrium (2). The highly overlapping but more elevated plasma concentrations of EGF and hyaluran in women with severe endometriosis than in women with mild or no endometriosis (1) can similarly be viewed as a cause or as a consequence of endometriosis. A second problem is that the relationship between histologic appearance and G-E changes in cells is not clear. It is tempting to speculate, however, that slow and progressive changes in histologic appearance might reflect G-E changes. Third, it is poorly established to what extend transmissible epigenetic changes in tissue cells are reversible or irreversible. Assuming that metaplastic endometriosis-like tissue reflect epigenetic changes, it is unclear whether this tissue will return to normal endometrium or to healthy tissue if these epigenetic or other cellular changes are reversed.

Studies with the aim to explain progression of endometriosis and/or to address prevention and therapy (1) should preferably consider the existing views on the pathophysiology of endometriosis. Control groups should not be composed of women who could be linked to an endometriosis predisposition or an active pathology such as women with unexplained infertility or hydrosalpinges. Considering the invasion of

endometrial stromal cells, it is attractive to address this invasion as a therapy or prevention of endometriosis. Unfortunately, all attempts have failed in the past (2). If endometriosis would be initiated by a cumulative set of G-E incidents, prevention of endometriosis and of recurrences after surgery is conceivable by reducing the volume of retrograde menstruation and its associated oxidative stress, and by addressing the peritoneal microbiome by preventing upper genital tract infections or by modulating the transmural migration of the intestinal microbiome through diet and exercise. The completeness of surgical excision of deep endometriosis remains debated as recurrence rates after incomplete conservative disc excision or shaving are not higher than after large segmental bowel resections. Although speculative, this might suggest that the peripheral layer of deep endometriosis nodules and the satellite microscopic endometriotic nests at distance are composed of inactive and stable, possibly reversible, forms of early endometriosis-like cells induced by the nodule.

In conclusion, the role of endometrial stromal cell mobility and invasion and, more particularly, the role of EGF and hyaluran in the pathophysiology of endometriosis remains unclear. Future studies should be designed to validate or invalidate the different hypotheses and models of endometriosis. At present it seems wise to distinguish between the initiation of endometriosis and its subsequent growth. Differences in plasma or peritoneal fluid concentrations or in endometrium between women with and without endometriosis can be interpreted as cause and consequence and will remain unclear until these differences are studied prospectively in young women without endometriosis. Future studies hopefully will address the link between histologic appearances and epigenetic changes in endometriosis-like tissue.

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