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Short Comment

The Unclear Role of Lgr5+ Cells in Eutopic Endometrium of Women with Endometriosis

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The endometrium is a highly dynamic tissue that is fully reconstituted after each menstrual cycle during the reproductive period, and throughout the entire life-span if hormonal supplementation is administered [1]. Functionally, the endometrium is composed of two functionally distinct layers, the superficial stratum called *functionalis* and the deeper stratum, called *basalis*. This unique high regenerative capacity is mostly due to the existence of endometrial stem cells that are controlled by the endometrial niche which represents the specific physiological microenvironment in which stem cell proliferation and cell fate decisions are regulated [2]. In the human endometrium, the stem cell niche seems to be located at the endothelium of the spiral arterioles in the basal layer, providing support to both the epithelial and stromal compartments [3-5]. Furthermore, bone marrow stem cells contribute to the repair and regeneration of tissues and organs [6], including endometrium [7,8] by forming endometrial stromal cells [9] and glandular and luminal epithelium.

The leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) is a seven transmembrane receptor described as a stem cell marker in a variety of tissues, including the small intestine and hair follicles [10,11], as well as the endometrium [12,13]. However, its fuction in the latter is unclear. It has been demonstrated that roughly half of the LGR5+ population in healthy endometrium co-express the pan-leukocyte marker CD45, as well as CD163, a monocyte and macrophage specific maker, suggesting a myeloid nature of these cells [13]. Although LGR5 seems to be down-regulated by progesterone through progesterone binding sites in its promoter [12], its expression remains constant throughout the menstrual cycle in both healthy and endometrium of women with endometriosis suggesting that is not hormonally regulated [13,14].

Endometriosis is a chronic estrogen-dependent disease characterized by the presence of endometrial tissue outside the uterine cavity causing acute pelvic pain and/or infertility/subfertility and affecting approximately 10% of reproductive age women [15]. Tipically, endometriotic lesions are located in the pelvic region; although distant lesions in lung, liver, and even in the eyes have been reported [16]. Despite several theories, such as retrograde menstruation, coelomic metaplasia and/or embryonic rests have been proposed to explain the origin of endometriosis, none of these hypotheses account for cases of distant lesions outside the pelvis. Alternatively, some studies have shown that bone marrow stem cells have the capacity to engraft endometriotic lesions, suggesting that bone marrow stem cells could play a role in the origin of endometriosis [17-20]. In fact, an association between endometriosis and immune disorders has been established, suggesting that a single bone marrow disorder may be common to both bone marrow-derived ectopic endometrium and other immune phenomenon, which could contribute to the development of the disease [21].

In a rodent model of induced endometriosis, cells selectively migrated from endometriosis lesions specifically to the eutopic endometrium, and not to other organs, through extravasation, modifying its normal gene expression profile [22]. These migrating cells were mostly located close to blood vessels and they aberrantly expressed the epithelial marker Cytokeratin (CK) in the stromal compartment toghether with LGR5 and Wnt7a [22], the latter two known to be stem cell markers. The activation of the Wnt signaling pathways suggests that Epithelial-to-Mesenchymal Transition (EMT) is involved in the process of extravasation. In a similar rodent model of induced endometriosis, circulating endometriotic cells originated microscopic endometriotic lesions in the lungs, suggesting an hematogenous dissemination of mesenchymal stem cells through EMT [23]. EMT is an important process in metastasis, as cells are able to change from an epithelial to a mesenchymal phenotype, allowing the extravasation of the cells and their migration to other tissues. Acumulated evidence showed that the induction of EMT induces cancer stem cell phenotype in tumor cells and seems to be closely integrated [24].

Molecular and anatomical changes in endometriotic eutopic endometrium have been widely described [25-27]. In fact, a previous study from our group showed an abnormal epithelial phenotype in the stromal compartment of the eutopic endometrium of women with endometriosis [28], as well as in mice with induced endometriosis [22]. In the first study, up to 70% and 80% of the patients with endometriosis presented an abnormal co-localization of LGR5 with the epithelial markers CK and ECAD, respectively, in the stromal compartment

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of the eutopic endometrium. This co-expression was not found in healthy women, showing that LGR5+ cells do not have the same protein expression in women with endometriosis [28]. These results suggest that this marker may play a role in the pathophysiology of this disease, probably through EMT.

Although endometriosis is considered a benign disease, it shares some features with malignant diseases, such as the capacity to induce distant lesions, tissue invasion and chronic inflammatory state [20,29]. Cancer cells in blood circulation that selectively migrate, can engraft the original tumor and contribute to metastasis. Actually, a bidirectional communication between primary and metastatic tumors has been demonstrated [30]. Interestingly, a substantial reduction in liver metastasis was observed when primary colon tumors were depleted of LGR5+ cells [31], highlighting that these cells may have a role in the progression of certain tumors [32]. As a matter of fact, Tumor-Associated Macrophages (TAMs) can exhibit both pro- and anti-inflammatory properties depending on the microenvironment and their polarization [33]. In tumors and endometriosis lesions, classically activated macrophages (M1) play a pro-inflammatory role exhibiting anti-tumor immunity, while alternatively activated macrophages (M2) display immunosuppressive properties contributing to tumor/lesion progression [33]. These data suggest that macrophages are important in inducing and maintaining the role of cancer stem cells and tumor progression by a close cross-talk among them. It has been described that in endometriotic lesions, M2 are higher than M1 favouring the lesion development [34]. This data suggest that endometriotic lesions could have similar features than cancerous tumors.

Regarding the eutopic endometrium, in normal conditions, M2 increase in the secretory and menstrual phases of the menstrual cycle which produces an anti-inflammatory phenotype favouring embryo implantation [34]. However, this increase does not occur in endometriosis endometrium [34]. We recently described that M2 in endometriosis exhibit a pro-inflammatory transcriptomic phenotype instead of their normal anti-inflammatory phenotype [35]. These results indicate that macrophages have functional defects in endometrium of women with endometriosis. In another study, we described that LGR5+ cells from eutopic endometrium of women with endometriosis overexpressed CD163 (marker of M2) and that these cells over-express unique genes in women with Deep Infiltrating Endometriosis (DIE) compared to other types of endometriosis and control patients [28]. These genes are related to immune system responses, hematological system development, and infertility, and could determine the aggressiveness of the disease, as well as impairement in reproductive outcomes by promoting a disadvantageous environment for embryo implantation [28]. In agreement with these results, a recent deconvolution meta-analyses described that the majority of macrophages in eutopic endometrium of women with endometriosis in advanced stages (III-IV) display a M2 phenotype [36]. By extrapolation, and knowing that half of the endometrial LGR5+ cells over-expressed a M2 macrophage phenotype, it is tempting to propose that LGR5+ cells could be involved in the modulation of the endometrial niche in eutopic endometrium of women with endometriosis. They could produce a higher pro-inflammatory phenotype in this tissue with deleterius consequences for the reproductive outcomes in women suffering from endometriosis.

In conclusion, LGR5 is considered to be a stem cell marker whose expresion remains constant throughout the menstrual cycle in healthy and endometriosis endometrium and it seems to not be influenced by progesterone. Moreover, the LGR5+ cells display EMT features. However, half of these cells co-express the pan-leukocyte marker CD45, illustrating a M2-like phenotype based on their transcriptomic profile. These macrophages have a unique genetic pro-inflamatory profile in the eutopic endometrium of women with DIE that could be imparing implantation and playing a role in infertility in patients with endometriosis. Furthermore, macrophages may also act as endometrial niche modulator cells. This accumulated evidence show that LGR5+ cells may play an important role in endometrial pathophysiology, since they seem to be involve in stemness but also in niche regulation (macrophages) influencing the normal homeostasis of the endometrium. Whether stem cells are affected by immune cells in eutopic endometrium and the role of LGR5 in this interaction is a great field of investigation but it is still unknown and warrants further investigation.

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