

ENDOMETRIAL STEM/PROGENITOR CELLS: CLINICAL RELEVANCE

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The human endometrium is a dynamic remodeling tissue undergoing more than 400 cycles of proliferation, differentiation, shedding and regeneration during a woman's reproductive years. Endometrial regeneration also follows parturition, almost complete resection and in post-menopausal women taking estrogen replacement therapy. Disorders of endometrial proliferation are common, leading to endometriosis, adenomyosis, endometrial hyperplasia and endometrial cancer. Injury to the endometrial lining may result in scarring and Asherman's syndrome, while endometrial hypo-proliferation may lead to an inadequate endometrium for embryo implantation in both natural and IVF cycles. We hypothesised that adult stem/progenitor cells are likely responsible for mediating the remarkable regenerative capacity of human endometrium, and that a consequence of their dysfunction maybe endometrial proliferative disorders and gynaecological disease.¹

Initial studies aimed at identifying adult stem/progenitor cells in human endometrium focused on functional approaches as there are no specific stem cell markers. Candidate epithelial and stromal stem/progenitor cells were first identified as clonogenic cells² and as side population (SP) cells.³ Clonogenic epithelial and stromal cells demonstrated defining adult stem cell attributes of self renewal, high proliferative potential and differentiation in vitro.⁴ Specifically, clonally-derived epithelial cells differentiated into large gland-like structures in 3D Matrigel cultures, and single clonogenic stromal cells underwent multilineage differentiation into 4 mesodermal lineages (adipogenic, smooth muscle, osteogenic and chondrogenic). Furthermore, dissociated human endometrial cells transplanted under the kidney capsule of immunocompromised mice reconstituted endometrial tissue with glands, stroma, and myometrium.⁵ Together these data support the concept that human endometrium harbours rare populations of two types of adult stem cell, an epithelial progenitor cell and a mesenchymal stem cell (MSC).

We recently identified the first set of markers that partially purifies human endometrial stromal cells with MSC-like properties.⁶ The co-expression of CD146 and PDGF-receptor β enabled the prospective isolation of a small population of clonogenic, multipotent stromal cells, which underwent differentiation into multiple mesenchymal lineages, and expressed surface markers characteristic of bone marrow MSC. Examining the co-expression of these markers in full thickness endometrial sections demonstrated that human endometrial MSC are located around blood vessels in both the basalis and functionalis layers, indicating that they may be shed during menstruation. Currently there are no known markers that identify endometrial epithelial progenitor cells.

Candidate endometrial epithelial and stromal stem/progenitor cells have been identified in vivo in mouse^{7,8} and human endometrium as label retaining cells (LRC). The LRC technique identifies adult stem cells on the basis of their relatively infrequent rate of cell division compared to more mature cells. In xenografts of human endometrium, epithelial LRC did not express estrogen receptor- α (ER α), as observed in mouse endometrium,⁷ suggesting that neighboring ER α -expressing niche cells transmit estrogen's proliferative signals to the candidate endometrial stem/progenitor cells. In mouse endometrium, many stromal LRC were found in a perivascular location at the endometrial-myometrial junction, coinciding with the location of human CD146⁺PDGFR β ⁺ MSC-like cells in human endometrium.

Endometrial carcinoma is the most common gynaecological malignancy in women and arises from hyperplastic or atrophic endometrium. Human endometrial epithelial stem/progenitor cells are the most likely targets of carcinogenesis in this tissue. These epithelial progenitors may acquire genetic mutations or epigenetic changes enabling them to transform into cancer stem cells, likely responsible for the initiation, maintenance, and progression of endometrial carcinoma. A small population of clonogenic cells has been identified in the 3 grades of type I endometrial endometrioid carcinoma, in type II tumours and in endometrial hyperplasia. Clonogenic endometrial carcinoma cells also underwent self renewal in vitro. Isolated endometrial carcinoma cells transplanted into immunocompromised mice generated tumors with similar morphology to the parent tumors. These tumors recapitulated cytokeratin, vimentin, ER α , and progesterone receptor expression of the parent tumor, indicating that the tumor-initiating cells differentiated into tumor cells comprising the bulk of the endometrial carcinoma. This evidence of rare cells with clonogenic, self-renewing, differentiating and tumorigenic properties suggests that these candidate cancer stem cells may be responsible for production of tumor cells comprising endometrial carcinoma.

Recent demonstrations of endometrial cells found in menstrual blood that express mesenchymal stem cell and pluripotency markers⁹ suggest that these cells maybe the perivascular MSC of the functionalis, and that they may play a role in the development of endometriosis if they are regurgitated into the peritoneal cavity during menstruation. Other evidence suggests that endometrial stem/progenitor cells may originate from bone-marrow-derived cells and that they may contribute to the progression of endometriosis lesions.¹⁰ These observations suggest that endometrial stem/progenitor cells may play a key role in the pathogenesis of endometriosis.

In summary, accumulating evidence indicates that rare populations of epithelial progenitors and MSC exist in human endometrium. The identification of markers that partially purify endometrial MSC has revealed their perivascular location in normal endometrium. These markers will facilitate a more detailed characterisation of endometrial MSC and will enable the investigation of their possible roles in the pathogenesis of endometrial proliferative disorders. However, there is a pressing need to identify markers of epithelial stem/progenitor cells. Preliminary evidence suggests that endometrial stem/progenitor cells may have clinical relevance to common gynaecological diseases associated with abnormal endometrial proliferation, such as endometriosis, and that endometrial cancer stem cells may be responsible for endometrial cancer initiation, progression and metastasis. The endometrium may also provide a readily available source of mesenchymal stem-like cells for tissue engineering purposes with possible applications in endometrial repair and urogynaecology.

¹Gargett CE Hum Reprod Update 2007;13:87-101; ²Chan RWS et al Biol Reprod 2004;70:1738-50; ³Kato K et al Hum Reprod 2007;22:1214-23; ⁴Gargett CE et al Biol Reprod 2009 (in press); ⁵Masuda H et al PNAS 2007;104:1925-30; ⁶Schwab KE & Gargett CE Hum Reprod 2007;22:2903-11; ⁷Chan RWS & Gargett CE Stem Cells 2006;24:1529-38; ⁸Cervello I et al Hum Reprod 2007;22:45-51; ⁹Patel AN et al Cell Transplan 2008; 13:303-11; ¹⁰Du H & Taylor HS Stem Cells 2007; 25:2082-6