Biology of Reproduction, 2022, **107(5)**,1166–1176
https://doi.org/10.1093/biolre/ioac158
Advance access publication date 10 August 2022
Review

Stromal cells of the endometrium and decidua: in search of a name and an identity†

Maria Jose Ruiz-Magaña[1], Tatiana Llorca[1,2], Rocio Martinez-Aguilar[1,2], Ana Clara Abadia-Molina[1,2], Carmen Ruiz-Ruiz[1,2,*] and Enrique G. Olivares[1,2,3,*]

[1]Instituto de Biopatología y Medicina Regenerativa, Centro de Investigación Biomédica, Universidad de Granada, Granada, Spain
[2]Departamento de Bioquímica y Biología Molecular III e Inmunología, Universidad de Granada, Granada, Spain
[3]Unidad de Gestión Clínica Laboratorios, Complejo Hospitalario Universitario de Granada, Granada, Spain

***Correspondence:** Departamento de Bioquímica y Biología Molecular III e Inmunología, Facultad de Medicina, Avenida de la Investigación, 11, Granada 18016, Spain. Tel: +34958246631; E-mail: mcarmenr@ugr.es; Tel: +34958248809; E-mail: engarcia@ugr.es

†**Grant Support:** Financial support was provided by Proyectos de I + D + I through the Programa Operativo Feder Andalucía (Grant B-CTS-228-UGR20).
Maria Jose Ruiz-Magaña and Tatiana Llorca, Carmen Ruiz-Ruiz and Enrique G. Olivares contributed equally to the work.

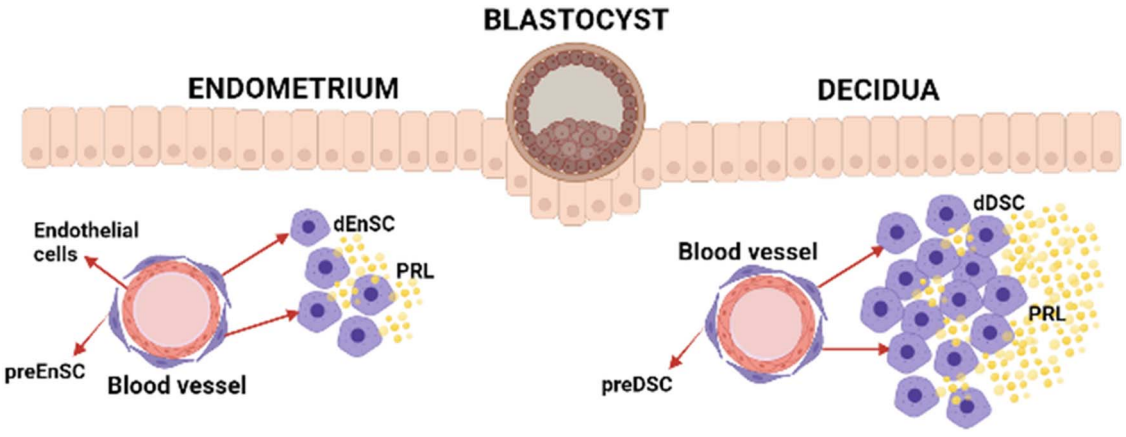
Abstract

Human endometrial and decidual stromal cells are the same cells in different environments (nonpregnancy and pregnancy, respectively). Although some authors consider decidual stromal cells to arise solely from the differentiation of endometrial stromal cells, this is a debatable issue given that decidualization processes do not end with the formation of the decidua, as shown by the presence of stromal cells from both the endometrium and decidua in both undifferentiated (nondecidualized) and decidualized states. Furthermore, recent functional and transcriptomic results have shown that there are differences in the decidualization process of endometrial and decidual stromal cells, with the latter having a greater decidualization capacity than the former. These differences suggest that in the terminology and study of their characteristics, endometrial and decidual stromal cells should be clearly distinguished, as should their undifferentiated or decidualized status. There is, however, considerable confusion in the designation and identification of uterine stromal cells. This confusion may impede a judicious understanding of the functional processes in normal and pathological situations. In this article, we analyze the different terms used in the literature for different types of uterine stromal cells, and propose that a combination of differentiation status (undifferentiated, decidualized) and localization (endometrium, decidua) criteria should be used to arrive at a set of accurate, unambiguous terms. The cell identity of uterine stromal cells is also a debatable issue: phenotypic, functional, and transcriptomic studies in recent decades have related these cells to different established cells. We discuss the relevance of these associations in normal and pathological situations.

Summary Sentence
Decidual stromal cells show a greater capacity for decidualization than endometrial stromal cells, so studies of these stromal cells should clearly distinguish between these two cell types.

Graphical Abstract

Decidualization from precursor endometrial stromal cells (preEnSCs) to decidualized endometrial stromal cells (dEnSCs) in the endometrium, and from precursor decidual stromal cells (preDSCs) to decidualized decidual stromal cells (dDSCs) in the decidua. Figure created in BioRender.com



Keywords: decidual stromal cells, decidualization, endometrial stromal cells, endometriosis, follicular dendritic cells, mesenchymal stem cells, perivascular cells

Received: April 8, 2022. **Revised:** July 29, 2022. **Accepted:** August 2, 2022

Introduction

The decidua constitutes the maternal part of the placenta in intimate contact with the fetal trophoblast, and develops in mammals (including humans) with hemochorial placentation. It is responsible for the regulation of maternal–fetal tolerance and the control of trophoblast invasion [1–3]; in the absence of decidua, excessive trophoblast invasion occurs and results in placenta accreta [4]. During the late luteal phase of the menstrual cycle, the nonpregnant endometrium undergoes a process of differentiation (decidualization) controlled by progesterone and other ovarian hormones. If pregnancy does not occur, the endometrium is shed with menstruation, but if blastocyst implantation takes place, the decidualization process continues through the effect of pregnancy hormones, and the endometrium gives rise to the decidua [5]. Decidualization directly or indirectly involves all cells of the endometrium and decidua, that is, stromal, epithelial, endothelial, and immune cells [6], but it is the endometrial and decidual stromal cells (EnSCs and DSCs) which have been most thoroughly investigated during this process [7]. Uterine stromal cells (uSCs) of both the endometrium and decidua have been analyzed in two different cellular situations, that is, undifferentiated and differentiated (decidualized), and in two different physiological locations, that is, the endometrium (nongestation) and decidua (gestation). The decidualization of uSCs is, however, a dynamic multistep process that involves: (1) fibroblast proliferation around the vessels; (2) distancing of the differentiated cells from the vessels and extravascular localization; (3) changes in cell morphology toward a rounded or polygonal shape (Figure 1); and (4) secretion of factors such as prolactin (PRL) and insulin-like growth factor-binding protein 1 (IGFBP1) [8, 9].

Uterine stromal cells have been studied at different stages of differentiation, and named accordingly, in prior histological studies [7, 10–14] and more recent transcriptomic analyses [15–19]. However, there is considerable confusion in the terms used to designate these cells, which arises primarily because some authors use the term decidual to refer only to differentiation (decidualization) from undifferentiated endometrial stromal cells [9, 16, 20, 21], whereas others use this term simply to indicate localization in the decidua of either differentiated or undifferentiated DSCs [22, 23]. Although EnSCs and DSCs are the same cells in two different physiological contexts, recent results have shown that DSCs have a greater capacity for decidualization than EnSCs [18, 19, 24]. These differences suggest that EnSCs and DSCs should be clearly distinguished taking into account both criteria, that is, differentiation and localization. In this article, we propose a set of terms for different uSCs based on the combination of both criteria. In addition, we discuss the phenotypic and functional characterization of uSCs and their relationships with different established cell types, in order to shed additional light on the nature and identity of these cells.

In search of a name

Names, abbreviations, confusion, and a proposal

According to early histological studies of the nongestational endometrium, undifferentiated, elongated stromal cells (fibroblasts) in the vicinity of the vessels undergo mitosis and differentiate into rounded, polygonal cells, increase in size and become epithelioid in appearance, leave the vessels, and spread to the upper two-thirds of the tissue. This process of differentiation in the endometrium was termed the predecidual reaction, and the differentiated endometrial stromal cells were called predecidual cells. Upon implantation, the process of differentiation continues from perivascular fibroblasts, and by convention, the endometrium was referred to as the decidua, and the differentiated stromal cells were termed decidual cells (Table 1) [7, 10–14, 25].

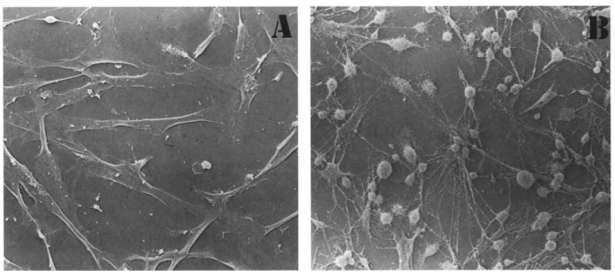


Figure 1. Effects of in vitro decidualization on decidual stromal cell morphology. (A) Undifferentiated decidual stromal cells (preDSCs) showed fibroblast-like morphological features. (B) Decidualized decidual stromal cells (dDSCs) showed a rounded morphology. 200×. From [23], with permission.

The acronym ESC used by some authors [19, 20, 26–28] to refer to endometrial stromal cells is used more frequently as the abbreviation for embryonic stem cells, and is thus potentially confusing. Instead, many authors use EnSCs as the abbreviation for endometrial stromal cells [16, 24, 29]. Another potential source of confusion is use of the term decidual cells and its abbreviation DC to refer to differentiated EnSCs [16], despite the fact that DC is a well-established and more widespread abbreviation for dendritic cells. A 1995 study [9] used the term precursor decidual cells for undifferentiated fibroblasts in the decidua, thus reflecting both differentiation and location criteria. Following on from this designation, Olivares et al. [23] used DSC precursors or predecidual stromal cells (preDSCs) for undifferentiated decidual stromal cells, and decidualized decidual stromal cells (dDSCs) for the differentiated cell counterpart. The abbreviation preDSCs to indicate undifferentiated decidual stromal cells was used thereafter by others [30, 31]. The acronym dDSC is not redundant, as the lower case d indicates the differentiation stage (decidualization) while the upper case D denotes the location (decidua). To collectively designate preDSCs and dDSCs, the acronym DSCs has been used. This is the system proposed for DSCs in a consensus paper on terminology for human placental cells [32]. In consonance with these terms, endometrial stromal cells precursors were designated preEnSCs, and decidualized endometrial stromal cells were called dEnSCs. The collective term EnSCs is used for preEnSCs and dEnSCs [24, 33]. Thus, uSCs decidualize from preEnSCs in the endometrium during the menstrual cycle, and from preDSCs in the decidua during pregnancy [9, 23, 34].

Decidualization, however, like all differentiation processes, is a multistage process with intermediate steps between precursors and differentiated cells. Recent transcriptomic studies of the human endometrium and decidua confirmed the existence of successive cell stages from undifferentiated uSCs ("pre") to decidualized cells ("d"), with the expression of PRL and other genes such as *IGFBP1* as markers of terminal decidualization stages [16–19, 35]. In light of these antecedents for terminology and usage, below, we will use the abbreviations EnSCs and DSCs and their derivatives for stromal cells of endometrium and decidua, respectively.

Table 1. Terms used to designate stromal cells in the human endometrium and decidua

Method of isolation	Methods of study	Tissue	Undifferentiated uterine stromal cells	Differentiated uterine stromal cells	References
Tissue sections	Light microscopy, electron microscopy	Endometrium Decidua (different gestational ages)	Fibroblasts, endometrial stromal fibroblasts, fibroblast-like cells (FLC)	Predecidual cells, pseudodecidual cells Decidual cells	[7, 10–14]
	Immunohistochemistry	Endometrium Decidua (different gestational ages)	Endometrial stroma cells (ESC) Predecidual stroma cells (preDSC)[a]	Predecidual stroma cells (preDSC) Decidual stroma cells (DSC)	[31]
Tissue digestion and density gradient isolation	Inmunocytochemistry	Decidua (8–17 weeks)	Decidual cells	Large round PRL+ decidual cells	[87]
		Decidua (term)	Decidual cells	Decidualized cells	[21]
Tissue digestion and cell culture	RIA, SDS-PAGE, RNA blot hybridization analysis	Endometrium (proliferative and secretory phases)	Endometrial stromal cells	PRL-producing endometrial stromal cells	[88]
	Immunocytochemistry, RIA	Endometrium (proliferative phase)	Endometrial stromal cells	Decidualized cells	[21]
	Immunocytochemistry, RIA, RNA blot hybridization analysis, flow cytometry, western blot	Endometrium (proliferative phase) Decidua (term)	Endometrial stromal cells Decidual fibroblast cells, precursor decidual cells	Decidualized endometrial stromal cells Terminally differentiated decidual cells	[9]
	Immunohistochemistry, flow cytometry	Decidua (first trimester)	Stromal cell precursors (preDSCs)	Decidualized cells (dDSCs)	[23]
	Flow cytometry, immunofluorescence	Decidua (first trimester)	Predecidual stromal cells (PreDSCs)	Differentiated decidual stromal cells (DSCs)	[22]
	SC-RNA sequencing, immunohistochemistry	Endometrium (secretory phase)	Endometrial stromal cells (EnSCs)	Decidual cells (DCs)	[16]
	Flow cytometry, ELISA, RT-PCR, western blot	Endometrium (proliferative and menstrual phase)	preEnSCs	Decidualized EnSCs	[24]
Tissue digestion, cell sorting, and cell culture	Microarray analysis, qRT-PCR, immunocytochemistry, immunofluorescence	Endometrium (proliferative and secretory phases)	Endometrial stromal fibroblasts (eSF)	Decidualized eSF	[71]
Tissue digestion, magnetic bead separation, and cell culture	Immunocytochemistry, RNA sequencing, qRT-PCR, western blot, multiplex suspension bead immunoassay	Endometrium (secretory phase)	Endometrial stromal fibroblasts (eSF)	Decidual cells	[39]
Tissue digestion, fresh cells	SC-RNA sequencing flow cytometry, immunohistochemistry	Decidua (first trimester)	Perivascular cells (PV)	Decidual stromal cells (dS)	[18]
	SC-RNA sequencing, immunofluorescence	Endometrium (all phases)	Stromal fibroblasts	Decidualized stromal fibroblasts	[19]
	SC-RNA sequencing flow cytometry, immunohistochemistry, in situ hybridization	Endometrium (all phases)	Stromal-nondecidualized endometrial (eS) population	Decidualized endometrial (dS) population	[15]
Established cell lines	RNA sequencing	Endometrium[b]	Endometrial stromal fibroblasts (ESF)	Decidual stromal cells (DSC)	[20]
	qRT-PCR, immunoblotting, immunofluorescence. Immunohistochemistry, RNA sequencing	Induced pluripotent stem cell lines	Endometrial stromal fibroblasts (EMSFs)	In vitro decidualization (IVD)	[46]
	qRT-PCR, immunoblotting, in situ hybridization, RNA sequencing	Embryonic stem cell lines, induced pluripotent stem cell lines	Endometrial stromal fibroblasts (ESF)	Decidualized ESFs (dESFs)	[45]

[a]Cells in an intermediate differentiation stage between undifferentiated and fully decidualized DSCs. [b]These authors used the term *endometrial stromal cells* (ESC) as a collective term for both endometrial stromal fibroblasts (ESF) and decidual stromal cells (DSC).

Differences between endometrial and decidual stromal cells

As noted earlier, EnSCs and DSCs are obviously the same cells, although they are located in different physiological environments (nongestation and gestation). It is plausible, however, that the gestational environment induces phenotypic and functional variations in uSCs. For example, Richards and colleagues [9] found differences in the decidualization capacity of EnSCs and DSCs in vitro. Moreover, Kyurkchiev and colleagues [30] reported that EnSCs had a restricted potential for in vitro differentiation compared to DSCs. Ruiz-Magaña and colleagues compared preEnSC lines from menstrual blood and endometrial biopsies with preDSC lines from the first trimester of pregnancy, and found that the two cell types had an equivalent antigenic phenotype similar to that of mesenchymal stem cells (MSCs) (Table 2). Compared to preEnSCS, however, preDSCs showed a significantly greater capacity for decidualization in vitro (estimated as the proportions of rounded cells, cells in apoptosis, and the amount of PRL secretion by dEnSCs and dDSCs) [24]. Decidualization is the result of a dialog between cAMP signaling and progesterone receptor (PGR) signaling [36]. Increased intracellular cAMP sensitizes uSCs to the action of progesterone, while cAMP activates protein kinase A (PKA)—an enzyme consisting of two regulatory subunits (PKA R) and two catalytic subunits (PKA C)—thereby inducing dissociation of both types of subunit. The dissociated PKA C subunits phosphorylate cytoplasmic target proteins, diffuse into the nucleus, and modulate the activity of transcription factors by phosphorylation [37]. These factors may interact with ligand-activated PGR to initiate transcription of decidua-specific genes [36]. When EnSCs and DSCs were compared, no difference was found in either basal or decidualization-induced PGR protein expression. Moreover, decidualization did not regulate PKA C protein expression, and no differences in expression were detected between dEnSCs and dDSCs. The protein expression of PKA R was, however, significantly greater in dDSCs than in dEnSCs, although the downstream effects of this difference on activated transcription factors remain to be investigated [24]. The authors concluded that the environment of pregnancy plays a role, and that the decidualization capacity of uSCs increased from the endometrium to the decidua [24].

Interestingly, this process is halted in diseases such as endometriosis [38]. The differences between EnSCs and DSCs observed in cell lines were confirmed in single-cell RNA sequencing (SC-RNA seq) studies of fresh cells, in which low numbers of dEnSCs expressing PRL in the mid-to-late secretory phase of the menstrual cycle were detected compared to the higher numbers of PRL-expressing dDSCs detected in first-trimester decidua [18, 19]. In view of these findings, as described in the previous section, we proposed that localization together with differentiation status should be used to name the different uSCs [32]. It should be noted, however, that some authors [16, 20, 39] have used the terms decidual cells or DSC to designate differentiated EnSCs (Table 1)—a usage that is inconsistent with the differences noted earlier between these two populations of cells.

In search of an identity

Hematopoietic or mesenchymal identity?

The possible origin of DSCs in bone marrow, the expression of antigens associated with hematopoietic cells, and the development of immune activities led some earlier authors to suggest that DSCs were potential hematopoietic cells [34, 40, 41]. However, the finding that MSCs also originated from bone marrow [42], together with the absence of CD45 expression (leucocyte common antigen) and the expression of mesenchymal markers by DSCs, supported their mesenchymal lineage albeit without contradicting the possible origin of DSCs in bone marrow [43]. In addition, early histological studies based on morphological features indicated that undifferentiated uSCs were fibroblasts (Table 1). Furthermore, the expression of α-smooth muscle actin (ACTA2), vimentin (VIM), and desmin—cell filaments detected in DSCs—along with the contractile activity of these cells, linked DSCs to other contractile mesenchymal cell types such as myofibroblasts, vascular smooth muscle cells (vSMCs), and pericytes [43, 44]. Recently, some authors reported the in vitro differentiation of human pluripotent stem cells to endometrial stromal fibroblasts (eSFs), which confirmed the inclusion of uSCs in the mesenchymal lineage [45, 46]. This differentiation involved sequential steps through a series of intermediate progenitor

Table 2. Antigen expression by human preEnSC, preDSC, bone marrow MSC, and preFDC lines obtained and maintained in equivalent culture conditions, as determined by flow cytometry [24, 47, 48, 57, 66, 80, 85, 89]

Antigen	preEnSCs	preDSCs	BM-MSCs	PreFDCs
CD10[a,b]	+	+	+	+
CD13[b]	+	+	+	+
CD15	−	−	−	−
CD19[c]	−	−	−	ND
CD29[b]	+	+	+	+
CD31	−	−	−	−
CD34[c]	−	−	−	−
CD44[b]	+	+	+	+
CD45[c]	−	−	−	−
CD54	+	+	+	+
CD62P	−	−	−	ND
CD73[b,c]	+	+	+	+
CD90[b,c]	+	+	+	+
CD105[b,c]	+	+	+	+
CD106	−/+[d]	−/+[d]	−/+[d]	−/+[d]
CD140b[e]	+	+	ND	+
CD146[e]	+	+	+	−
α-SM actin[b]	+	+	+	+
BAFF[f]	+	+	−	+
CXCL12	+	+	ND	+
CXCL13[f]	+	+	−	+
Cytokeratin	−	−	ND	ND
HLA-DR[c]	−	−	−	−
HLA-G	−/+[d]	−/+[d]	−	ND
MFGE8[f]	ND	+	ND	+
Nestin[b]	+	+	+	+
OCT3/4	+	ND	+	ND
Podoplanin[b]	+	+	+	+
Prolactin[g]	+	+	−	+
STRO-1	−/+[d]	+	+	+
SUSD2[e]	+	+	+	ND

preEnSC: data from cell lines obtained from menstrual blood and endometrial biopsies; preDSC: from first trimester pregnancy; BM-MSC: from bone marrow aspirates; preFDC, from tonsillectomies. ND, not determined. [a]Endometrial stomal cell marker. [b]Antigens expressed by more than 95% of cells. [c]Antigens meeting the minimal criteria for identification as mesenchymal stem cells [58]. [d]Some lines expressed the antigen and some did not. [e]Endometrial mesenchymal stem cell marker. [f]Follicular dendritic cell marker. [g]Under decidualization conditions.

cells that, according to the authors, mimic the in vivo stages of uterine development during embryogenesis: pluripotent stem cells, intermediate mesenchymal progenitors, Müllerian duct progenitors, and endometrial stromal progenitors. Expression of the mesenchymal lineage markers platelet-derived growth factor beta (CD140b), and VIM by these latter cells supported their identity as a type of mesenchymal cell. Endometrial stromal progenitors were then further differentiated to eSFs. These eSFs were finally decidualized, as confirmed by the expression of decidualization markers FOXO1, PRL, HAND2, and IGFBP1 [45, 46]. The expression of CD140b and VIM by preEnSC and preDSC lines, and the ability of these lines to decidualize, confirm the relationship of these cells with endometrial stromal progenitors (Table 2) [24, 43, 45, 47].

Perivascular cells

First-trimester preDSC and preEnSC lines were reported to have the following antigenic phenotype: CD45− CD34− ACTA2+ CD140b+ CD146+ SUSD2+ PRL− [47, 48]. Clones obtained from these cell lines showed the same antigenic phenotype and functional properties as the original lines, indicating that these lines comprised a uniform cell population. Confocal microscopic examination of first-trimester decidua sections showed that cells with this antigenic phenotype were located in the intima and media of decidual vessels [47, 48] (Figure 2). The fact that perivascular cells present in the intima (pericytes) and in the media (vSMCs) of the vessels expressed the same antigens as those detected in preDSCs [49] confirms a close relationship between these latter cells and the former two types of perivascular cell [47]. Interestingly, all these cell types additionally show contractile capacity as indicated by ACTA2 expression, which further supports their relatedness [47, 49, 50]. Studies of first-trimester human decidua with SC-RNA seq supported this conclusion, as two perivascular stromal cell populations (PV1 and PV2) expressed the same CD45− CD34− ACTA2+ CD140b+ CD146+ SUSD2+ PRL− antigen profile as preDSCs [18, 47]. Darzi and colleagues also associated CD140b, CD146, and SUSD2 expression with perivascular cells in the endometrium [51]. Wang and colleagues, in their SC-RNA seq study of cells in the human endometrium, detected different ACTA2+ vSMC populations that expressed CD140b, CD146, and SUSD2 [19]. Likewise, SC-RNA seq studies in the mouse endometrium identified two populations of perivascular cells: CD45− ACTA2+ CD140b+ CD146+ vSMCs, and CD45− ACTA2− CD140b+ CD146+ pericytes [52]. The perivascular localization places these cells in a privileged position in the processes of leucocyte chemotaxis from the peripheral blood to the endometrium and decidua. Indeed, preDSCs have been found to exert a chemotactic effect on peripheral blood natural killer cells and monocytes [47, 48, 53]. Moreover, the contractile activity of uSCs may have an effect on blood flow in the vessel they surround [44, 47].

Decidualization induces changes in the morphology, localization, antigenic phenotype, and functions of uSCs (Figure 1). Upon decidualization by progesterone and cAMP of preDSC lines, a significant decrease in the expression of ACTA2, CD140b, CD146, and SUSD2 was observed, along with the expression of decidualization markers (PRL, FOXO1) in differentiated cells (dDSCs) (Figure 3) [24, 48]. These in vitro data are consistent with results obtained in vivo. In decidua sections analyzed by confocal microscopy, a decrease in the expression of ACTA2, CD140b, CD146, and SUSD2 was also detected in dDSCs located away from the vessels [48] (Figure 2). Equivalent results were observed in three subpopulations of dDSCs from first-trimester human decidua identified by SC-RNA seq (designated dS1, dS2, and dS3): decreased expression of ACTA2, CD140b, CD146, and SUSD2, along with increased expression of PRL, IGFBP1, and FOXO-1 [18] (Figure 3). Garcia-Alonso and colleagues also used SC-RNA seq to study the human endometrium, and found a stromal-nondecidualized endometrial (eS) population and a decidualized endometrial (dS) population, the latter also showing decreased ACTA2 expression and increased decidualization markers IGFBP1, FOXO1, and IL15 [15]. In other work done in vitro, human pluripotent stem cells were differentiated to eSFs, and after decidualization, these latter cells also showed a decrease in CD140b and SUSD2 expression [45, 46]. Antigens such as CD140b, CD146, and SUSD2 participate in the interaction of stromal cells with endothelial cells, in vascular homeostasis, and in angiogenesis [54], so that the distance between dEnSC or dDSCs and the vessels probably determines the degree to which their expression is inhibited. The same phenomenon occurs with CD140b expression by perivascular precursors of follicular dendritic cells (FDC), which inhibited the expression of this antigen upon differentiation in the extravascular space [55]. (A more detailed comparison of FDC and uSCs is provided later in the section headed Lymph node stromal cells.) The expression of ACTA2 by preEnSCs and preDSCs shapes the fibroblastic appearance of these cells in vitro and in vivo. Upon decidualization and decreased expression of this protein, contractility decreases and the cells adopt a rounded appearance [47]. Attenuation of this activity is probably involved in successful blastocyst implantation [56].

Bone marrow MSCs and endometrial MSCs

It was recently shown that human preDSC lines exhibit an antigenic phenotype compatible with that of bone marrow mesenchymal stem cells (BM-MSCs) (Tables 2 and 3). Predecidual stromal cells express stem cell markers, have clonogenic activity, differentiate to the mesenchymal lineage, and show immunoregulatory activity in vivo and in vitro [57] (Table 3). Furthermore, preDSCs meet the minimal criteria proposed by the International Society for Cellular Therapy to define human MSCs [58], so preDSCs may be considered authentic MSCs in the decidua. Studies with preDSC clones demonstrated that cells with the capacity to decidualize also presented the characteristics of MSCs [57]. Equivalent results were reported by other authors in research with preEnSCs [22, 24, 59]. The fact that preEnSCs and preDSCs, as discussed earlier, are related to perivascular cells, which in turn have properties of MSCs [60, 61], supports the association of uSCs with MSCs. Nevertheless, when BM-MSC lines were decidualized in vitro under conditions equivalent to preDSCs and preEnSCs, it was observed that like decidualized uSCs, BM-MSCs changed their morphology to a round shape and expressed PRL mRNA, but unlike decidualized uSCs, BM-MSCs were unable to secrete PRL. This indicates that despite the possible origin of uSCs from BM-MSCs [62–65], the latter must colonize the endometrium and decidua so that the molecular microenvironment allows them to acquire the characteristics of uSCs [24, 66]. Research in mice and humans has shown that cells from the bone marrow colonize the uterus in adulthood, primarily in response to endometrial inflammation and pregnancy [62–65]. Several authors have

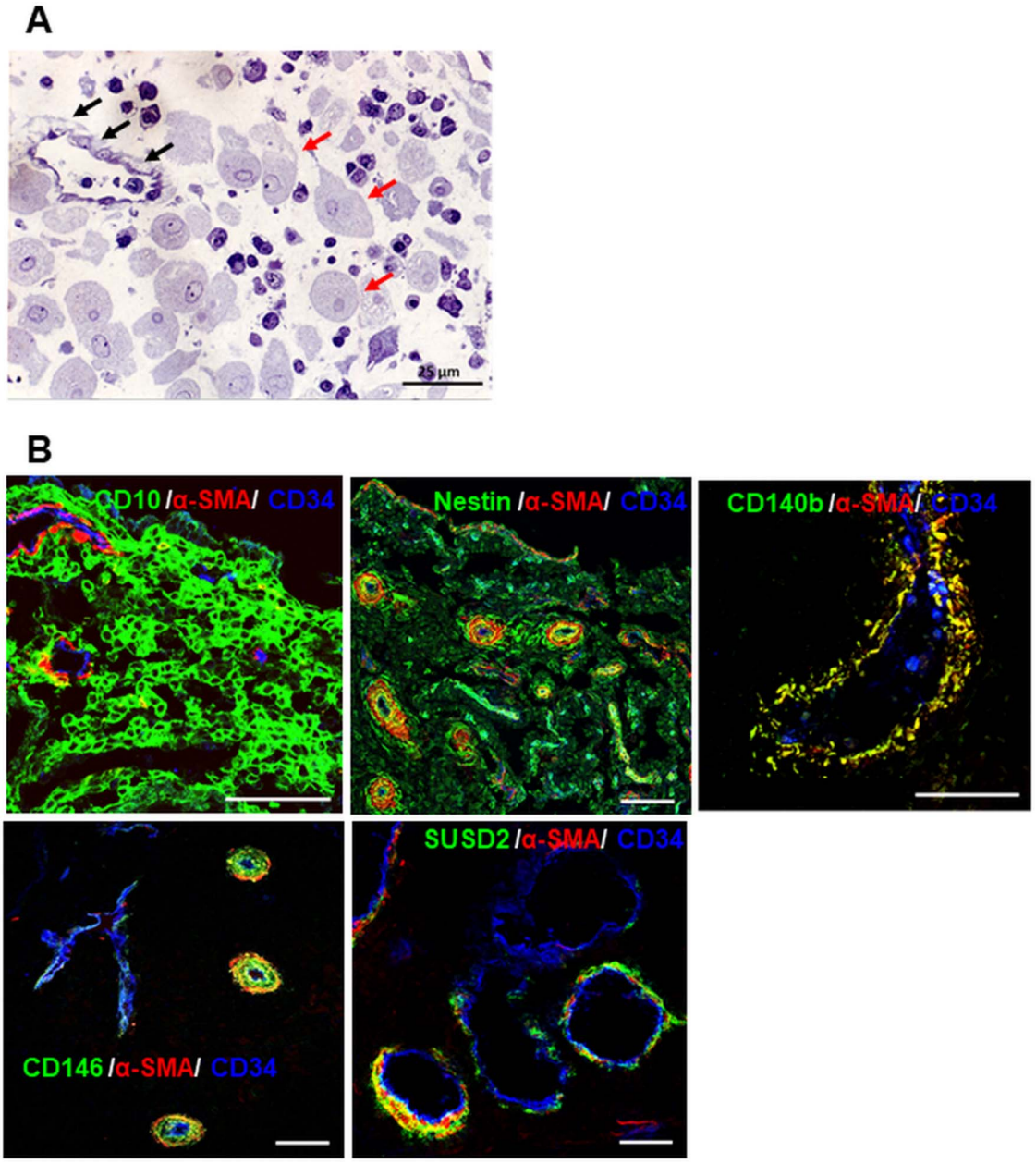


Figure 2. Decidual stromal cells in first-trimester human decidua. (A) Semithin cryostatic section of early human decidua stained with toluidine blue, showing preDSCs (black arrows) and dDSCs (red arrowheads). Scale bar: 25 μm. (B) Perivascular α-SM actin-positive cells coexpressed CD10, nestin, CD140b, CD146, and SUSD2. Anti-CD34-stained endothelial cells. Scale bars: 100 μm. These experiments were done in four independent samples. From [48], with permission.

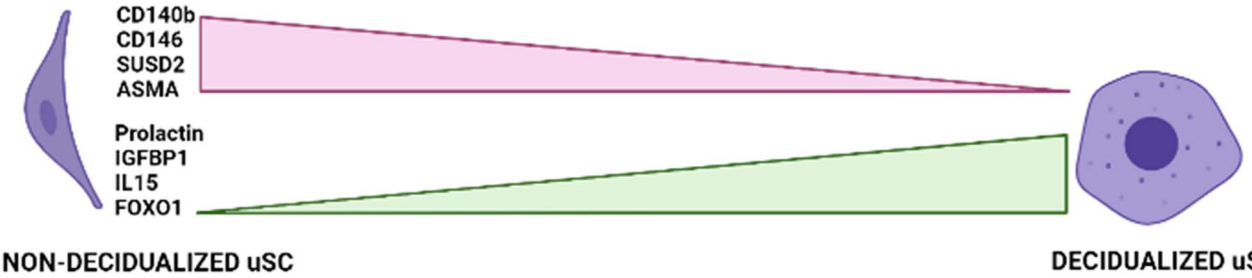


Figure 3. Evolution of the expression of different markers by uSCs during the decidualization process. Figure created in BioRender.com.

also identified cells with the characteristics of MSCs in the human endometrium, for example, endometrial MSCs or eMSCs. These multipotent, clonogenic, self-renewing cells have the capacity to differentiate in vitro into mesenchymal lineages. Like preEnSCs and preDSCs, eMSCs express MSC markers (together with CD140b, CD146, and SUSD2), exert

Table 3. Comparison of the phenotypic and functional characteristics of bone marrow mesenchymal stem cells (BM-MSCs), endometrial mesenchymal stem cells (eMSCs), precursors of endometrial and decidual stromal cells (preEnSCs/preDSCs), and precursors of follicular dendritic cells (preFDCs)

Criteria considered	BM-MSCs	eMSCs	preEnSCs/preDSCs	preFDCs	References
Antigen phenotype (see Table 2)					[24, 47, 48, 51, 57, 66, 71, 80, 85, 89, 90]
-Endometrial stomal cell marker CD10	+	+	+	+	
-MSC/pericyte markers	+	+	+	+	
-eMSC markers (CD140b, CD146, SUSD2)	+	+	+	+	
-FDC markers	−	ND[a]	+	+	
International Society for Cellular Therapy minimal criteria	+	+	+	+	[24, 57, 58, 89, 91, 92]
Perivascular location	+(Bone marrow)	+ (Endo-metrium)	+(Endo-metrium, decidua)	+ (Secon-dary lymphoid organs)	[11, 47, 55, 60, 70, 71, 89]
Pluripotency stem cell factors	+(OCT-4, NANOG[a]	−(OCT-4, NANOG)	+ (OCT-4, NANOG, ABCG)	+ (OCT-4)	[57, 89, 93–96]
Clonogenicity	+	+	+	+	[57, 69, 89, 92, 97]
Mesenchymal differentiation	+	+	+	+	[57, 58, 89, 91, 92]
Decidual differentiation	−	+	+	+	[24, 66, 73]
Apoptosis resistance	+	ND	+	+	[89, 98, 99]
Cell contractility	+	ND	+	+	[44, 47, 80, 100–102]
Chemotactic activity	+	ND	+	+	[47, 48, 89, 103]
In vitro immunoregulatory activity	+	+	+	+	[66, 80, 89, 104–108]
In vivo immunoregulatory activity	+	+	+	ND	[57, 106, 109–113]
Haematopoietic cell supportive activity	+	ND	+	+	[66, 80, 89, 104, 114, 115]
Presence in ectopic sites	ND	+	+	+	[73, 82, 83, 116]

ND: Not determined.[a]Positive in fetal BM-MSCs, negative in adults.

immunoregulatory activity in vivo and in vitro, decidualize, are located in perivascular areas, and are related to pericytes and vSMCs (Table 3) [51, 67–71]. Furthermore, MSCs with properties similar to eMSC were also detected in the human term decidua basalis [72]. It was shown that eMSCs are precursors of eSFs, and upon decidualization these cells down-modulate the expression of CD146 and SUSD2 while up-modulating the expression of decidualizing markers such as PRL [39, 71, 73], as was also found in dDSCs [18, 48]. Although preEnSCs and preDSCs were obtained by selection in cultures of endometrial and decidual samples, respectively [24], whereas eMSCs were obtained from the endometrium with monoclonal antibodies and cell sorting [51], their phenotypic and functional characteristics, perivascular localization, and capacity for decidual and mesenchymal differentiation suggest a close relationship among these three cell types (Table 3). Therefore, preEnSC, preDSC, and eMSC (from the endometrium or decidua) are probably the same cell type located in perivascular areas (intima and media), that differentiate into fibroblasts surrounding the vessels. These fibroblasts continue to differentiate, moving away from the vessels and developing into decidualized round cells that inhibit the expression of CD140b, CD146, SUSD2, and ACTA2, and express PRL along with other markers of decidualization.

Lymph node stromal cells

In mouse and human tissues, different populations of lymph node stromal cells (LNSCs) have been identified on the basis of their location and chemokine expression profiles [74, 75]. These stromal cells display chemotaxis, lymphocyte antiapoptotic activity, and differentiation, thus contributing to the organization of secondary lymphoid organs (SLOs), and helping to regulate immune responses and mediate immune tolerance [74, 76, 77]. Moreover, LNSCs are crucial in the formation of tertiary lymphoid structures (TLSs)—ectopic foci that develop at sites of chronic inflammation [78]. One type of LNSCs is FDCs, that is, cells located in the follicles of SLOs [79]. There is evidence of a relationship between DSCs and FDCs based on similarities in their antigen phenotype (CD45− CD31− CD21+ CD35+ BAFF+ CXCL13+ podoplanin+), as well as their lymphocyte antiapoptotic activity, cell contractility, and the perivascular location of their precursors. Furthermore, FDC precursors (preFDCs), like preDSCs, can be decidualized in vitro, as evidenced by the change of decidualized FDC to a rounder cell morphology and their secretion of PRL [47, 66, 80]. In addition, like DSCs, FDCs are also related to MSCs [66, 81] (Tables 2 and 3). In this connection, a transcriptomic analysis of human FDCs, EnSCs, and mesenchymal cell types demonstrated that FDCs

and EnSCs are closely related, and that both types of cells are also related to MSCs [20]. Furthermore, Krautler and colleagues demonstrated that mouse preFDCs derived from perivascular cells expressed CD140b and MFGE8 [55], two antigens also expressed by human preDSCs [47] (Table 2). Like FDCs in TLSs, DSCs and EnSCs have been detected in ectopic foci: DSCs were found in deciduosis, and EnSCs were observed in endometriosis [82, 83].

Endometrial stromal cells in ectopic sites: endometriosis

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterus, most frequently in the peritoneum and on the ovaries, although endometriosis foci may occur in distant locations such as the skin, nasal mucosa, brain, and lung. The relationship between EnSCs and MSCs may explain the presence of endometriosis foci in distant extraperitoneal locations. In these cases, MSC-related precursors transported by the blood from the bone marrow may home to these tissues erroneously [84]. In addition, MSC-related preEnSCs present in menstrual blood may induce peritoneal foci by retrograde menstruation [24, 84, 85]. As noted in the previous section, EnSCs and DSCs share phenotypic and functional properties with FDCs [20, 47, 55, 66, 80], and one of their common characteristics is the presence of stromal cells in ectopic foci associated with inflammatory tissues [78] (Tables 2 and 3). Endometriosis may represent a situation equivalent to TLSs. Although the decidua and the endometrium cannot be considered SLOs (because they both lack the characteristic compartmentalization in T and B zones), uSCs share many characteristics with LNSCs, one of them being their presence in ectopic sites [33]. Like FDCs, EnSCs may attract leucocytes to ectopic sites. Interactions between EnSCs and macrophages appear to be essential in the maintenance of these foci [86]. In a murine cell model of endometriosis, Martinez-Aguilar and colleagues demonstrated that the intraperitoneal injection of human preEnSCs in mice generated endometriotic-like nodules. The presence in these nodules of human preEnSCs together with murine macrophages demonstrated the chemotactic activity of preEnSCs on macrophages in nodule formation [85]. In the search for new approaches to treatment, potentially informative avenues of study are to elucidate the molecular dialog between EnSCs and macrophages during the development of endometriosis, to identify the molecules that participate in this dialog, and to determine whether they could be blocked with chemokine receptor antagonists.

Conclusions

The process of decidualization from uSC precursors (preEnSCs and preDSCs) occurs in both the endometrium and the decidua, and is an active process throughout pregnancy. Although preEnSCs and preDSCs correspond to the same cell type, the latter display a greater decidualization capacity, probably determined by the gestational environment. Because of these differences, studies of uSCs should take into account and identify not only their differentiation stage, but also their location in the endometrium or decidua. Studies of the antigenic phenotype, localization, functions, and transcriptome demonstrate that preEnSCs and preDSCs are perivascular cells closely related to MSCs. These uSCs also show close relationships with FDCs, and like these latter cells, uSCs can be detected in ectopic locations as in endometriosis.

Conflict of interest

The authors have declared that no conflict of interest exists.

Data availability

There are no new data associated with this article.

Authors' contributions

M.J.R.-M. developed the content, focus, and organization of the manuscript, carried out the literature search, prepared the figures and tables, reviewed the manuscript, and approved the final version. T.L. developed the content, focus, and organization of the manuscript, carried out the literature search, prepared the figures and tables, reviewed the manuscript, and approved the final version. R.M.-A. developed the content, focus, and organization of the manuscript, carried out the literature search, reviewed the manuscript, and approved the final version. A.C.A.-M. developed the content, focus, and organization of the manuscript, drafted and reviewed the manuscript, and approved the final version. C.R.-R. conceived the idea, developed the content, focus, and organization of the manuscript, drafted and reviewed the manuscript, approved the final version, and coordinated the team of authors. E.G.O. conceived the idea, developed the content, focus, and organization of the manuscript, drafted and reviewed the manuscript, approved the final version, and coordinated the team of authors.

Acknowledgment

This article contributes to COST Action CA17116 "International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches (SPRINT)," supported by COST (European Cooperation in Science and Technology). We thank K. Shashok for editing the English text of the manuscript.

References

1. Macklon NS, Brosens JJ. The human endometrium as a sensor of embryo quality. *Biol Reprod* 2014; **91**:98.
2. Nancy P, Tagliani E, Tay CS, Asp P, Levy DE, Erlebacher A. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. *Science* 2012; **336**: 1317–1321.
3. Sharma S, Godbole G, Modi D. Decidual control of trophoblast invasion. *Am J Reprod Immunol* 2016; **75**:341–350.
4. Jauniaux E, Burton GJ. Placenta accreta spectrum: a need for more research on its aetiopathogenesis. *BJOG* 2018; **125**: 1449–1450.
5. Moffett A, Loke C. Immunology of placentation in eutherian mammals. *Nat Rev Immunol* 2006; **6**:584–594.
6. Ramathal CY, Bagchi IC, Taylor RN, Bagchi MK. Endometrial decidualization: of mice and men. *Semin Reprod Med* 2010; **28**: 017–026.
7. Pakurar ASBJ, Bigbee JW. *Digital Histology*. John Wiley & Sons, Inc, Hoboken, New Jersey; 2004.
8. Bergeron C. Morphological changes and protein secretion induced by progesterone in the endometrium during the luteal phase in preparation for nidation. *Hum Reprod* 2000; **15**: 119–128.

9. Richards RG, Brar AK, Frank GR, Hartman SM, Jikihara H. Fibroblast cells from term human decidua closely resemble endometrial stromal cells: induction of prolactin and insulin-like growth factor binding protein-1 expression. *Biol Reprod* 1995; **52**:609–615.
10. Enders AC. Current topic: structural responses of the primate endometrium to implantation. *Placenta* 1991; **12**:309–325.
11. Ferenczy A, Guralnick M. Endometrial microstructure: structure-function relationships throughout the menstrual cycle. *Semin Reprod Endocrinol* 1983; **1**:205–219.
12. Kara F, Cinar O, Erdemli-Atabenli E, Tavil-Sabuncuoglu B, Can A. Ultrastructural alterations in human decidua in miscarriages compared to normal pregnancy decidua. *Acta Obstet Gynecol Scand* 2007; **86**:1079–1086.
13. Lawn AM, Wilson EW, Finn CA. The ultrastructure of human decidual and predecidual cells. *J Reprod Fertil* 1971; **26**: 85–90.
14. Wynn RM. Ultrastructural development of the human decidua. *Am J Obstet Gynecol* 1974; **118**:652–670.
15. Garcia-Alonso L, Handfield LF, Roberts K, Nikolakopoulou K, Fernando RC, Gardner L, Woodhams B, Arutyunyan A, Polanski K, Hoo R, Sancho-Serra C, Li T *et al*. Mapping the temporal and spatial dynamics of the human endometrium in vivo and in vitro. *Nat Genet* 2021; **53**:1698–1711.
16. Lucas ES, Vrljicak P, Muter J, Diniz-da-Costa MM, Brighton PJ, Kong CS, Lipecki J, Fishwick KJ, Odendaal J, Ewington LJ, Quenby S, Ott S *et al*. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window. *Commun Biol* 2020; **3**:37.
17. Suryawanshi H, Morozov P, Straus A, Sahasrabudhe N, Max KEA, Garzia A, Kustagi M, Tuschl T, Williams Z. A single-cell survey of the human first-trimester placenta and decidua. *Sci Adv* 2018; **4**:eaau4788.
18. Vento-Tormo R, Efremova M, Botting RA, Turco MY, Vento-Tormo M, Meyer KB, Park JE, Stephenson E, Polanski K, Goncalves A, Gardner L, Holmqvist S *et al*. Single-cell reconstruction of the early maternal-fetal interface in humans. *Nature* 2018; **563**:347–353.
19. Wang W, Vilella F, Alama P, Moreno I, Mignardi M, Isakova A, Pan W, Simon C, Quake SR. Single-cell transcriptomic atlas of the human endometrium during the menstrual cycle. *Nat Med* 2020; **26**:1644–1653.
20. Kin K, Nnamani MC, Lynch VJ, Michaelides E, Wagner GP. Cell-type phylogenetics and the origin of endometrial stromal cells. *Cell Rep* 2015; **10**:1398–1409.
21. Tabanelli S, Tang B, Gurpide E. In vitro decidualization of human endometrial stromal cells. *J Steroid Biochem Mol Biol* 1992; **42**: 337–344.
22. Dimitrov R, Kyurkchiev D, Timeva T, Yunakova M, Stamenova M, Shterev A, Kyurkchiev S. First-trimester human decidua contains a population of mesenchymal stem cells. *Fertil Steril* 2010; **93**:210–219.
23. Olivares EG, Montes MJ, Oliver C, Galindo JA, Ruiz C. Cultured human decidual stromal cells express B7-1 (CD80) and B7-2 (CD86) and stimulate allogeneic T cells. *Biol Reprod* 1997; **57**: 609–615.
24. Ruiz Magana MJ, Puerta JM, Martinez-Aguilar R, Llorca T, Blanco O, Munoz-Fernandez R, Olivares EG, Ruiz-Ruiz C. Endometrial and decidual stromal precursors show a different decidualization capacity. *Reproduction* 2020; **160**:83–91.
25. Noyes RW, Hertig AT, Rock J. Reprint of: dating the endometrial biopsy. *Fertil Steril* 2019; **112**:e93–e115.
26. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev* 2014; **35**:851–905.
27. Okada H, Tsuzuki T, Murata H. Decidualization of the human endometrium. *Reprod Med Biol* 2018; **17**:220–227.
28. Zhu X, Yu F, Yan G, Hu Y, Sun H, Ding L. Human endometrial perivascular stem cells exhibit a limited potential to regenerate endometrium after xenotransplantation. *Hum Reprod* 2021; **36**: 145–159.
29. Liu Y, Liang S, Yang F, Sun Y, Niu L, Ren Y, Wang H, He Y, Du J, Yang J, Lin J. Biological characteristics of endometriotic mesenchymal stem cells isolated from ectopic lesions of patients with endometriosis. *Stem Cell Res Ther* 2020; **11**:346.
30. Kyurkchiev S, Shterev A, Dimitrov R. Assessment of presence and characteristics of multipotent stromal cells in human endometrium and decidua. *Reprod Biomed Online* 2010; **20**: 305–313.
31. Miehe U, Neumaier-Wagner P, Kadyrov M, Goyal P, Alfer J, Rath W, Huppertz B. Concerted upregulation of CLP36 and smooth muscle actin protein expression in human endometrium during decidualization. *Cells Tissues Organs* 2005; **179**:109–114.
32. Silini AR, Di Pietro R, Lang-Olip I, Alviano F, Banerjee A, Basile M, Borutinskaite V, Eissner G, Gellhaus A, Giebel B, Huang YC, Janev A *et al*. Perinatal derivatives: where do we stand? A roadmap of the human placenta and consensus for tissue and cell nomenclature. *Front Bioeng Biotechnol* 2020; **8**:610544.
33. Szukiewicz D, Stangret A, Ruiz-Ruiz C, Olivares EG, Soritau O, Susman S, Szewczyk G. Estrogen- and progesterone (P4)-mediated epigenetic modifications of endometrial stromal cells (EnSCs) and/or mesenchymal stem/stromal cells (MSCs) in the etiopathogenesis of endometriosis. *Stem Cell Rev Rep* 2021; **17**: 1174–1193.
34. Montes MJ, Aleman P, Garcia-Tortosa C, Borja C, Ruiz C, Garcia-Olivares E. Cultured human decidual stromal cells express antigens associated with hematopoietic cells. *J Reprod Immunol* 1996; **30**:53–66.
35. Gellersen B, Brosens IA, Brosens JJ. Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives. *Semin Reprod Med* 2007; **25**:445–453.
36. Gellersen B, Brosens J. Cyclic AMP and progesterone receptor cross-talk in human endometrium: a decidualizing affair. *J Endocrinol* 2003; **178**:357–372.
37. Skalhegg BS, Tasken K. Specificity in the cAMP/PKA signaling pathway. Differential expression, regulation, and subcellular localization of subunits of PKA. *Front Biosci* 2000; **5**:D678–D693.
38. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Vigano P. Endometriosis. *Nat Rev Dis Primers* 2018; **4**:9.
39. Murakami K, Lee YH, Lucas ES, Chan YW, Durairaj RP, Takeda S, Moore JD, Tan BK, Quenby S, Chan JK, Gargett CE, Brosens JJ. Decidualization induces a secretome switch in perivascular niche cells of the human endometrium. *Endocrinology* 2014; **155**: 4542–4553.
40. Kearns M, Lala PK. Bone marrow origin of decidual cell precursors in the pseudopregnant mouse uterus. *J Exp Med* 1982; **155**: 1537–1554.
41. Lysiak JJ, Lala PK. In situ localization and characterization of bone marrow-derived cells in the decidua of normal murine pregnancy. *Biol Reprod* 1992; **47**:603–613.
42. Simmons PJ, Torok-Storb B. Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. *Blood* 1991; **78**:55–62.
43. Oliver C, Montes MJ, Galindo JA, Ruiz C, Olivares EG. Human decidual stromal cells express alpha-smooth muscle actin and show ultrastructural similarities with myofibroblasts. *Hum Reprod* 1999; **14**:1599–1605.
44. Kimatrai M, Oliver C, Abadia-Molina AC, Garcia-Pacheco JM, Olivares EG. Contractile activity of human decidual stromal cells. *J Clin Endocrinol Metab* 2003; **88**:844–849.
45. Cheung VC, Peng CY, Marinic M, Sakabe NJ, Aneas I, Lynch VJ, Ober C, Nobrega MA, Kessler JA. Pluripotent stem cell-derived endometrial stromal fibroblasts in a cyclic, hormone-responsive, coculture model of human decidua. *Cell Rep* 2021; **35**:109138.
46. Miyazaki K, Dyson MT, Coon VJ, Furukawa Y, Yilmaz BD, Maruyama T, Bulun SE. Generation of progesterone-responsive endometrial stromal fibroblasts from human induced pluripotent

stem cells: role of the WNT/CTNNB1 pathway. *Stem Cell Reports* 2018; **11**:1136–1155.
47. Munoz-Fernandez R, de la Mata C, Prados A, Perea A, Ruiz-Magana MJ, Llorca T, Fernandez-Rubio P, Blanco O, Abadia-Molina AC, Olivares EG. Human predecidual stromal cells have distinctive characteristics of pericytes: cell contractility, chemotactic activity, and expression of pericyte markers and angiogenic factors. *Placenta* 2018; **61**:39–47.
48. Ruiz-Magana MJ, Martinez-Aguilar R, Llorca T, Abadia-Molina AC, Ruiz-Ruiz C, Olivares EG. Decidualization modulates the mesenchymal stromal/stem cell and pericyte characteristics of human decidual stromal cells. Effects on antigen expression, chemotactic activity on monocytes and antitumoral activity. *J Reprod Immunol* 2021; **145**:103326.
49. Smyth LCD, Rustenhoven J, Scotter EL, Schweder P, Faull RLM, Park TIH, Dragunow M. Markers for human brain pericytes and smooth muscle cells. *J Chem Neuroanat* 2018; **92**:48–60.
50. Avolio E, Alvino VV, Ghorbel MT, Campagnolo P. Perivascular cells and tissue engineering: current applications and untapped potential. *Pharmacol Ther* 2017; **171**:83–92.
51. Darzi S, Werkmeister JA, Deane JA, Gargett CE. Identification and characterization of human endometrial mesenchymal stem/stromal cells and their potential for cellular therapy. *Stem Cells Transl Med* 2016; **5**:1127–1132.
52. Kirkwood PM, Gibson DA, Smith JR, Wilson-Kanamori JR, Kelepouri O, Esnal-Zufiaurre A, Dobie R, Henderson NC, Saunders PTK. Single-cell RNA sequencing redefines the mesenchymal cell landscape of mouse endometrium. *FASEB J* 2021; **35**:e21285.
53. Carlino C, Stabile H, Morrone S, Bulla R, Soriani A, Agostinis C, Bossi F, Mocci C, Sarazani F, Tedesco F, Santoni A, Gismondi A. Recruitment of circulating NK cells through decidual tissues: a possible mechanism controlling NK cell accumulation in the uterus during early pregnancy. *Blood* 2008; **111**:3108–3115.
54. Wiater J, Niedziela M, Posmysz A, Wartalski K, Gajda B, Smorag Z, Rajfur Z, Karasinski J. Identification of perivascular and stromal mesenchymal stem/progenitor cells in porcine endometrium. *Reprod Domest Anim* 2018; **53**:333–343.
55. Krautler NJ, Kana V, Kranich J, Tian Y, Perera D, Lemm D, Schwarz P, Armulik A, Browning JL, Tallquist M, Buch T, Oliveira-Martins JB *et al.* Follicular dendritic cells emerge from ubiquitous perivascular precursors. *Cell* 2012; **150**:194–206.
56. Brosens JJ, de Souza NM, Barker FG. Uterine junctional zone: function and disease. *Lancet* 1995; **346**:558–560.
57. Munoz-Fernandez R, De La Mata C, Requena F, Martin F, Fernandez-Rubio P, Llorca T, Ruiz-Magana MJ, Ruiz-Ruiz C, Olivares EG. Human predecidual stromal cells are mesenchymal stromal/stem cells and have a therapeutic effect in an immune-based mouse model of recurrent spontaneous abortion. *Stem Cell Res Ther* 2019; **10**:177.
58. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**:315–317.
59. Dimitrov R, Timeva T, Kyurkchiev D, Stamenova M, Shterev A, Kostova P, Zlatkov V, Kehayov I, Kyurkchiev S. Characterization of clonogenic stromal cells isolated from human endometrium. *Reproduction* 2008; **135**:551–558.
60. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L, Norotte C, Teng PN *et al.* A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell* 2008; **3**:301–313.
61. Shi S, Gronthos S. Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. *J Bone Miner Res* 2003; **18**:696–704.
62. Diniz-da-Costa M, Kong CS, Fishwick KJ, Rawlings T, Brighton PJ, Hawkes A, Odendaal J, Quenby S, Ott S, Lucas ES, Vrljicak P, Brosens JJ. Characterization of highly proliferative decidual precursor cells during the window of implantation in human endometrium. *Stem Cells* 2021; **39**:1067–1080.
63. Du H, Taylor HS. Contribution of bone marrow-derived stem cells to endometrium and endometriosis. *Stem Cells* 2007; **25**:2082–2086.
64. Tal R, Shaikh S, Pallavi P, Tal A, Lopez-Giraldez F, Lyu F, Fang YY, Chinchanikar S, Liu Y, Kliman HJ, Alderman M 3rd, Pluchino N *et al.* Adult bone marrow progenitors become decidual cells and contribute to embryo implantation and pregnancy. *PLoS Biol* 2019; **17**:e3000421.
65. Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. *JAMA* 2004; **292**:81–85.
66. Munoz-Fernandez R, Prados A, Leno-Duran E, Blazquez A, Garcia-Fernandez JR, Ortiz-Ferron G, Olivares EG. Human decidual stromal cells secrete C-X-C motif chemokine 13, express B cell-activating factor and rescue B lymphocytes from apoptosis: distinctive characteristics of follicular dendritic cells. *Hum Reprod* 2012; **27**:2775–2784.
67. Aghajanova L, Horcajadas JA, Esteban FJ, Giudice LC. The bone marrow-derived human mesenchymal stem cell: potential progenitor of the endometrial stromal fibroblast. *Biol Reprod* 2010; **82**:1076–1087.
68. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. *Hum Reprod Update* 2016; **22**:137–163.
69. Masuda H, Anwar SS, Buhring HJ, Rao JR, Gargett CE. A novel marker of human endometrial mesenchymal stem-like cells. *Cell Transplant* 2012; **21**:2201–2214.
70. Schwab KE, Gargett CE. Co-expression of two perivascular cell markers isolates mesenchymal stem-like cells from human endometrium. *Hum Reprod* 2007; **22**:2903–2911.
71. Spitzer TL, Rojas A, Zelenko Z, Aghajanova L, Erikson DW, Barragan F, Meyer M, Tamaresis JS, Hamilton AE, Irwin JC, Giudice LC. Perivascular human endometrial mesenchymal stem cells express pathways relevant to self-renewal, lineage specification, and functional phenotype. *Biol Reprod* 2012; **86**:58.
72. Khanmohammadi M, Mukherjee S, Darzi S, Paul K, Werkmeister JA, Cousins FL, Gargett CE. Identification and characterisation of maternal perivascular SUSD2(+) placental mesenchymal stem/stromal cells. *Cell Tissue Res* 2021; **385**:803–815.
73. Barragan F, Irwin JC, Balayan S, Erikson DW, Chen JC, Houshdaran S, Piltonen TT, Spitzer TL, George A, Rabban JT, Nezhat C, Giudice LC. Human endometrial fibroblasts derived from mesenchymal progenitors inherit progesterone resistance and acquire an inflammatory phenotype in the endometrial niche in endometriosis. *Biol Reprod* 2016; **94**:118.
74. Chang JE, Turley SJ. Stromal infrastructure of the lymph node and coordination of immunity. *Trends Immunol* 2015; **36**:30–39.
75. Pikor NB, Cheng HW, Onder L, Ludewig B. Development and immunological function of lymph node stromal cells. *J Immunol* 2021; **206**:257–263.
76. Gentek R, Bajenoff M. Lymph node stroma dynamics and approaches for their visualization. *Trends Immunol* 2017; **38**:236–247.
77. Rodda LB, Lu E, Bennett ML, Sokol CL, Wang X, Luther SA, Barres BA, Luster AD, Ye CJ, Cyster JG. Single-cell RNA sequencing of lymph node stromal cells reveals niche-associated heterogeneity. *Immunity* 2018; **48**:1014–1028.e6.
78. Buckley CD, Barone F, Nayar S, Benezech C, Caamano J. Stromal cells in chronic inflammation and tertiary lymphoid organ formation. *Annu Rev Immunol* 2015; **33**:715–745.
79. Aguzzi A, Kranich J, Krautler NJ. Follicular dendritic cells: origin, phenotype, and function in health and disease. *Trends Immunol* 2014; **35**:105–113.
80. Munoz-Fernandez R, Prados A, Tirado-Gonzalez I, Martin F, Abadia AC, Olivares EG. Contractile activity of human follicular dendritic cells. *Immunol Cell Biol* 2014; **92**:851–859.
81. Munoz-Fernandez R, Blanco FJ, Frecha C, Martin F, Kimatrai M, Abadia-Molina AC, Garcia-Pacheco JM, Olivares EG. Follicular

dendritic cells are related to bone marrow stromal cell progenitors and to myofibroblasts. *J Immunol* 2006; **177**:280–289.
82. Bolat F, Canpolat T, Tarim E. Pregnancy-related peritoneal ectopic decidua (deciduosis): morphological and clinical evaluation. *Turk Patoloji Derg* 2012; **28**:56–60.
83. Yin X, Pavone ME, Lu Z, Wei J, Kim JJ. Increased activation of the PI3K/AKT pathway compromises decidualization of stromal cells from endometriosis. *J Clin Endocrinol Metab* 2012; **97**:E35–E43.
84. Taylor HS. Bone marrow in the pathophysiology of endometriosis. *Fertil Steril* 2020; **113**:942.
85. Martinez-Aguilar R, Romero-Pinedo S, Ruiz-Magana MJ, Olivares EG, Ruiz-Ruiz C, Abadia-Molina AC. Menstrual blood-derived stromal cells modulate functional properties of mouse and human macrophages. *Sci Rep* 2020; **10**:21389.
86. Capobianco A, Rovere-Querini P. Endometriosis, a disease of the macrophage. *Front Immunol* 2013; **4**:9.
87. Braverman MB, Bagni A, de Ziegler D, Den T, Gurpide E. Isolation of prolactin-producing cells from first and second trimester decidua. *J Clin Endocrinol Metab* 1984; **58**:521–525.
88. Huang JR, Tseng L, Bischof P, Janne OA. Regulation of prolactin production by progestin, estrogen, and relaxin in human endometrial stromal cells. *Endocrinology* 1987; **121**:2011–2017.
89. Prados A, Munoz-Fernandez R, Fernandez-Rubio P, Olivares EG. Characterization of mesenchymal stem/stromal cells with lymphoid tissue organizer cell potential in tonsils from children. *Eur J Immunol* 2018; **48**:829–843.
90. Schwab KE, Hutchinson P, Gargett CE. Identification of surface markers for prospective isolation of human endometrial stromal colony-forming cells. *Hum Reprod* 2008; **23**:934–943.
91. Gargett CE, Schwab KE, Zillwood RM, Nguyen HP, Wu D. Isolation and culture of epithelial progenitors and mesenchymal stem cells from human endometrium. *Biol Reprod* 2009; **80**:1136–1145.
92. Rossignoli F, Caselli A, Grisendi G, Piccinno S, Burns JS, Murgia A, Veronesi E, Loschi P, Masini C, Conte P, Paolucci P, Horwiz EM *et al*. Isolation, characterization, and transduction of endometrial decidual tissue multipotent mesenchymal stromal/stem cells from menstrual blood. *Biomed Res Int* 2013; **2013**:1–14.
93. Guillot PV, Gotherstrom C, Chan J, Kurata H, Fisk NM. Human first-trimester fetal MSC express pluripotency markers and grow faster and have longer telomeres than adult MSC. *Stem Cells* 2007; **25**:646–654.
94. Gurung S, Williams S, Deane JA, Werkmeister JA, Gargett CE. The transcriptome of human endometrial mesenchymal stem cells under TGFbetaR inhibition reveals improved potential for cell-based therapies. *Front Cell Dev Biol* 2018; **6**:164.
95. Musina RA, Belyavski AV, Tarusova OV, Solovyova EV, Sukhikh GT. Endometrial mesenchymal stem cells isolated from the menstrual blood. *Bull Exp Biol Med* 2008; **145**:539–543.
96. Patel AN, Park E, Kuzman M, Benetti F, Silva FJ, Allickson JG. Multipotent menstrual blood stromal stem cells: isolation, characterization, and differentiation. *Cell Transplant* 2008; **17**:303–311.
97. Colter DC, Class R, DiGirolamo CM, Prockop DJ. Rapid expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow. *Proc Natl Acad Sci U S A* 2000; **97**:3213–3218.
98. Dimitriou H, Perdikogianni C, Martimianaki G, Choumerianou DM, Pelagiadis J, Kalmanti M. Are mesenchymal stromal cells from children resistant to apoptosis? *Cell Prolif* 2009; **42**:276–283.
99. Leno-Duran E, Ruiz-Magana MJ, Munoz-Fernandez R, Requena F, Olivares EG, Ruiz-Ruiz C. Human decidual stromal cells secrete soluble pro-apoptotic factors during decidualization in a cAMP-dependent manner. *Hum Reprod* 2014; **29**:2269–2277.
100. Kimatrai M, Blanco O, Munoz-Fernandez R, Tirado I, Martin F, Abadia-Molina AC, Olivares EG. Contractile activity of human decidual stromal cells. II. Effect of interleukin-10. *J Clin Endocrinol Metab* 2005; **90**:6126–6130.
101. Kinner B, Zaleskas JM, Spector M. Regulation of smooth muscle actin expression and contraction in adult human mesenchymal stem cells. *Exp Cell Res* 2002; **278**:72–83.
102. Nasu K, Nishida M, Matsumoto H, Bing S, Inoue C, Kawano Y, Miyakawa I. Regulation of proliferation, motility, and contractivity of cultured human endometrial stromal cells by transforming growth factor-beta isoforms. *Fertil Steril* 2005; **84**:1114–1123.
103. Hirota Y, Osuga Y, Koga K, Yoshino O, Hirata T, Morimoto C, Harada M, Takemura Y, Nose E, Yano T, Tsutsumi O, Taketani Y. The expression and possible roles of chemokine CXCL11 and its receptor CXCR3 in the human endometrium. *J Immunol* 2006; **177**:8813–8821.
104. Blanco O, Leno-Duran E, Morales JC, Olivares EG, Ruiz-Ruiz C. Human decidual stromal cells protect lymphocytes from apoptosis. *Placenta* 2009; **30**:677–685.
105. da Silva Meirelles L, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. *Stem Cells* 2008; **26**:2287–2299.
106. Luz-Crawford P, Torres MJ, Noel D, Fernandez A, Toupet K, Alcayaga-Miranda F, Tejedor G, Jorgensen C, Illanes SE, Figueroa FE, Djouad F, Khoury M. The immunosuppressive signature of menstrual blood mesenchymal stem cells entails opposite effects on experimental arthritis and graft versus host diseases. *Stem Cells* 2016; **34**:456–469.
107. Shokri MR, Bozorgmehr M, Ghanavatinejad A, Falak R, Aleahmad M, Kazemnejad S, Shokri F, Zarnani AH. Human menstrual blood-derived stromal/stem cells modulate functional features of natural killer cells. *Sci Rep* 2019; **9**:10007.
108. Yang F, Zheng Q, Jin L. Dynamic function and composition changes of immune cells during normal and pathological pregnancy at the maternal-fetal Interface. *Front Immunol* 2019; **10**:2317.
109. Dalal J, Gandy K, Domen J. Role of mesenchymal stem cell therapy in Crohn's disease. *Pediatr Res* 2012; **71**:445–451.
110. Darzi S, Deane JA, Nold CA, Edwards SE, Gough DJ, Mukherjee S, Gurung S, Tan KS, Vashi AV, Werkmeister JA, Gargett CE. Endometrial mesenchymal stem/stromal cells modulate the macrophage response to implanted polyamide/gelatin composite mesh in immunocompromised and immunocompetent mice. *Sci Rep* 2018; **8**:6554.
111. Ringden O, Baygan A, Remberger M, Gustafsson B, Winiarski J, Khoein B, Moll G, Klingspor L, Westgren M, Sadeghi B. Placenta-derived decidua stromal cells for treatment of severe acute graft-versus-host disease. *Stem Cells Transl Med* 2018; **7**:325–331.
112. Ringden O, Gustafsson B, Sadeghi B. Mesenchymal stromal cells in pediatric hematopoietic cell transplantation a review and a pilot study in children treated with decidua stromal cells for acute graft-versus-host disease. *Front Immunol* 2020; **11**:567210.
113. Xu X, Wang Y, Zhang B, Lan X, Lu S, Sun P, Li X, Shi G, Zhao Y, Han H, Du C, Wang H. Treatment of experimental colitis by endometrial regenerative cells through regulation of B lymphocytes in mice. *Stem Cell Res Ther* 2018; **9**:146.
114. Alcayaga-Miranda F, Cuenca J, Luz-Crawford P, Aguila-Diaz C, Fernandez A, Figueroa FE, Khoury M. Characterization of menstrual stem cells: angiogenic effect, migration and hematopoietic stem cell support in comparison with bone marrow mesenchymal stem cells. *Stem Cell Res Ther* 2015; **6**:32.
115. Mendez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, Scadden DT, Ma'ayan A, Enikolopov GN, Frenette PS. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *Nature* 2010; **466**:829–834.
116. Shi K, Hayashida K, Kaneko M, Hashimoto J, Tomita T, Lipsky PE, Yoshikawa H, Ochi T. Lymphoid chemokine B cell-attracting chemokine-1 (CXCL13) is expressed in germinal center of ectopic lymphoid follicles within the synovium of chronic arthritis patients. *J Immunol* 2001; **166**:650–655.