



REVIEW

Uterine natural killer cells: Time for a re-appraisal? [version 1; peer review: 2 approved]

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Abstract

The presence of unusual natural killer cells in human endometrium has been recognized for 30 years, but despite considerable research effort, the *in vivo* role of uterine natural killer (uNK) cells in both normal and pathological pregnancy remains uncertain. uNK cells may differentiate from precursors present in endometrium, but migration from peripheral blood in response to chemokine stimuli with *in situ* modification to a uNK cell phenotype is also possible. uNK cells produce a wide range of secretory products with diverse effects on trophoblast and spiral arteries which may play an important role in implantation and early placentation. Interactions with other decidual cell populations are also becoming clear. Recent evidence has demonstrated subpopulations of uNK cells and the presence of other innate lymphoid cell populations in decidua which may refine future approaches to investigation of the role of uNK cells in human pregnancy.

Keywords

uterine natural killer cell, uNK cell, human pregnancy, decidua

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Introduction

Granulated cells were recognized in endometrial stroma almost a century ago, but despite light and electron microscopic evidence for a lymphocyte origin in humans¹, mouse^{2,3}, and rat⁴, they were regarded as stromal cells until identified as unusual natural killer (NK) cells using monoclonal antibodies⁵⁻⁷. The term uterine NK (uNK) cell has been commonly adopted, although “decidual NK cell” and “endometrial NK cell” are also used to reflect their presence only in endometrium. uNK cells, characterized as CD45⁺CD56^{bright}CD16⁺CD9⁺, increase in number in luteal phase endometrium and early pregnancy decidua⁷⁻¹⁰. A substantial number remain in later pregnancy^{11,12}, although fewer have cytoplasmic granules, explaining why early studies relying on identifying cytoplasmic granules reported their virtual absence at full term¹³. This distribution suggests a role in pregnancy and this has been the focus of studies over the last 30 years.

Despite suggestions of a detrimental role of NK cells in early pregnancy failure, uNK cells are considered to be a positive force for healthy pregnancy, although their precise role remains uncertain. The recent identification of molecularly distinct uNK cell subgroups¹⁴ and other innate lymphoid cells (ILCs) in human decidua¹⁵⁻¹⁷ suggests that a re-appraisal may be timely. The aim of this review is to provide a brief overview of views on the origin and function of uNK cells that have developed over the last 30 years and consider future directions.

Origin of uterine natural killer cells

There is no consensus regarding the origin of uNK cells; their gene expression patterns differ from those of peripheral blood NK (pbNK) cells¹⁸, but whether they differentiate locally or are recruited to endometrium (or both) is uncertain. Hematopoietic precursor cells (HPCs) have been reported in non-pregnant endometrium¹⁹ and early pregnancy decidua²⁰⁻²² at a frequency of 0.1% to 4%. HPCs purified from decidua and cultured in decidual stromal cell (DSC)-conditioned medium or various cytokine combinations produced CD56^{bright}CD16⁺CD9⁺ uNK-like cells²⁰⁻²². Additional evidence for local differentiation comes from detection of increased CD56⁺ uNK cells in human proliferative endometrium transplanted into non-obese diabetic/severe combined immunodeficiency/ γ C^{null} immunodeficient mice subjected to menstrual cycle-mimicking hormone treatment²³. In contrast, Male *et al.*²⁴ did not detect HPCs in non-pregnant endometrium and suggested the possibility of local differentiation from stage 3 immature NK cells, although the cells detected in these studies express markers that are characteristic of type 3 ILCs and produce interleukin-22 (IL-22)¹⁷. Human endometrium produces several factors implicated in NK cell differentiation, including IL-15²⁵, IL-7, Flt3L²⁶, SCF (KL)²⁷⁻²⁹, and transforming growth factor beta 1 (TGF β 1)³⁰, many of which are increased in the luteal phase and early pregnancy.

Rather than differentiation from HPCs, it is possible that locally secreted chemokines/cytokines could attract pbNK cells to endometrium and also mediate further local differentiation. Purified CD16⁺CD9⁻ pbNK cells converted into CD16⁺CD9⁺

uNK-like cells after culture with DSC-conditioned medium or TGF β 1^{20,31}, and a uNK cell-type phenotype (CD56^{bright}CD16⁺CD9⁺KIR⁺, VEGF-A producing, low cytotoxicity) was induced by exposure of pbNK cells to hypoxia, TGF β 1, and demethylating agents³¹. DSCs produce chemoattractants implicated in recruitment of pbNK cells to endometrium, including C-X-C motif chemokine 10 (CXCL10), CXCL12, CX3CL1, and chemerin^{32,33}, and compared with non-pregnant and male cells, pbNK cells from pregnant women have increased ability to migrate through DSCs²⁶. Furthermore, pbNK cells acquire a uNK cell-type chemokine receptor pattern after co-culture with DSCs. NK cell populations could also be recruited into endometrium in pregnancy in response to trophoblast³⁴.

uNK cells consistently localize to areas of stromal decidualization, including progesterone-treated endometrium, intrauterine decidua in ectopic pregnancy, and extrauterine decidua in normal pregnancy. This indicates a role for DSCs in uNK cell differentiation or recruitment (or both) and clearly demonstrates that they are not (all) dependent on trophoblast. It seems likely that both recruitment from blood and local differentiation play a role but perhaps with different contributions in non-pregnant and pregnant endometrium. A developing population is suggested by phenotypic differences with increasing gestation, and there is reduced expression of HLA-C-specific killer immunoglobulin-like receptors (KIRs) from 6 to 12 weeks³⁵, increased NKG2D expression from 8 to 12 weeks³⁶, increased expression of NKp80 and NKG2D, and a population with reduced CD56 brightness in second (13 to 20 weeks) compared with first (6 to 12 weeks) trimester^{11,37}. Functional changes may also reflect an evolving population. Altered cytokine/growth factor expression and differing effects on trophoblast invasion have been reported in CD56⁺ uNK cells from 8 to 10 compared with 12 to 14 weeks of gestational age³⁸⁻⁴⁰, and a reduced proportion of cells expressing granzyme and perforin^{13,37}, reduced CD56⁺ cells in proximity to extravillous trophoblast (EVT), and altered interactions with HTR-8/SVneo trophoblast-like cells have been reported in the second compared with the first trimester of pregnancy³⁷. These phenotypic and functional variations may reflect further local differentiation of immature NK cells or recruitment and further differentiation of additional populations from peripheral blood. CD56⁺ cells also proliferate in endometrium, and the highest expression of the proliferation marker Ki67 (>40%) is in the mid/late luteal phase⁴¹ and this could account for phenotypic differences as the menstrual cycle and pregnancy progress. The biological significance of the phenotypic and functional changes related to gestational age is not known. In addition, whether any altered decidual NK cell populations in pathological pregnancy represent alteration of a resident uNK cell population or recruitment of an additional population has not been established.

Interaction with trophoblast

uNK cells express a range of receptors, including KIRs and leukocyte immunoglobulin-like receptors (LILRs) that can recognize HLA-E, HLA-G, and HLA-C, which are expressed by EVT⁴²⁻⁴⁵. uNK cell expression of these receptors differs from that of pbNK cells and is biased toward HLA-E and HLA-C1

recognition³⁵. It was suggested that the bias toward HLA-C recognition resulted from pregnancy⁴⁶, but studies using uNK cells from menstrual blood indicate that this receptor repertoire is established in non-pregnant endometrium and does not differ between consecutive menstrual cycles^{47,48}. Expression of these specific receptors by uNK cells suggests that they interact with EVT, and specific KIR/HLA-C combinations have been associated with pregnancy complications, including pre-eclampsia, fetal growth restriction, and recurrent miscarriage⁴⁹⁻⁵². However, an epidemiological study of Japanese couples did not support this proposal, noting similar rates of pre-eclampsia in couples comprising Japanese women and Caucasian men and couples comprising Japanese men and women⁵³. Furthermore, no association of HLA-C/KIR genotype with pre-eclampsia was noted in a recent Danish study, although this was confined to severe pre-eclampsia⁵⁴.

There were early suggestions that uNK cells may limit EVT invasion by cytotoxicity, and some studies have suggested that uNK cells are capable of cytotoxic activity. Co-culture of IL-2-activated CD56^{bright} decidual NK cells with an EVT-like cell line HTR-8/SV40neo led to granulysin accumulation in the EVT cells, and transfection of granulysin into HTR-8/SC40neo cells induced their apoptosis⁵⁵. Furthermore, a more recent study detected cytotoxic activity by IL-2-stimulated CD56⁺ cells (>90% purity) from early pregnancy decidua against both cytotrophoblast and the NK target K562, an activity that was inhibited by decidual macrophages⁵⁶. Nevertheless, in most studies, uNK cells have been poorly cytotoxic to both classic NK cell targets and trophoblast⁵⁷, and the consensus is that uNK cells are not cytotoxic in healthy pregnancy. uNK cells can acquire cytotoxic ability when decidua is infected by pathogens such as cytomegalovirus and toxoplasma, suggesting a possible role in protection against infection⁵⁸.

There are many reports of cytokine, chemokine, and growth factor production by uNK cells, mainly at a gestational age of 8 to 14 weeks, when trophoblast invasion and spiral artery remodeling are maximal; a summary is given in [Table 1](#) but the list is not exhaustive. Several different approaches have been used for tissue disaggregation, uNK cell purification, and mechanisms and durations of cell activation; this may explain the variation between different studies.

Given the phenotypic changes, it is not surprising that the uNK cell secretome varies with gestational age. uNK cell production of IL-1 β , IL-6, CXCL8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN γ) was increased at 12 to 14 weeks compared with 8 to 10 weeks of gestation³⁹, whereas angiopoietin 2 (Ang2) and vascular endothelial growth factor-C (VEGF-C) secretion were higher at the earlier gestational age³⁸. Increased cytokine levels at 12 to 14 weeks may tie in with reports that interactions between pbNK cells and soluble HLA-G induce a pro-inflammatory/pro-angiogenic senescence-associated secretory phenotype with increased secretion of, among others, IL-1 β , IL-6, and CXCL8⁵⁹⁻⁶¹, although this has not been demonstrated for uNK cells. uNK cell secretory products are also altered by trophoblast; uNK cell secretion of Ang1, VEGF-C, IL-6,

CXCL8, and TGF β 1 were reduced by co-culture with EVT and cytotrophoblast⁴⁰. In contrast, increased IFN γ mRNA was reported after incubation of uNK cells with cytotrophoblast⁶². Interaction of HLA-C (expressed by EVT) with the activating receptors KIR2DS1 and KIR2DS4 expressed by uNK cells stimulates their production of cytokines, including GM-CSF, which can stimulate trophoblast invasion *in vitro*^{63,64}. Furthermore, a recent study demonstrated that, when co-cultured with EVT, a subset of uNK cells (CD49a⁺Eomes⁺) secrete growth-promoting factors, including pleiotrophin and osteoglycin; this effect is stimulated by HLA-G/ILT2 crosstalk⁶⁵.

Among other chemokines and growth factors, uNK cells stimulate trophoblast invasion by production of CXCL8 and CXCL10⁶⁶, although decidual CD3⁺ T cells, which produce higher levels of CXCL8, did not stimulate EVT invasion⁶⁷. Other cytokines produced by uNK cells, such as tumor necrosis factor alpha (TNF α) and IFN γ , inhibit invasion of EVT cells by various mechanisms, including trophoblast apoptosis, inhibition of proliferation, and reduced matrix metalloproteinase (MMP) production^{68,69}. The effect of uNK cells on EVT invasion may also depend on gestational age; in keeping with increased production of cytokines such as CXCL8, uNK cell supernatants at 12 to 14 weeks of gestation stimulated trophoblast invasion, whereas those at 8 to 10 weeks had no effect⁷⁰. In contrast, others have reported reduced trophoblast migration from villous explants co-cultured with decidual CD56⁺ cells, and the effect was mediated by IFN γ ^{62,71}.

uNK cells have a complex array of secretory products which may alter with different approaches to purification and activation. Despite the many and varied reports, the *in vivo* relevance of these studies remains unclear. Examination of any one cytokine is unlikely to reflect its importance *in vivo*, which may vary with gestational age; for example, a role in spiral artery remodeling may shift in later gestation to promoting trophoblast invasion. In regard to the role of uNK cells in the regulation of trophoblast invasion, it is important to remember that the cells are confined to decidua/endometrium, whereas even in the first trimester of normal pregnancy, interstitial trophoblast invades into inner myometrium⁷². Trophoblast also invades into myometrium in placenta accreta spectrum disorders, in which decidua (and uNK cells) are absent⁷³. Therefore, other factors, including the inherent invasive capacity of EVT following epithelial-mesenchymal transition^{74,75} and other maternal cell populations, must play a role.

Interaction with spiral arteries

Remodeling of spiral arteries in decidua basalis and underlying superficial myometrium is essential for healthy pregnancy and it is now accepted that, in addition to trophoblast, maternal uterine cells play a role^{76,77}, although the presence of trophoblast may be required for the uNK cell effect⁷⁸. Morphological changes in spiral arteries and arterioles in luteal phase endometrium and intrauterine decidua in ectopic pregnancy also suggest a trophoblast-independent effect⁷⁶.

uNK cells from decidua of 8 to 10 weeks, but not 12 to 14 weeks, of gestation can induce separation of vascular smooth muscle

Table 1. Cytokines, chemokines, and growth factor production by uterine natural killer cells.

Publication	Cytokines, chemokines, and growth factors detected	Cell preparation	Gestational age	Conditions
El Costa <i>et al.</i> ⁴⁵	IFN γ , TNF α , MIP-1 α , MIP-1 β , GM-CSF	MACS-negative selection, 96% CD3-CD56+	8-12 weeks	Engagement of NKp30 (but not NKp46)
Higuma-Myojo <i>et al.</i> ⁷⁹	TGF, minor populations of CD56+ cells producing other cytokines	Ficoll, flow cytometry	6-12 weeks	Mononuclear cells stimulated with PMA/ionomycin/brefeldin 4 hours, flow cytometry
Lash <i>et al.</i> ³⁸	Ang1, Ang2, PDGF-BB (low), KGF (low), ICAM-1 (low), VEGF-C, PIGF, TGF β 1	MACS-positive selection, >95% CD56+	8-10 weeks, 12-14 weeks	No stimulation, Fastquant, ELISA
Lash <i>et al.</i> ³⁹	IL-1 β , IL-4, IL-6, IL-8, IL-10, IL-13, GM-CSF, IFN γ , RANTES, TNF α	MACS-positive selection >95% CD56+	8-10 weeks, 12-14 weeks	No stimulation, Fastquant, ELISA
Hanna <i>et al.</i> ⁶⁶	CXCL8 (IL-8), CXCL10 (IP-10), CCL5 (RANTES), CCL22, MIP-1 α , MIP-1 β , PIGF, VEGF-A, VEGF-B, VEGF-C	Flow cytometry cell sorting, >99% CD56 ^{bright} CD16-CD3-	First trimester	IL-15 72 hours
Sotnikova <i>et al.</i> ⁸²	IFN γ	Dynabeads-positive selection	7-10 weeks	Incubation with autologous cytotrophoblast
Engert <i>et al.</i> ⁸⁰	GRO, MCP1, I-309, RANTES, IL-8, IL-1 β , EGF, VEGF, TPO, M-CSF, ENA, oncostatin M, IL-10, GRO α , angiogenin, IL-1 α , IL-4, IL-12p40p70, IFN γ , SCF, SDF-1, MCP-2 (detected in >50% samples)	MACS, >90% pure	7-8 weeks	No stimulation, protein array
Saito <i>et al.</i> ⁸¹	G-CSF, GM-CSF, M-CSF, TNF α , IFN γ , LIF	Flow cytometry sorting	7-9 weeks	No stimulation
Fraser <i>et al.</i> ⁸²	CXCL16, HB-EGF, HGF, IL-1 β , IL-8, TGF β 1, UPA, TIMP-1	MACS-positive selection, 93.6 \pm 1.3% CD56+, 80 \pm 4% viability after 24 hours	9.1-13.7 weeks	IL-15, SCF
Wallace <i>et al.</i> ⁸³	IL-6, IL-8, CXCL10	MagCelect-negative selection, CD56+ 95.7 \pm 0.92%, viability after 6 hours 84.6 \pm 2.8%	8-14 weeks	IL-15, SCF
Wallace <i>et al.</i> ⁸⁴	Angiogenin, sIL2-R, endostatin, PIGF, IL-1RA, MIG, MIP-1 α , MIP-1 β , RANTES	MACS-positive selection, 93.6 \pm 1.3% CD56+	9-14 weeks	IL-15, SCF
Wallace <i>et al.</i> ⁸⁵	TNF α , CXCL10, IFN γ , IL-8, PIGF (mRNA)	MagCelect-negative selection, CD56+ 95.7 \pm 0.92%, viability after 6 hours 84.6 \pm 2.8%	9-14 weeks	IL-15, SCF
Kennedy <i>et al.</i> ⁶³	GM-CSF, CCL3, CCL1, XCL1	Flow cytometry and intracellular cytokine detection; or MACS positive selection and ELISA	First trimester	Activation of KIR2DS4
Chen <i>et al.</i> ⁸⁶	Angiogenin, bFGF, VEGF-A, VEGFR, IL-1 α	MACS-positive selection, 91.3% CD16-CD56+	LH+7 non-pregnant endometrium	
Fu <i>et al.</i> ⁶⁵	Pleiotrophin, osteopontin, osteoglycin	Ficoll, MACS-negative selection	First trimester	Co-culture with EVT

Ang, angiopoietin; bFGF, basic fibroblast growth factor; CCL, C-C motif chemokine; EGF, epidermal growth factor; ELISA, enzyme-linked immunosorbent assay; ENA, epithelial neutrophil-activating protein; EVT, extravillous trophoblast; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRO, growth-regulated oncogene; HB-EGF, heparin-binding epidermal growth factor; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; KGF, keratinocyte growth factor; LIF, leukocyte inhibitory factor; MACS, magnetic-activated cell sorting; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MIG, monokine induced by interferon-gamma; MIP, macrophage inflammatory protein; PDGF-BB, platelet-derived growth factor beta; PIGF, placental growth factor; RANTES, regulated upon activation, normal T cell expressed, and secreted; SCF, stem cell factor; SDF-1, stromal cell-derived factor 1; sIL2-R, soluble interleukin-2 receptor; TGF, transforming growth factor; TIMP-1, tissue inhibitor of metalloproteinase 1; TNF α , tumor necrosis factor alpha; TPO, thrombopoietin; UPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

cells and loss of extracellular matrix via secretion of Ang1, Ang2, VEGF-C, and IFN γ ⁸⁷. uNK cells (and macrophages) also produce MMPs that can break down collagen in an *in vitro* spiral artery model⁸⁸. uNK cell supernatants also mediate vascular smooth muscle cell dedifferentiation and this effect is seen at 12 to 14 weeks but not 8 to 10 weeks of gestation⁸⁹. Other chemokines and growth factors have been implicated in the uNK cell effect on spiral arteries. For example, Choudhury *et al.*⁹⁰ suggested that IL-6 and CXCL8 secreted by EVT activate secretion of C-C motif chemokine 14 (CCL14) and CXCL6 by endothelial cells which then recruit uNK cells and macrophages to spiral arteries. Both IL-6 and CXCL8 also induce dedifferentiation of vascular smooth muscle cells in a chorionic plate artery model⁹¹.

Altered decidual leucocytes have been reported in pre-eclampsia, although results have varied⁹²⁻⁹⁴; there have been reports of reduced⁹⁵⁻⁹⁸, unchanged⁹⁹, and increased^{100,101} uNK cells compared with controls. Uterine artery Doppler studies in early pregnancy can predict women at increased risk of developing pre-eclampsia in later pregnancy¹⁰²; compared with post-delivery samples, these high-risk samples allow investigation when the pathogenetic lesion develops, before compensatory measures are in place, and this approach has been used to investigate uNK cell function in pregnancies at high risk of developing pre-eclampsia. uNK cells from 9- to 14-week gestational age pregnancies with abnormal Doppler wave forms showed reduced expression of KIR2DL/S1,3,5 and LILRB1⁸⁵, reduced stimulation of trophoblast outgrowth from villous explants⁸³, reduced *in vitro* induction of apoptosis in vascular smooth muscle cells and endothelial cells⁸², increased angiogenic growth factor secretion⁸⁴, and reduced ability to destabilize endothelial structures¹⁰³. These results all suggest that uNK cells from pregnancies at increased risk of pre-eclampsia display altered effects on trophoblast invasion and spiral arteries and emphasize the likely importance of uNK cells in early pregnancy. Nevertheless, in common with trophoblast invasion, spiral artery remodeling extends into inner myometrium. CD14⁺ macrophages and CD3⁺ T cells are present in the wall and adventitia of spiral arteries in both decidua and superficial myometrium¹⁰⁴, suggesting that these cells also have a role, either alone or in collaboration with uNK cells.

Interactions with other cells

uNK cells may also interact with other cell types in non-pregnant and pregnant endometrium. uNK cells interact with CD14⁺ cells in decidua to produce IDO (indoleamine-2,3-dioxygenase), which induces regulatory T cells¹⁰⁵. This interaction appears to be mediated by IFN γ and TGF β and is not seen with pbNK cells or CD14⁺ cells. uNK cells also form conjugates with immature dendritic cells in first-trimester decidua¹⁰⁶⁻¹⁰⁸ which can induce uNK cell proliferation and cytotoxicity¹⁰⁹. It has also been suggested that uNK cells induce apoptosis of CD209 (DC-SIGN)⁺ dendritic cells in decidua¹⁰⁸. Evidence from mouse pregnancy suggests that IL-10 secreted by uNK cells regulates dendritic cell phenotype and function, and IL-10 deficiency and dendritic cell expansion are associated with early pregnancy failure¹¹⁰.

In addition to affecting their recruitment or differentiation (or both), DSCs may affect uNK cell function; cultured first-trimester DSCs inhibited proliferation, cytotoxicity, IFN γ production, and upregulation of activation receptor expression by pbNK cells¹¹¹. In non-pregnant endometrium, uNK cells may clear senescent decidual cells at the end of the menstrual cycle, playing a crucial role in endometrial homeostasis¹¹².

Summary

Knowledge has increased dramatically since their recognition as unusual NK cells, but despite considerable research effort, the *in vivo* role of uNK cells remains unclear. Recent advances suggest that a re-appraisal may be timely. Whether uNK cell phenotype and function differ between non-pregnant and pregnant endometrium, between decidua basalis and parietalis, or at different sites within decidua (such as those related to spiral arteries) and at different gestational ages remains largely unknown. Pre-eclampsia, fetal growth restriction, and recurrent pregnancy failure have been associated with altered uNK cell numbers and function and specific KIR/HLA-C combinations but the significance of these observations is not fully established. uNK cells produce a wide range of chemokines, cytokines, growth factors, and MMPs, and many have been shown to have specific effects on trophoblast or spiral arteries, but *in vivo* translation is difficult. Gestational age differences in phenotype and function suggest that including samples across a range of gestational weeks in the first trimester may result in skewing of data.

The starting point for most studies of uNK cell function is decidua retrieved from pregnancy terminations or miscarriages. uNK cells within these samples have been exposed directly to EVT or to soluble HLA-G with possible functional effects. Investigations of uNK cells purified from non-pregnant endometrium are relatively infrequent, although several studies have reported increased uNK cells in luteal phase endometrium in recurrent early pregnancy failure¹¹³⁻¹¹⁶. A recent study of uNK cells from timed luteal phase endometrium reported increased expression of angiogenin, VEGF-A, and basic fibroblast growth factor (bFGF) in women with recurrent miscarriage compared with fertile controls⁸⁶. Recent studies indicate that menstrual blood may act as a surrogate for endometrial NK cells^{47,48,117} and this approach may increase the scope for future studies.

A single-cell RNA-sequencing (scRNA-seq) study of first-trimester decidua recently defined three distinct uNK cell populations¹⁵. The first (termed dNK1) contained more cytoplasmic granules, higher cytoplasmic granule proteins, and higher expression of KIR genes able to bind to HLA-C; LILRB1, which has high affinity for HLA-G, was expressed only by the dNK1 subset, suggesting that this subset interacts particularly with EVT. The second population (dNK2) also expressed activating NKG2C and NKG2E and inhibitory NKG2A receptors for HLA-E molecules, whereas the third population (dNK3) did not express these receptors but did express CCL5, suggesting a role in the regulation of EVT invasion via C-C motif chemokine receptor 1 (CCR1). This report demonstrates subpopulations of uNK cells which are likely to have diverse functions.

Similar studies of pathological pregnancy and non-pregnant endometrium, including endometrial NK cell populations in women with recurrent early pregnancy failure, may clarify the roles of specific uNK cell subsets in pathological pregnancy. The suggestion that there are subsets of NK cells in human decidua is supported by a report of production of growth-promoting factors by CD49a⁺Eomes⁺ uNK cells via interactions with HLA-G⁶⁵, as well as the demonstration of a subpopulation of “pregnancy-trained” uNK cells in repeated compared with first pregnancies, characterized by high expression of the receptors NKG2C and LILRB1 and increased IFN γ and VEGF-A secretion¹¹⁸.

Besides uNK cells, other innate lymphoid cells have been identified in human decidua^{15–17}, including CD56⁺CD94⁻ non-cytotoxic type 1 ILCs (ILC1s), CD56⁻CD117⁺CD127⁺ lymphoid tissue inducer (LTI)-like cells, and CD56⁺CD94⁻CD117⁺CD127⁺NKp44⁺ type 3 ILCs (ILC3s). These ILCs may contribute to the cytokine production reported by decidual CD56⁺ cells. For example, ILC1s may contribute to IFN γ production, while ILC3s produce IL-22 and CXCL8, which may regulate neutrophil recruitment¹¹⁹. The distribution and function of the different ILC populations are still unknown, although it has been suggested that ILC3 cytokine production may be regulated by programmed cell death (PD-1) expressed by ILC3s and its ligand PD-L1 expressed by EVT¹²⁰.

It is now clear that “uNK cells” are not a single population and the relative importance of these subpopulations may change as gestation progresses. ILCs in decidua may contribute to the reported cytokine production by CD56⁺ uNK cells and this may differ according to different purification and activation protocols. Abnormal function in pathological pregnancy could affect specific uNK cell subpopulations or ILCs. Rather than referring to “uNK cells”, perhaps we should dissect populations more precisely and consider the functional contribution of ILCs. Technical advances may allow localization of different subpopulations, and investigation of pathological pregnancies may provide valuable clues to function. The advent of scRNA-seq technology provides an exciting way forward to unravel the role of uNK cells in normal and pathological pregnancy, making it possible to target specific cell populations for more accurate diagnosis and potential intervention.

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