



妊娠早期母胎界面免疫微环境与妊娠相关疾病

丁小雨, 魏海明*

中国科学技术大学生命科学与医学部免疫学研究所, 合肥 230027

* 联系人, E-mail: ustcwhm@ustc.edu.cn

收稿日期: 2023-08-07; 接受日期: 2023-08-29; 网络版发表日期: 2024-01-11

国家自然科学基金(批准号: 81930037, U19A2024)与国家重点研发计划(批准号: 2022YFA1103603)资助

摘要 妊娠期胎儿绒毛外滋养层细胞(extravillous trophoblasts, EVT_{TS})侵入母体子宫蜕膜组织。然而, 母体免疫系统识别半基因不合的胎儿并支持其在体内发育的现象与经典的免疫排斥理论相悖。母体免疫系统对非自体胎儿建立免疫耐受的同时还需要抵御感染, 因此需要母胎微环境高度协调以促进成功妊娠。而复发性自然流产(recurrent spontaneous abortion, RSA)、子痫前期(preeclampsia, PE)和感染等发生不良妊娠结局的风险较高, 研究表明这与母胎界面免疫微环境失衡密切相关。本综述主要介绍了妊娠早期母胎界面免疫微环境, 尤其是当前对蜕膜NK(decidua NK cell, dNK)细胞的功能认识。此外, 也讨论了RSA, PE和感染状态下, 母胎界面免疫微环境改变, 尤其是dNK细胞变化, 对妊娠结局的影响。旨在总结和进一步认识正常和异常妊娠过程中的母胎界面免疫微环境变化, 为妊娠疾病的治疗提供理论依据。

关键词 母胎界面免疫微环境, 蜕膜NK细胞, 复发性自然流产, 子痫前期, 感染

妊娠过程中囊胚诱导子宫内膜发生蜕膜化, 主要特征为孕酮和雌激素刺激小纺锤形子宫内膜基质细胞分化为大圆形蜕膜基质细胞。此外, 蜕膜化还表现为免疫细胞聚积, 子宫内膜动脉变得更加曲折和拉长^[1]。在人类中, 非妊娠子宫内膜在每个月经周期(月经周期的第23~25天左右)也会经历蜕膜化^[2]。在没有囊胚附着的情况下, 变厚的蜕膜会随着经血流出^[2]。相比之下, 小鼠的蜕膜化必须依赖受精作用。建立和维持母胎免疫耐受对于预防母体对半基因不合胎儿的免疫排斥反应及支持成功妊娠至关重要^[3]。在妊娠早期, 免疫细胞占人类蜕膜细胞的40%。其中, NK细胞约占免疫细胞的70%, 巨噬细胞和T细胞占10%~30%^[4]。在小鼠中,

CD49a⁺Eomes⁺组织驻留NK细胞在妊娠早期开始富集直到妊娠中期比例达到最高^[5]。怀孕期间蜕膜富含的NK细胞称为蜕膜NK(decidua NK cell, dNK)细胞。妊娠早期免疫细胞, 尤其是dNK细胞, 对于维持免疫耐受、促进血管生成、促进滋养细胞入侵以及胚胎发育至关重要。本综述阐述了由表达CD27和CD11b定义的三种类型dNK细胞亚群的不同作用, 并总结了dNK细胞在健康怀孕期间的五大生理功能。

母胎界面免疫微环境失衡导致母体无法对胚胎维持免疫耐受及支持胚胎发育, 进而引起不良妊娠结局。越来越多的研究表明, 母胎界面免疫异常是导致RSA以及PE等的重要原因之一。此外, 在病原体感染情况

引用格式: 丁小雨, 魏海明. 妊娠早期母胎界面免疫微环境与妊娠相关疾病. 中国科学: 生命科学, 2024, 54: 147–160

Ding X Y, Wei H M. Immune microenvironment at the maternal-fetal interface in early pregnancy and pregnancy-related diseases (in Chinese). Sci Sin Vitae, 2024, 54: 147–160, doi: [10.1360/SSV-2023-0171](https://doi.org/10.1360/SSV-2023-0171)

下, 免疫细胞发挥免疫防御作用帮助抵抗感染并促进成功妊娠. 本文对dNK细胞在上述异常妊娠情况下表型及功能变化进行了讨论.

1 母胎界面免疫微环境的组成

母胎界面免疫微环境主要由母体蜕膜免疫细胞和基质细胞, 以及胚胎滋养层细胞所组成. 蜕膜组织主要由蜕膜基质细胞、血管内皮细胞、腺上皮细胞和免疫细胞组成. 妊娠早期, 免疫细胞占蜕膜细胞的40%. 其中, NK细胞可占70%, 巨噬细胞(macrophages, MΦ)占比10%~20%, T细胞占比10%左右. 而DC细胞, B细胞和NKT细胞占比非常少^[6].

1.1 dNK细胞的来源、分型和功能

dNK细胞是妊娠早期最主要的免疫细胞亚群, 在正常妊娠过程中发挥至关重要的作用. 关于dNK细胞的起源目前主要有三种观点: dNK细胞可以从表达CD122和转录因子E4BP4的CD34⁺子宫驻留祖细胞(区别于CD34⁺血管内皮细胞)分化而来^[7], 也可以从增殖的组织驻留NK(tissue resident NK, trNK)细胞和妊娠训练的dNK(pregnancy treated decidual NK, PTdNK)细胞增殖产生^[8], 或在转化生长因子(transforming growth factor beta, TGF-β)作用下从外周血NK(peripheral blood NK, pNK)细胞转化成蜕膜样NK细胞^[9].

dNK细胞的表型和功能与pNK细胞不同. CD56^{bright}CD16⁻CD49a⁺细胞占人类dNK细胞的大多数, 而CD56^{dim}CD16⁺CD49a⁻pNK细胞是主要的pNK细胞亚群. 杀伤细胞凝集素样受体(lectin-like receptors, KLR)家族成员NKG2A, NKG2C和NKG2E, 和杀伤细胞免疫球蛋白样受体(killer cell immunoglobulin-like receptors, KIR)家族成员KIR2DL1, KIR2DL2/3和KIR2DL4在dNK细胞上高表达. 这些抑制性受体抑制dNK细胞对半同种异体胎儿的细胞毒性. 此外, dNK细胞表达NK细胞激活受体NKp46, NKp30和NKp44. 只有NKp46的活化才能诱导dNK细胞脱颗粒和免疫突触形成. NKp30和NKp44在dNK细胞和pNK细胞中由不同的剪接变体表达. dNK细胞中NKp30和NKp40的抑制亚型抑制抗体刺激期间的细胞毒性^[10]. 此外, dNK细胞中颗粒溶血素(antimicrobial peptide granulysin, GNLY)、颗粒酶A(granzyme A, GZMA)和颗粒酶B

(granzyme B, GZMB)含量比pNK细胞中更丰富. 然而, dNK细胞的细胞毒性远低于pNK细胞. dNK细胞具有区别于pNK细胞的独特表型特征, 这与其在怀孕过程中的重要功能密切相关^[11].

基于CD11b和CD27的表达可以按照功能性成熟程度将妊娠早期dNK细胞划分为3个不同细胞亚群^[12], 包括CD11b⁻CD27⁻, CD27⁺和CD11b⁺CD27⁻dNK细胞^[13]. 人蜕膜中约60%的NK细胞为CD11b⁻CD27⁻细胞亚群, 而外周血NK细胞90%以上为CD11b⁺CD27⁻细胞亚群^[14,15]. 研究表明, CD27⁺细胞亚群分泌细胞因子的能力最强, 可以通过分泌IFN-γ抑制炎症性Th17细胞极化^[16]. CD11b⁺CD27⁻细胞具有杀伤功能, 研究发现流产患者中这群细胞通过下调miRNA-483促进胰岛素样生长因子1(insulin-like growth factor-1, IGF-1)的分泌, 表现出增强的细胞毒作用^[17]. 因此, 推测CD11b⁺CD27⁻dNK细胞可能通过分泌IGF-1杀死病原体感染的细胞. CD11b⁻CD27⁻作为蜕膜中主要的NK细胞亚群, 表现出不成熟的特征, 并具备向其他亚群分化的潜能^[15]. 这群细胞具有CD49a⁺EOMES⁺trNK细胞的表型和功能特征, 被证明具有分泌生长因子的功能并促进胚胎发育^[18], 这在dNK细胞功能部分会详细介绍. Vento-Tormo等人^[19]通过单细胞RNA测序将孕早期dNK细胞划分为三个主要亚群(dNK1, dNK2和dNK3). dNK1细胞表达更高水平的KIR(KIR2DS1, KIR2DS4, KIR2DL1, KIR2DL2和KIR2DL3), 识别EVTs细胞表面表达的人白细胞抗原(human leukocyte antigen, HLA)-C受体. 同时, dNK1细胞也高表达白细胞免疫球蛋白样受体B1(leukocyte immunoglobulin-like receptor subfamily B member 1, LILRB1, 也称为ILT2), 可以与EVTs细胞表面表达HLA-G分子相互作用. 因此, dNK1细胞能够促进滋养层侵袭性, 血管重塑和维持免疫耐受. dNK2和dNK1共同表达杀伤细胞凝集素样受体NKG2A, NKG2C和NKG2E. 此外, dNK2细胞还表达高水平的X-C基序趋化因子配体1(X-C Motif Chemokine Ligand 1, XCL1). 通过与X-C基序趋化因子受体XCR1互作, dNK2促进EVTs和树突状细胞cDC1募集. dNK3细胞比例较低, 显示出趋化因子配体5(C-C chemokine ligand 5, CCL5)的高表达. C-C基序趋化因子受体1(C-C chemokine receptor type 1, CCR1, CCL5的受体)由EVTs表达. 这表明dNK3细胞具有调节EVTs侵袭中的作用^[19].

1.2 dMΦ细胞的来源、分型和功能

蜕膜巨噬(decidual macrophage, dMΦ)细胞是母胎界面另一种重要的免疫细胞, 可极化为M1和M2两种表型. 随着妊娠进程, dMΦ细胞表现出复杂的时空变化. 目前关于dMΦ的来源尚无定论, 人早期妊娠蜕膜组织中有大量Ki67⁺的巨噬细胞推测可能是由已存在的子宫内膜巨噬细胞增殖而来^[20], 另外母胎界面多种细胞表达趋化因子CCL2, 提示dMΦ也可能从外周循环系统中招募而来^[21]. 研究表明, 在胚胎着床前子宫蜕膜巨噬细胞主要表现为M1型, 当滋养细胞侵入子宫内时, 巨噬细胞极化为M1/M2混合细胞群体, 胎盘发育形成后直到分娩以M2型占据主导地位^[5]. M1/M2型巨噬细胞间极化平衡对于正常妊娠的建立和维持至关重要, 包括促进胚胎植入、母胎界面免疫耐受的建立和维持、螺旋动脉重铸、滋养细胞入侵、凋亡细胞吞噬和分娩发动. CD11b⁺巨噬细胞对于维持卵巢中的黄体(通过分泌黄体酮来维持早期怀孕)是必需的, 白喉毒素(diphtheria toxin, DT)处理CD11b-DTR小鼠以清除巨噬细胞导致早期植入失败, 通过补充黄体酮可以挽救植入异常^[22]. 巨噬细胞通过抑制T细胞和NK细胞的活化促进母胎界面免疫耐受. 巨噬细胞表达免疫抑制分子, 如白细胞介素10(interleukin 10, IL-10)、吲哚胺2,3双加氧酶(indoleamine-2,3-dioxygenase, IDO)、TGF-β和前列腺素E2(prostaglandin E2, PGE2)等^[23], 抑制具有细胞毒性的白细胞活化, 进而诱导免疫耐受. 妊娠早期dMΦ表达B7家族共刺激分子B7-H1和B7-DC, 通过与它们的共同受体PD-1结合抑制T细胞活性^[24]. M2型巨噬细胞通过产生TGF-β诱导dNK细胞分化为杀伤毒性小、分泌细胞因子能力强的NK细胞亚群, 维持免疫耐受^[25]. 通过产生蛋白水解酶MMP-7和-9, 巨噬细胞导致血管平滑肌细胞层之间凝聚力的破坏和松弛, 为螺旋动脉重铸、滋养细胞入侵做准备^[26]. 妊娠期间, 当细胞发生凋亡时, 母胎界面的巨噬细胞能够快速识别并通过吞噬作用迅速清除凋亡细胞^[27]. 妊娠晚期巨噬细胞大量产生炎性介质, 包括IL-1β, IL-6, TNF-α, MMP和NO^[28-30], 有助于分娩发动^[31]. 因此, 妊娠期保持M1/M2型巨噬细胞的动态平衡, 对于促进成功妊娠必不可少. 此外, 按照CD11c表达高低, CD14⁺dMΦ被分为CD11c^{low}和CD11c^{high}两个亚群^[32]. 其中,

CD11c^{low}dMΦ细胞占总巨噬细胞的67%左右, 而CD11c^{high}dMΦ细胞占比约33%. CD11c^{low}dMΦ细胞表达CD206和CD209水平高, 主要发挥维持稳态和促进生长发育的功能. 而CD11c^{high}dMΦ细胞表达CD206和CD209水平更低, 起抗原加工呈递作用^[33]. 根据CCR2和CD11c表达水平, dMΦ又被分为CCR2⁻CD11c^{low}和CCR2⁺CD11c^{high}和CCR2⁻CD11c^{high}三个亚群, 分别发挥抗原呈递、促炎和抗炎作用^[34,35].

1.3 dT细胞的分型和功能

母胎界面的T细胞包括CD4⁺T细胞和CD8⁺T细胞^[36]. 其中, CD4⁺T细胞可分化为Th1, Th2和Th17细胞和调节性T细胞(regulatory T cells, Treg细胞)^[37]. 在妊娠过程中, CD4⁺CD25^{Hi}FoxP3⁺Treg细胞数量大量增加以建立母胎免疫耐受微环境^[37]. 并且发现Treg细胞在自然早产、先兆子痫和复发性流产人群外周血中所占细胞比例呈现显著降低趋势^[38]. 一般认为, 母胎界面Th1/Th2细胞平衡向Th2偏移, Th17/Treg细胞平衡偏向于Treg^[39]. 妊娠期间Th1和Th2, Th17和Treg细胞间平衡被打破将导致妊娠并发症^[39]. 与dNK细胞相比, 蜕膜CD8⁺T(decidual CD8⁺T, CD8⁺dT)细胞占蜕膜总免疫细胞比例较小. 但CD8⁺dT细胞是母胎界面识别和响应病原体感染的关键细胞之一. 相比于外周血CD8⁺T细胞(peripheral blood CD8⁺T, CD8⁺pT), CD8⁺dT细胞中颗粒酶和穿孔素表达水平显著降低, 但mRNA水平仍然较高. 推测转录后修饰机制可能影响了CD8⁺dT中细胞溶解分子的蛋白表达. 同时, CD8⁺dT细胞表达PD1, CTLA4和LAG3等共抑制分子水平更高. CD8⁺dT降低效应反应, 有助于维持母体对胎儿的耐受. Adrian Erlebacher课题组研究发现^[40], 蜕膜基质细胞中吸引T细胞的炎症趋化因子基因的表现遗传沉默使得效应T细胞不能积聚在小鼠蜕膜内. 蜕膜基质细胞对于效应T细胞定位的调节可能允许母胎界面免疫耐受的建立和维持^[40]. 然而, CD8⁺dT在体外刺激下能够脱颗粒、增殖、产生IFN-γ和TNF-α及细胞溶解分子. 因此, CD8⁺dT仍然保留了促炎能力, 并非永久处于免疫抑制状态^[41]. 综上, T细胞对维持免疫耐受和抵御先天性感染至关重要. 它在总细胞中的占比异常和功能改变与胚胎着床失败及流产等不良妊娠具有显著相关性^[41].

2 dNK细胞的功能

2.1 dNK细胞促进螺旋动脉重塑

螺旋动脉重塑对确保胎儿在整个怀孕期间获得足够的营养和氧气十分必要。在人类和小鼠中都观察到螺旋动脉重塑,但它们的重塑过程不同。在人类怀孕期间,螺旋动脉重塑分为两个阶段。第一阶段独立于绒毛外滋养层细胞,蜕膜螺旋小动脉转变为高容量、低阻力的血管。第二阶段是EVTs侵袭和血管内滋养层细胞替代血管内皮细胞^[42]。而在小鼠中并没有观察到EVTs替代血管内皮细胞。人螺旋动脉重塑初始特征是血管平滑肌细胞(vascular smooth muscle cells, VSMCs)肿胀、细胞外基质(extracellular matrix, ECM)降解、VSMCs去分化以及部分血管内皮细胞和VSMCs凋亡^[42]。第二阶段EVTs入侵血管替代VSMCs和血管内皮细胞并形成栓塞^[42],从而排除富氧母体血液来创造缺氧环境。研究表明dNK细胞和dMΦ细胞局部聚集在蜕膜血管周围,与蜕膜螺旋动脉重塑有关。来自dNK细胞的条件培养基(conditioned medium, CM)可减少ECM中的胶原蛋白IV和层黏连蛋白并增强子宫肌层中的VSMC层分离。使用泛基质金属蛋白酶(matrix metalloproteinases, MMP)抑制剂处理可消除这种效应^[43]。说明dNK细胞通过分泌MMPs加速螺旋动脉周围ECM的降解。来自dNK细胞的CM可增强VSMC细胞系的体外去分化^[44]。还发现dNK细胞的CM可诱导绒毛膜板动脉(chorionic plate arteries, CPA)中VSMC的去分化,且这一过程依赖dNK细胞分泌的血管生成素(angiopoietin, Ang)-1或Ang-2^[45]。此外,人dNK细胞通过分泌血管内皮生长因子(vascular endothelial growth factor, VEGF)和胎盘生长因子(placental growth factor, PLGF)来促进血管生成^[46]。总之,人dNK细胞通过分泌MMPs, Ang-1, Ang-2和VEGF-α来促进螺旋动脉重塑,如图1所示。在小鼠中dNK细胞通过分泌IFN-γ促进血管生成和螺旋动脉重塑^[47]。

2.2 dNK细胞控制EVTs细胞的侵袭

在人类怀孕期间,适当的EVTs细胞浸润螺旋动脉并取代血管内皮细胞对于健康妊娠至关重要。EVTs细胞侵袭不足可导致先兆子痫并导致胎儿生长受限,而EVTs细胞侵袭过多可导致胎盘过度植入和产妇产后出血^[48]。人dNK细胞可增加EVTs细胞侵袭,同时抑制

EVTs细胞的过度侵袭,如图1所示。

EVTs细胞表达经典的I类主要组织相容性复合体(class I major histocompatibility complex, MHC-I),如HLA-C,和非经典MHC-I类分子,包括HLA-E和HLA-G,而dNK细胞表达识别HLA-C, HLA-E和HLA-G的受体。dNK细胞表达抑制性受体KIR2DL1和活化性受体的KIR2DS1/S4,可识别HLA-C2,以及抑制性受体KIR2DL2/L3和活化性受体的KIR2DS2,可识别HLA-C1^[49]。NK细胞上的KIR和EVTs细胞上的HLA-C之间的相互作用控制EVTs侵袭。体外和体内侵袭试验显示, dNK细胞表达和分泌白细胞介素(IL)-8(C-X-C motif chemokine ligand 8, CXCL8),干扰素诱导蛋白(interferon-inducible protein, IP)-10(C-X-C motif chemokine ligand 10, CXCL10)促进HLA-G滋养层向dNK细胞的迁移^[50]。此外,发现EVTs细胞表达HLA-G与dNK细胞上的KIR2DL4结合,激活IL-8的产生^[51]。同时,研究表明dNK细胞还可以通过IFN-γ和TNF-α增加EVTs细胞凋亡从而限制EVTs细胞侵袭^[13]。

2.3 dNK细胞维持母胎界面免疫耐受

母体免疫细胞和胎儿半基因不合的EVTs细胞在母胎界面相互识别,建立免疫抑制微环境。人类妊娠早期母胎界面约70%的免疫细胞是dNK细胞,这对于维持免疫耐受至关重要,如图1所示。

dNK细胞表达受体KIR2DL4和ILT2,它们与EVTs细胞上的HLA-G结合以维持耐受性。在不表达HLA-I的721.221细胞系上过表达HLA-G可以降低NK细胞系和dNK细胞靶细胞的细胞毒性^[52]。此外,约有2.5% dNK细胞表面有HLA-G,而表面HLA-G⁻ dNK中含有内化的HLA-G。使用细胞因子处理或病毒产物激活dNK细胞导致内化的HLA-G消失和细胞毒性的恢复^[53]。表明dNK细胞胞吞EVTs细胞表面的HLA-G来降低细胞毒性和维持耐受。此外,大多数dNK细胞表达T细胞免疫球蛋白黏液3(T-cell immunoglobulin and mucin domain containing 3, Tim-3),而大多数蜕膜基质细胞和滋养层表达Tim-3配体半乳糖凝集素9(galectin 9, Gal-9)^[54]。在使用单细胞RNA-seq分析鉴定的三个主要的人类蜕膜NK亚群中, Tim-3在dNK1亚群上高度表达^[19]。在用PMA和离子霉素刺激时,相比于Tim-3⁻ dNK, Tim-3⁺ dNK细胞产生更多的IL-4和更少的TNF-α和穿孔素。在LPS处理下,与滋养层共培养的

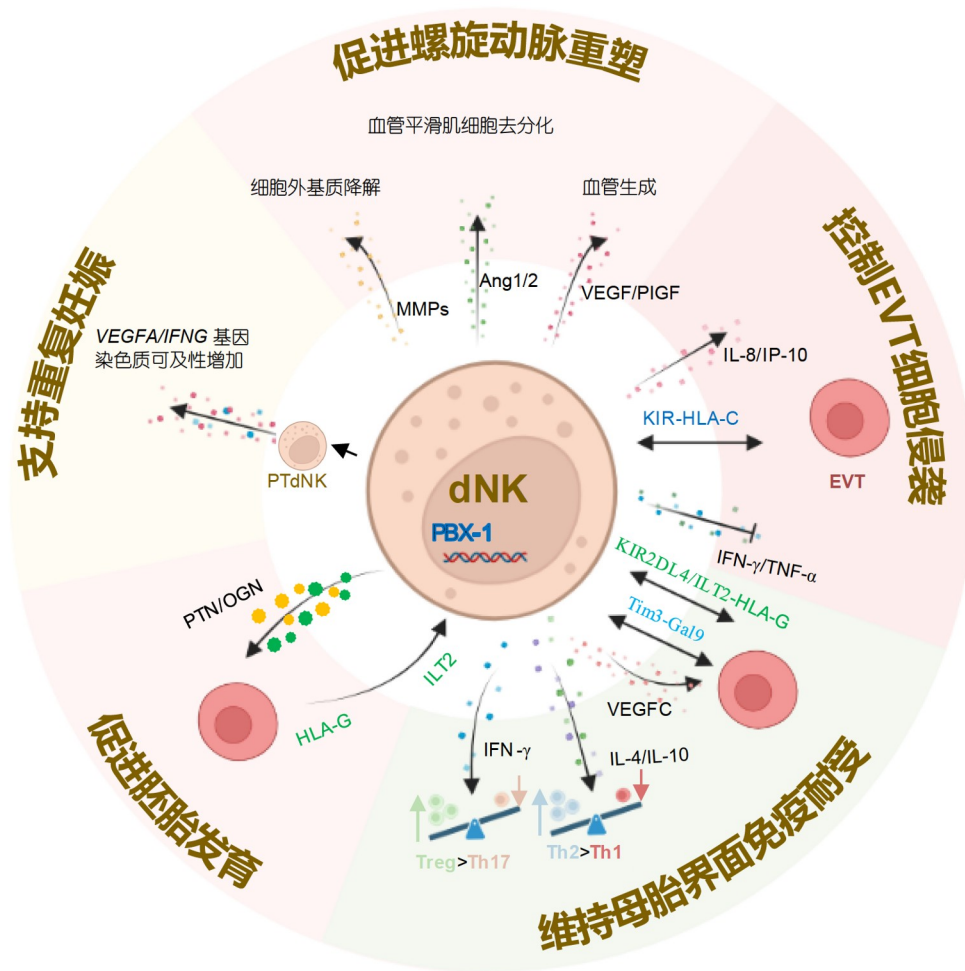


图 1 妊娠期dNK细胞的功能. dNK细胞在正常妊娠过程中发挥五大生理功能: dNK细胞通过多种方式促进螺旋动脉重塑; dNK细胞促进EVTs入侵同时抑制过度侵袭; dNK细胞有助于维持母胎界面免疫耐受; dNK细胞分泌生长促进因子促进胚胎发育; “记忆性”妊娠训练的dNK细胞支持经产妇女重复妊娠. 本图由BioRender.com创建

Figure 1 Function of dNK cells during pregnancy. dNK cells carry out five functions during normal pregnancy. dNK cells promote spiral artery remodeling in a variety of ways; dNK cells promote the invasion of EVTss while inhibiting excessive invasion; dNK cells contribute to maintain immune tolerance at the maternal-fetal interface; dNK cells promote embryonic development through the secretion of growth-promoting factors; “Memory” PTdNK cells support repeat pregnancy in post-parting women. The diagram was created with BioRender.com

dNK细胞一致产生更多的IL-4和更少的TNF- α , 这些效应被添加针对Tim-3的中和抗体所阻断^[54]. 此外, Gal-9/Tim-3抑制CD107a介导的脱颗粒, 降低dNK细胞对滋养层细胞系HTR-8的细胞毒性进而维持免疫耐受^[55]. 因此, 通过人dNK细胞表达的Tim-3识别EVTs细胞中的Gal-9有助于维持免疫耐受性. 另一项工作显示, dNK细胞分泌的VEGFC而非VEGF α 可抑制它对HTR-8和人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVECs)的细胞毒性^[46]. VEGFC的细胞保护可能与靶细胞中TAP-1表达、MHC I类组装的诱导和

HLA-E诱导表达有关^[46]. 这些发现表明, 人类dNK细胞分泌VEGFC以抑制对EVTs细胞的细胞毒性.

人dNK细胞也可以诱导Treg和Th2细胞并抑制Th17和Th1细胞来维持耐受. dNK细胞与同种异体蜕膜CD14⁺细胞互作可以诱导Treg细胞产生^[56]. dNK细胞和蜕膜CD14⁺细胞的互作是由可溶性因子IFN- γ 介导的. IFN- γ 促进蜕膜CD14⁺细胞中IDO表达, 从而诱导Treg细胞^[56]. 人CD56^{bright}CD27⁺dNK细胞产生的IFN- γ 抑制Th17细胞的诱导. 在小鼠中, 同种异体妊娠期间这种NK细胞缺失导致蜕膜Th17细胞的积累和广泛的

局部炎症并诱导胎儿丢失^[57]。此外, dNK细胞能产生Th2细胞因子IL-4和IL-10诱导Th2型极化, 并鉴定CD56^{bright}CXCR4⁺dNK细胞是妊娠早期建立免疫耐受的积极参与者^[13,58]。

总之, dNK细胞通过表达受体KIR2DL4, ILT2和Tim3或通过分泌VEGFC来抑制对EVTS细胞的细胞毒性进而维持耐受。此外, dNK细胞通过分泌细胞因子IFN- γ , IL-4和IL-10诱导T细胞耐受。

2.4 dNK细胞促进胚胎发育

在怀孕的前三个月胎盘尚未形成, 在此过程中蜕膜组织向胚胎供应养分。因此, dNK细胞可能参与促进胎儿发育。人dNK细胞被证明表达促生长因子(pleiotrophin, PTN)、骨甘氨酸(osteoglycin, OGN)等促进胚胎生长的因子, CD49a⁺Eomes⁺ trNK细胞是这些生长促进因子的主要来源。研究发现EVTS细胞上的HLA-G和dNK细胞上的受体ILT2诱导生长促进因子的表达。在小鼠trNK细胞中也得到上述结论。Nfil3^{-/-}小鼠与野生型小鼠相比, CD49a⁺Eomes⁺ trNK细胞以及PTN和OGN表达在怀孕期间明显降低。Nfil3^{-/-}小鼠胚胎表现出胎儿生长受限, 体重明显减轻, 骨骼和软骨发育明显延迟^[18]。已经确定了dNK细胞分泌生长促进因子(growth-promoting factors, GPFs)的机制。Zhou等人^[59]发现转录因子前B细胞白血病转录因子1(pre-B-cell leukemia transcription factor 1, PBX1)在人和小鼠trNK细胞中高表达。EVTS细胞上的HLA-G与dNK细胞上的ILT2结合, 通过活化AKT途径上调PBX1的表达。PBX1通过直接结合人和小鼠dNK细胞基因组中的启动子来促进PTN和OGN的表达^[59]。在NK细胞特异性Pbx1缺陷小鼠中, PTN和OGN表达降低, 胎儿生长严重受损。最近Du等人^[60]用人骨髓造血干细胞(human hematopoietic stem cells, HSCs)、脐带血HSCs或pNK细胞诱导产生表达促生长因子PTN和OGN的蜕膜样NK细胞。将诱导细胞输注到免疫缺陷的怀孕的NCG小鼠中, 发现蜕膜样NK细胞能够促进小鼠胚胎发育和改善动脉血流, 胎儿的重量和长度明显增加。一系列的工作证明了妊娠早期dNK细胞可以通过分泌生长因子直接滋养胚胎发育, 见图1。

2.5 “记忆性”dNK细胞亚群有助于支持重复妊娠

经产妇女与初产妇女相比, 发生宫内生长受限(in-

trauterine growth restriction, IUGR)和早产(small for gestational age, SGA)等“大产科综合征”的频率更低^[61], 且表现出更强的滋养层细胞侵袭和血管生成能力^[62]。研究表明, 这些现象与PTdNKs有关, 这群“记忆性”dNK表面高表达自然杀伤细胞2族成员C(natural-killer group 2-members C, NKG2C)受体和ILT2。PTdNKs在IFNG和VEGFA基因的增强子周围染色质可及性增加, 上述受体分别与HLA-E和HLA-G相互作用时, 导致IFN- γ 和VEGF α 的产生和分泌增加, 进而促进胎盘血管生成, 如图1所示^[8]。

综上所述, dNK在妊娠过程中发挥至关重要的作用, 能够促进螺旋动脉重塑, 控制EVTS细胞入侵, 维持免疫耐受, 促进胚胎发育以及产生妊娠记忆性。

3 母胎界面免疫微环境变化与妊娠相关疾病

3.1 复发性自然流产患者母胎界面免疫微环境变化

复发性自然流产(recurrent spontaneous abortion, RSA)被定义为在妊娠20~24周内与同一伴侣发生两次或两次以上临床公认的自然流产, 超过一半以上的RSA发生原因不明^[63]。目前认为免疫功能障碍占不明原因反复流产病例的一半以上^[64]。dNK, dM Φ 以及T细胞等亚群比例失衡和功能紊乱导致母胎界面免疫微环境异常和生殖障碍。RSA患者和对照组相比, 总的dNK细胞比例和数量差异在不同研究中得出的结论并不一致, 但普遍认为RSA患者来源的dNK细胞细胞毒性较高^[65,66]。RSA妊娠女性dNK细胞组织驻留标记分子CD49a较低, 而穿孔素, 颗粒酶B和IFN- γ 的表达水平高于年龄匹配的健康对照^[67]。RSA患者母胎界面具有细胞毒性作用的CD16⁺dNK细胞更多, 且这群细胞表达细胞毒性受体NKp46, NKp44和NKp30的水平更高^[66]。一项研究显示约60%的dNK细胞表达Tim-3。Tim-3⁺dNK比Tim-3⁻dNK细胞产生更多的Th2型细胞因子, 例如IL-4和IL-10, 而不是Th1型细胞因子, 例如TNF- α 和穿孔素^[54]。RSA患者与正常妊娠女性相比, Tim-3⁺dNK细胞比例明显降低, Th1/Th2型细胞因子平衡打破, 最终导致母胎免疫耐受紊乱^[54]。在妊娠过程中, 部分RSA患者外周血和蜕膜中Th17细胞比例和IL-23(Th17细胞因子)浓度显著增加, 而Treg细胞数量减

少^[68]. 缺乏蜕膜NK细胞介导的免疫调节反应, 导致了显著的Th17反应和广泛的局部炎症, 最终打破母胎免疫耐受性^[69]. 研究表明, RSA患者常常表现出M1/M2型巨噬细胞平衡紊乱, M1型巨噬细胞占主导地位^[70]. M1型巨噬细胞通过转运miR-146b-5p直接抑制TRAF6表达, 可抑制上皮-间充质转化(epithelial-mesenchymal transition, EMT)、迁移和滋养层侵袭, 从而参与RSA的发病机制^[71]. 排除胚胎染色体异常情况, RSA患者和正常妊娠女性相比, 促炎性细胞亚群CD11c^{high}dMΦ比例明显升高, 且巨噬细胞分泌IL-10的水平明显降低^[72]. 已知CD45⁺CD14⁺ dMΦ细胞也高表达COX-2, 而RSA患者果糖-1,6-二磷酸(fructose-1,6-bisphosphate, FBP)水平较低, 导致COX-2⁺M2型巨噬细胞分化不充分和胚胎丢失^[73]. 如图2A所示, 评估免疫细胞不同亚群的数量和功能变化可能有助于RSA患者妊娠结局的预测和干预.

3.2 子痫前期患者母胎界面免疫微环境变化

子痫前期, 尤其是早发型PE, 发病原因主要是胎盘特定细胞亚群(绒毛外滋养层)不能完全转化子宫螺旋动脉. 螺旋动脉重塑异常和滋养层细胞入侵子宫不足是PE发病的核心因素^[74]. 该疾病影响全世界2%~8%的妊娠^[75]. 鉴于妊娠早期dNK细胞在促进螺旋动脉重塑和滋养层细胞入侵中的关键作用, 因此dNK细胞功能障碍可能是子痫前期的启动因素^[76]. 然而, 由于临床标本的限制, 目前关于PE患者NK细胞的功能研究主要集中在孕中晚期, 而对启动因素(孕早期的dNK细胞功能)研究并不清楚. 关于PE患者中dNK细胞数量变化目前没有统一结论^[77]. 因此, 相比于关注dNK细胞绝对数量的改变, 探究功能变化似乎更有意义. 研究显示, 相比于早产和正常足月妊娠对照, PE患者dNK细胞NKp46表达水平更高, 而IFN- γ , IL-8和CD107a表达下调^[78]. 作者还发现PE患者蜕膜CD3⁺CD4⁺Foxp3⁺, CD4⁺CD25⁺或CD4⁺CD25⁺Foxp3⁺Treg细胞比例和产生TGF- β 1水平高于健康对照^[78]. 直接分离PE患者来源的Treg细胞与dNK细胞共培养或者外源性添加TGF- β 1均导致IFN- γ , IL-8和CD107a表达降低, 并抑制血管生成^[78]. 两项研究报道PE患者循环系统和胎盘床活检样本中Treg细胞比例低于健康对照^[79,80]. 可能是检测样本不同导致PE患者Treg细胞变化在不同研究中报道不一致. 关于Treg细胞通过调控其他免疫细

胞诱导PE疾病发生在这篇综述中有更详细的描述^[76]. 如果dNK细胞携带KIR AA基因型(丢失大部分或者全部活化性KIRs), 当与滋养层细胞表达的HLA-C2相互作用时会导致dNK细胞过度抑制, 血管生成受阻和螺旋动脉重铸缺陷, 最终使得PE风险增加^[81,82]. 正常妊娠过程中dNK细胞表面抑制性受体KIR2DL4与滋养层细胞表达HLA-G相互作用, dNK细胞不会杀伤滋养层细胞. 然而, PE患者的滋养层细胞表达HLA-G水平降低而受dNK细胞毒作用, 导致PE的发生^[83]. 在人和小鼠中缺陷抑制性受体CD94/NKG2A教育dNK细胞导致PE发生^[84]. 与健康对照相比, PE患者巨噬细胞极化失调. M1型巨噬细胞在PE患者的胎盘、蜕膜和周围子宫螺旋动脉中比在健康妊娠组织中更丰富^[85]. 与RSA妊娠疾病相似, PE患者T细胞分化偏向于促炎性 Th1和Th17细胞表型^[86]. 综上所述, 如图2B所示, PE发病机制与免疫细胞功能失衡密切相关.

3.3 细菌和病毒感染相关妊娠患者母胎界面免疫微环境变化

孕妇的病原体感染可能导致母体全身免疫反应的激活, 破坏母胎界面的稳态. 此外, 一些病原体可以通过胎盘屏障感染胎儿. 因此, 致病性微生物感染可能导致不良妊娠结局, 如流产、早产、死产和新生儿并发症. dNK细胞可以识别和消除这些病原体, 从而防止不良妊娠结局, 如图2C所示.

(1) 李斯特菌感染相关妊娠. 妊娠期单核细胞增生李斯特菌(*Listeria monocytogenes*, Lm)感染途径为口服或通过上行阴道感染母体蜕膜, 以此扩散到胎盘并感染胎儿. 妊娠期李斯特菌感染导致早产和死产, 并增加新生儿脑膜炎、败血症以及其他妊娠并发症的发病率^[87]. 研究发现人dNK细胞能够杀死人滋养层细胞系JEG3和原代EVTS细胞中的Lm, 但不会杀死JEG3细胞和EVTS细胞. 其机制是dNK细胞形成纳米管, 将GNLY, 而不是其他细胞死亡诱导细胞毒性颗粒蛋白转移到受感染的JEG3和EVTSs细胞中^[88]. 最近, Fang等人^[89]发现dNK细胞消除感染滋养层的细胞内细菌时, 还可以合成更多的脂质并通过载脂蛋白D(apolipoprotein D, APOD)将脂质转运到滋养层以避免其凋亡. 因此, dNK能够抑制胞内细菌感染, 同时保持母胎屏障完整来防止不良妊娠结局. 此外, 胎盘滋养层组成性分泌炎症小体相关细胞因子IL-1 β 和IL-18. 胎盘来源的

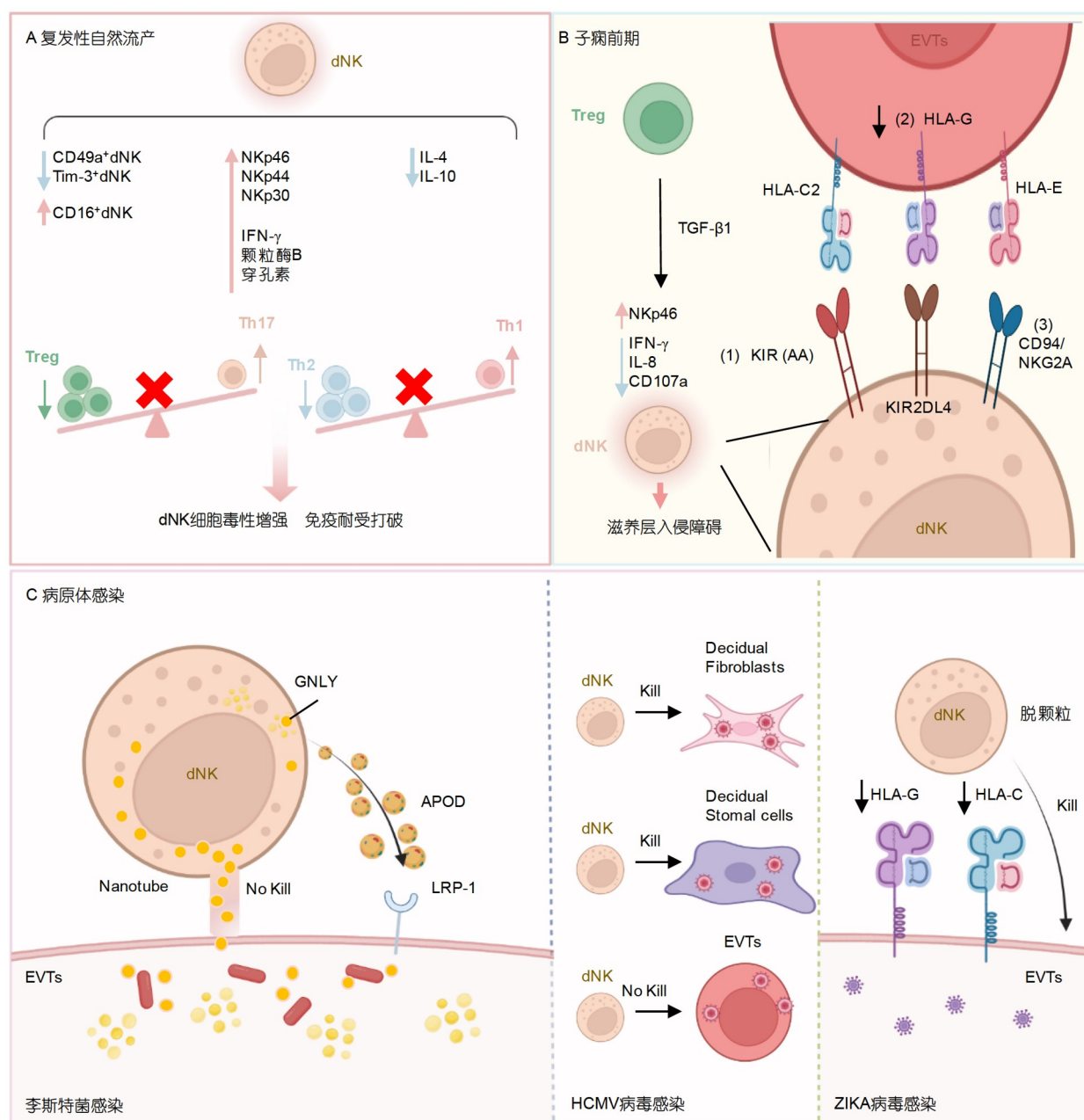


图 2 异常妊娠过程中dNK细胞的亚群及功能变化。A: 复发性自然流产患者中, dNK细胞亚群、表面受体表达和分泌细胞因子水平变化, M1/M2型巨噬细胞、Th1/Th2细胞和Treg/Th17细胞偏向性被打破; B: 子痫前期患者中, dNK细胞上携带KIR AA基因型等位基因, 当滋养层表达HLA-C2时会导致dNK细胞强烈抑制, 母体患PE的风险增加; C: dNK细胞抵抗病原体感染促进成功妊娠。dNK释放GNLY杀死胞内李斯特菌。dNK控制巨细胞病毒感染时, 不同靶细胞命运不同。dNK发挥细胞毒作用杀死寨卡病毒感染的EVTs细胞。本图由BioRender.com创建

Figure 2 Subsets and functional changes of dNK cells during abnormal pregnancy. A: In patients with recurrent spontaneous abortion, dNK cells show an altered the cell subpopulation, surface receptor expression, and secreted cytokine levels. And the bias of M1/M2 macrophages, Th1/Th2 cells and Treg/Th17 cells was broken; B: In patients with preeclampsia, the number of Treg cells is decreased. dNK cells carry the KIR AA genotype allele, which leads to strong inhibition of dNK cells and an increased risk of PE; C: dNK cells fight pathogen infection and promote successful pregnancy. dNK cells release GNLY to kill intracellular *Listeria monocytogenes*. dNK cells control HCMV infection with different target cell fates. dNK cells exert cytotoxic effects to kill ZIKA-infected EVTss. The diagram was created with BioRender.com

IL-1 β 引发单核细胞进行炎症小体诱导, 以防止Lm感染^[90].

(2) 巨细胞病毒和寨卡病毒感染相关妊娠. HCMV是疱疹病毒科的成员, 是全球垂直感染的最常见原因之一^[3]. HCMV感染蜕膜和胎盘中的成纤维细胞、内皮细胞、巨噬细胞和细胞滋养层^[91-93]. 当感染滋养层细胞时, HCMV感染性强弱与胎龄密切相关^[94]. dNK细胞可以有效地杀死HCMV感染的蜕膜成纤维细胞. 在与感染的蜕膜成纤维细胞共培养的dNK细胞中观察到免疫突触和脱颗粒增加以及NKp44和NKG2C的表达^[95]. TRAIL和FasL的中和抗体无法阻止dNK杀死受感染的蜕膜成纤维细胞, 说明与死亡受体-配体途径无关^[95]. 然而, dNK细胞未能杀死HCMV感染的滋养层细胞. 当与HCMV感染的蜕膜基质细胞(decidual stromal cells, DSCs)培养时, 妊娠早期dNK细胞增加CD107a表达并产生细胞因子IFN γ , TNF α 和GM-CSF^[96]. 特别是当DSCs表达HLA-C2时, KIR2DS1⁺dNK比KIR2DS1⁻dNK具有更高的细胞毒性功能^[96]. 然而, dNK对感染的JEG3和EVTS细胞无上述反应, 说明dNK可能使用独立于脱颗粒和细胞因子分泌的其他机制来控制滋养层细胞HCMV感染. 另一项研究表明, 感染的蜕膜基质细胞并未引起足月妊娠dNK细胞的脱颗粒反应, 可能原因是足月妊娠dNK不偏向于HLA-C的识别^[97]. 总之, dNK细胞通过脱颗粒杀死HCMV感染的蜕膜成纤维细胞和蜕膜基质细胞. 然而, dNK细胞不能杀死HCMV感染的滋养层. 体外实验证明HCMV感染基质细胞和上皮细胞, 诱导效应性CD8⁺T细胞释放颗粒溶素抵御感染^[98]. 黄病毒科的ZIKA病毒也可垂直传播并感染胎盘. 怀孕期间感染ZIKA病毒可能导致小头畸形等严重的新生儿发育异常^[99]. 孕早期ZIKV可以在各种母体和胎儿细胞中复制, 例如蜕膜巨噬细胞和基质细胞, 胎儿滋养层细胞和Hofbauer细胞以及脐带的间充质干细胞^[100]. 研究发现, 滋养层细胞系JEG3的ZIKA病毒感染可诱导内质网应激, 下调维持胚胎耐受的HLA-C和HLA-G的表达. 因此, dNK细胞释放颗粒并杀死感染ZIKA病毒的JEG3细胞^[101].

4 总结与展望

母胎界面通过维持复杂的免疫平衡来促进健康妊娠. 越来越多的证据表明, 蜕膜维持组织稳态和行使生

理功能依赖于组织中免疫细胞与结构细胞形成功能性的细胞回路. 免疫细胞能够响应生理和病理情况下母体或胎儿来源的内分泌信号、神经元信号以及代谢信号等. 在自身炎症或病原体感染期间, 母胎界面免疫细胞回路失调和破坏, 导致组织稳态的扰动和妊娠相关疾病的发生. 尽管目前对于免疫细胞与基质细胞等结构细胞间互作的程序和机制认识尚浅, 但是免疫细胞回路的破坏可能是人类妊娠相关疾病的基础. 加强对母胎界面免疫细胞与结构细胞群(包括蜕膜基质细胞、成纤维细胞、上皮细胞、血管内皮细胞和滋养层细胞等)相互作用的研究及母胎界面微环境与疾病关联性研究等, 对于解决妊娠相关疾病的治疗和探究宫内事件对人类健康长期影响的机制十分必要. 随着类器官培养技术的兴起和发展, 科学家已经成功构建出母体蜕膜类器官和胎儿滋养层类器官^[102,103]. 然而缺乏免疫系统的类器官培养体系一定程度上限制了对于临床疾病的病理研究和治疗手段开发^[104]. 建立包含免疫系统的蜕膜和胎盘类器官对于妊娠相关疾病的研究和治疗将具有重要意义.

一直以来, 科学家们致力于研究母胎界面免疫微环境对半基因杂合的胚胎高度耐受的机制. 母胎界面免疫系统允许自我和非我之间相互作用并支持非我的生长和发育, 这与经典免疫系统能够区分自我和非我并介导非我的排斥似乎是矛盾的. 器官移植作为现代医学的壮举之一, 为挽救患者的生命和改善患者生活质量做出了极大贡献. 然而, 移植术后的排斥反应, 尤其是急性移植排斥, 仍然是导致移植器官功能衰竭甚至是患者死亡的最主要原因. 以往的研究使我们认识到, 母胎界面免疫学特征之一是免疫细胞高度特化, 尤其是dNK细胞具有区别于pNK细胞和其他组织NK细胞独特的表型及功能. 其次, 母胎界面积累特定的免疫细胞类型, 例如dNK细胞、dM Φ 细胞和T细胞等, 而DC细胞和B细胞的浸润则十分罕见. 此外, 胎儿来源细胞表达非经典MHC, 尤其是HLA-G, 帮助维持免疫耐受. 母胎界面特定免疫细胞的聚集允许免疫系统在维持耐受的同时行使胚胎监测和抵抗病原体感染的功能. 因此, 胚胎植入作为诱导免疫耐受最成功的范例, 该领域的研究成果可能为器官移植免疫的研究提供了新的思路.

1970年代开始, Pierce等科学家^[105]提出肿瘤发生与胚胎发育存在诸多相似之处. 早期胚胎发育过程和

肿瘤形成过程中, 均表达*OTC-4*, *C-myc*和*c-Kit*等癌基因, 存在广泛基因组去甲基化, 共表达甲胎蛋白、癌胚抗原等生物标志物, 并且都具有特异性代谢酶活性. 胚胎植入过程中, 滋养层细胞侵入子宫内膜. 而肿瘤细胞通过相似的机制发生侵袭和转移. 在子宫内膜的胚胎植入点和肿瘤组织中均高表达血管内皮生长因子, 能够诱导血管生成, 从而为胚胎发育和肿瘤的生长提供丰富的血液供应^[106]. 通过全面描绘人类肝脏单细胞图谱, 科学家们已经揭示胚胎肝脏发育和肝癌(hepatocellular carcinoma, HCC)生态系统之间的共享程序——肿瘤-胚胎重编程, 并表明VEGF/NOTCH信号通路在维持HCC免疫抑制的肿瘤-胚胎生态系统中的重要作

用^[107]. 半基因不合的胚胎不会被母体免疫系统排斥, 这与肿瘤免疫逃逸存在相似之处. 胚胎滋养层细胞与肿瘤细胞表面MHC-I类分子表达下调或丢失, 同时表达非经典的HLA-G类分子, 从而逃避T细胞和NK细胞的免疫监视和识别攻击^[108]. 早期胚胎发育和肿瘤形成还能通过抑制因子IL-4, IL-10来调整宿主的防御功能导致宿主的免疫耐受. 因此, 将恶性肿瘤细胞的表型特征与早期胚胎发育程序联系起来, 同时发掘胚胎植入免疫调控与肿瘤免疫逃逸的共同机制, 能够为肿瘤的治疗和干预提供新靶点, 也可以作为肿瘤免疫治疗的潜在生物标志物, 这将为理解肿瘤免疫逃逸和治疗开辟新道路^[107].

参考文献

- 1 Ander S E, Diamond M S, Coyne C B. Immune responses at the maternal-fetal interface. *Sci Immunol*, 2019, 4: eaat6114
- 2 Noyes R W, Hertig A T, Rock J. Reprint of: dating the endometrial biopsy. *Fertil Steril*, 2019, 112: e93–e115
- 3 Megli C J, Coyne C B. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. *Nat Rev Microbiol*, 2022, 20: 67–82
- 4 Ng S W, Norwitz G A, Pavlicev M, et al. Endometrial decidualization: the primary driver of pregnancy health. *Int J Mol Sci*, 2020, 21: 4092
- 5 Liu S, Diao L, Huang C, et al. The role of decidual immune cells on human pregnancy. *J Reprod Immunol*, 2017, 124: 44–53
- 6 Zhou Y, Ding X, Wei H. Reproductive immune microenvironment. *J Reprod Immunol*, 2022, 152: 103654
- 7 Vacca P, Vitale C, Montaldo E, et al. CD34⁺ hematopoietic precursors are present in human decidua and differentiate into natural killer cells upon interaction with stromal cells. *Proc Natl Acad Sci USA*, 2011, 108: 2402–2407
- 8 Gamliel M, Goldman-Wohl D, Isaacson B, et al. Trained memory of human uterine NK cells enhances their function in subsequent pregnancies. *Immunity*, 2018, 48: 951–962.e5
- 9 Keskin D B, Allan D S J, Rybalov B, et al. TGFβ promotes conversion of CD16⁺ peripheral blood NK cells into CD16[−] NK cells with similarities to decidual NK cells. *Proc Natl Acad Sci USA*, 2007, 104: 3378–3383
- 10 Siewiera J, Gouilly J, Hocine H R, et al. Natural cytotoxicity receptor splice variants orchestrate the distinct functions of human natural killer cell subtypes. *Nat Commun*, 2015, 6: 10183
- 11 Kopcow H D, Allan D S J, Chen X, et al. Human decidual NK cells form immature activating synapses and are not cytotoxic. *Proc Natl Acad Sci USA*, 2005, 102: 15563–15568
- 12 Chen Y W, Tian Z G, Peng H. Heterogeneity of liver NK cells (in Chinese). *Sci Sin Vitae*, 2023, 53: 250–261 [陈雅雯, 田志刚, 彭慧. 肝脏NK细胞亚群的异质性. 中国科学: 生命科学, 2023, 53: 250–261]
- 13 Xu X, Zhou Y, Fu B, et al. Uterine NK cell functions at maternal-fetal interface. *Biol Reprod*, 2022, 107: 327–338
- 14 Fu B, Wang F, Sun R, et al. CD11b and CD27 reflect distinct population and functional specialization in human natural killer cells. *Immunology*, 2011, 133: 350–359
- 15 Fu B Q, Jin J, Sun R, et al. CD27/CD11b defines human NK cell subsets and functions in tumor and pregnancy (in Chinese). The 9th National Immunology Academic Conference. 2014, 14–15 [傅斌清, 金晶, 孙纳, 等. CD27/CD11b界定人NK细胞亚群及其在肿瘤和妊娠中的功能. 第九届全国免疫学学术大会. 2014, 14–15]
- 16 Fu B, Tian Z, Wei H. Subsets of human natural killer cells and their regulatory effects. *Immunol*, 2014, 141: 483–489
- 17 Ni F, Sun R, Fu B, et al. IGF-1 promotes the development and cytotoxic activity of human NK cells. *Nat Commun*, 2013, 4: 1479
- 18 Fu B, Zhou Y, Ni X, et al. Natural killer cells promote fetal development through the secretion of growth-promoting factors. *Immunity*, 2017, 47: 1100–1113
- 19 Vento-Tormo R, Efremova M, Botting R A, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. *Nature*, 2018, 563:

347–353

- 20 Sun F, Wang S, Du M. Functional regulation of decidual macrophages during pregnancy. *J Reprod Immunol*, 2021, 143: 103264
- 21 Svensson-Arvelund J, Enerudh J. The role of macrophages in promoting and maintaining homeostasis at the fetal-maternal interface. *Am J Rep Immunol*, 2015, 74: 100–109
- 22 Care A S, Diener K R, Jasper M J, et al. Macrophages regulate corpus luteum development during embryo implantation in mice. *J Clin Invest*, 2013, 123: 3472–3487
- 23 Silvano A, Seravalli V, Strambi N, et al. Tryptophan metabolism and immune regulation in the human placenta. *J Reprod Immunol*, 2021, 147: 103361
- 24 Sayama S, Nagamatsu T, Schust D J, et al. Human decidual macrophages suppress IFN- γ production by T cells through costimulatory B7-H1: PD-1 signaling in early pregnancy. *J Reprod Immunol*, 2013, 100: 109–117
- 25 Co E C, Gormley M, Kapidzic M, et al. Maternal decidual macrophages inhibit NK cell killing of invasive cytotrophoblasts during human pregnancy. *Biol Reprod*, 2013, 88: 155
- 26 Smith S D, Dunk C E, Aplin J D, et al. Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy. *Am J Pathol*, 2009, 174: 1959–1971
- 27 Ma L N, Zhang D J, Wu X K. The role of uterine macrophages in normal and pathological pregnancy (in Chinese). *Int J Obstet and Gynecol*, 2023, 50: 65–69 [马丽娜, 张多加, 吴效科. 子宫巨噬细胞在正常妊娠及病理性妊娠中的作用. *国际妇产科学杂志*, 2023, 50: 65–69]
- 28 Pavlov O, Pavlova O, Ailamazyan E, et al. Original article: characterization of cytokine production by human term placenta macrophages *in vitro*. *Am J Rep Immunol*, 2008, 60: 556–567
- 29 Huang W C, Sala-Newby G B, Susana A, et al. Classical macrophage activation up-regulates several matrix metalloproteinases through mitogen activated protein kinases and nuclear factor- κ B. *PLoS ONE*, 2012, 7: e42507
- 30 Gomez-Lopez N, StLouis D, Lehr M A, et al. Immune cells in term and preterm labor. *Cell Mol Immunol*, 2014, 11: 571–581
- 31 Hibbs Jr J B, Taintor R R, Vavrin Z, et al. Nitric oxide: a cytotoxic activated macrophage effector molecule. *Biochem Biophys Res Commun*, 1988, 157: 87–94
- 32 Houser B L, Tilburgs T, Hill J, et al. Two unique human decidual macrophage populations. *J Immunol*, 2011, 186: 2633–2642
- 33 Houser B L. Decidual macrophages and their roles at the maternal-fetal interface. *Yale J Biol Med*, 2012, 85: 105–118
- 34 Jiang X, Wang H. Macrophage subsets at the maternal-fetal interface. *Cell Mol Immunol*, 2020, 17: 889–891
- 35 Jiang X, Du M R, Li M, et al. Three macrophage subsets are identified in the uterus during early human pregnancy. *Cell Mol Immunol*, 2018, 15: 1027–1037
- 36 Nancy P, Erlebacher A. T cell behavior at the maternal-fetal interface. *Int J Dev Biol*, 2014, 58: 189–198
- 37 Wang W, Sung N, Gilman-Sachs A, et al. T helper (Th) cell profiles in pregnancy and recurrent pregnancy losses: Th1/Th2/Th9/Th17/Th22/Tfh cells. *Front Immunol*, 2020, 11: 2025
- 38 Robertson S A, Care A S, Moldenhauer L M. Regulatory T cells in embryo implantation and the immune response to pregnancy. *J Clin Invest*, 2018, 128: 4224–4235
- 39 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
- 40 Nancy P, Tagliani E, Tay C S, et al. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. *Science*, 2012, 336: 1317–1321
- 41 van der Zwan A, Bi K, Norwitz E R, et al. Mixed signature of activation and dysfunction allows human decidual CD8⁺ T cells to provide both tolerance and immunity. *Proc Natl Acad Sci USA*, 2018, 115: 385–390
- 42 Erlebacher A. Immunology of the maternal-fetal interface. *Annu Rev Immunol*, 2013, 31: 387–411
- 43 Robson A, Harris L K, Innes B A, et al. Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. *Faseb J*, 2012, 26: 4876–4885
- 44 Ma Y, Yu X, Zhang L, et al. Uterine decidual niche modulates the progressive dedifferentiation of spiral artery vascular smooth muscle cells during human pregnancy. *Biol Reprod*, 2021, 104: 624–637
- 45 Robson A, Lash G E, Innes B A, et al. Uterine spiral artery muscle dedifferentiation. *Hum Reprod*, 2019, 34: 1428–1438
- 46 Kalkunte S S, Mselle T F, Norris W E, et al. Vascular endothelial growth factor C facilitates immune tolerance and endovascular activity of

- human uterine NK cells at the maternal-fetal interface. *J Immunol*, 2009, 182: 4085–4092
- 47 Ashkar A A, Di Santo J P, Croy B A. Interferon γ contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. *J Exp Med*, 2000, 192: 259–270
- 48 Huppertz B. Traditional and new routes of trophoblast invasion and their implications for pregnancy diseases. *Int J Mol Sci*, 2019, 21: 289
- 49 Chazara O, Xiong S, Moffett A. Maternal KIR and fetal HLA-C: a fine balance. *J Leukocyte Biol*, 2011, 90: 703–716
- 50 Hanna J, Goldman-Wohl D, Hamani Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. *Nat Med*, 2006, 12: 1065–1074
- 51 Rajagopalan S, Bryceson Y T, Kuppusamy S P, et al. Activation of NK cells by an endocytosed receptor for soluble HLA-G. *PLoS Biol*, 2006, 4: e9
- 52 Pazmany L, Mandelboim O, Vales-Gomez M, et al. Protection from natural killer cell-mediated lysis by HLA-G expression on target cells. *Science*, 1996, 274: 792–795
- 53 Tilburgs T, Evans J H, Crespo A C, et al. The HLA-G cycle provides for both NK tolerance and immunity at the maternal-fetal interface. *Proc Natl Acad Sci USA*, 2015, 112: 13312–13317
- 54 Li Y H, Zhou W H, Tao Y, et al. The Galectin-9/Tim-3 pathway is involved in the regulation of NK cell function at the maternal-fetal interface in early pregnancy. *Cell Mol Immunol*, 2016, 13: 73–81
- 55 Sun J, Yang M, Ban Y, et al. Tim-3 is upregulated in NK cells during early pregnancy and inhibits NK cytotoxicity toward trophoblast in Galectin-9 dependent pathway. *PLoS ONE*, 2016, 11: e0147186
- 56 Vacca P, Cantoni C, Vitale M, et al. Crosstalk between decidual NK and CD14⁺ myelomonocytic cells results in induction of Tregs and immunosuppression. *Proc Natl Acad Sci USA*, 2010, 107: 11918–11923
- 57 Fu B, Li X, Sun R, et al. Natural killer cells promote immune tolerance by regulating inflammatory T_H17 cells at the human maternal-fetal interface. *Proc Natl Acad Sci USA*, 2013, 110: E231–E240
- 58 Tao Y, Li Y H, Zhang D, et al. Decidual CXCR4⁺ CD56^{bright} NK cells as a novel NK subset in maternal-foetal immune tolerance to alleviate early pregnancy failure. *Clin Transl Med*, 2021, 11: e540
- 59 Zhou Y, Fu B, Xu X, et al. PBX1 expression in uterine natural killer cells drives fetal growth. *Sci Transl Med*, 2020, 12: eaax1798
- 60 Du X, Zhu H, Jiao D, et al. Human-induced CD49a⁺ NK cells promote fetal growth. *Front Immunol*, 2022, 13: 821542
- 61 Yeh C C, Chao K C, Huang S J. Innate immunity, decidual cells, and preeclampsia. *Reprod Sci*, 2013, 20: 339–353
- 62 Prefumo F, Ganapathy R, Thilaganathan B, et al. Influence of parity on first trimester endovascular trophoblast invasion. *Fertil Steril*, 2006, 85: 1032–1036
- 63 Dimitriadis E, Menkhorst E, Saito S, et al. Recurrent pregnancy loss. *Nat Rev Dis Primers*, 2020, 6: 98
- 64 Baek K H, Lee E J, Kim Y S. Recurrent pregnancy loss: the key potential mechanisms. *Trends Mol Med*, 2007, 13: 310–317
- 65 Kuon R J, Weber M, Heger J, et al. Uterine natural killer cells in patients with idiopathic recurrent miscarriage. *Am J Rep Immunol*, 2017, 78: e12721
- 66 El-Azzamy H, Dambaeva S V, Katukurundage D, et al. Dysregulated uterine natural killer cells and vascular remodeling in women with recurrent pregnancy losses. *Am J Rep Immunol*, 2018, 80: e13024
- 67 Li H, Hou Y, Zhang S, et al. CD49a regulates the function of human decidual natural killer cells. *Am J Rep Immunol*, 2019, 81: e13101
- 68 Wang W J, Hao C F, Yi-Lin C F, et al. Increased prevalence of T helper 17 (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. *J Reprod Immunol*, 2010, 84: 164–170
- 69 Fu B, Tian Z, Wei H. TH17 cells in human recurrent pregnancy loss and pre-eclampsia. *Cell Mol Immunol*, 2014, 11: 564–570
- 70 Zhao Q Y, Li Q H, Fu Y Y, et al. Decidual macrophages in recurrent spontaneous abortion. *Front Immunol*, 2022, 13: 994888
- 71 Ding J, Zhang Y, Cai X, et al. Extracellular vesicles derived from M1 macrophages deliver miR-146a-5p and miR-146b-5p to suppress trophoblast migration and invasion by targeting TRAF6 in recurrent spontaneous abortion. *Theranostics*, 2021, 11: 5813–5830
- 72 Wu Z, Wang M, Liang G, et al. Pro-inflammatory signature in decidua of recurrent pregnancy loss regardless of embryonic chromosomal abnormalities. *Front Immunol*, 2021, 12: 772729
- 73 Zhou W J, Yang H L, Mei J, et al. Fructose-1,6-bisphosphate prevents pregnancy loss by inducing decidual COX-2⁺ macrophage differentiation. *Sci Adv*, 2022, 8: eabj2488
- 74 Zhang D, Zhang J J. Expression regulation mechanisms and biological functions of autotaxin (in Chinese). *Sci Sin Vitae*, 2022, 52: 1148–1162

[张地, 张俊杰. Autotaxin表达调控机制及其生物学功能. 中国科学: 生命科学, 2022, 52: 1148–1162]

- 75 Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*, 2014, 121: 14–24
- 76 Deer E, Herrock O, Campbell N, et al. The role of immune cells and mediators in preeclampsia. *Nat Rev Nephrol*, 2023, 19: 257–270
- 77 Wei X, Yang X. The central role of natural killer cells in preeclampsia. *Front Immunol*, 2023, 14: 1009867
- 78 Zhang J, Dunk C E, Shynlova O, et al. TGF β 1 suppresses the activation of distinct dNK subpopulations in preeclampsia. *Ebiomedicine*, 2019, 39: 531–539
- 79 Santner-Nanan B, Peek M J, Khanam R, et al. Systemic increase in the ratio between Foxp3⁺ and IL-17-producing CD4⁺ T cells in healthy pregnancy but not in preeclampsia. *J Immunol*, 2009, 183: 7023–7030
- 80 Sasaki Y, Darmochwal-Kolarz D, Suzuki D, et al. Proportion of peripheral blood and decidual CD4⁺ CD25^{bright} regulatory T cells in pre-eclampsia. *Clin Exp Immunol*, 2007, 149: 139–145
- 81 Moffett A, Chazara O, Colucci F, et al. Variation of maternal KIR and fetal HLA-C genes in reproductive failure: too early for clinical intervention. *Reprod Biomed Online*, 2016, 33: 763–769
- 82 Hiby S E, Walker J J, O'Shaughnessy K M, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med*, 2004, 200: 957–965
- 83 Wedenoja S, Yoshihara M, Teder H, et al. Fetal HLA-G mediated immune tolerance and interferon response in preeclampsia. *Ebiomedicine*, 2020, 59: 102872
- 84 Shreeve N, Depierreux D, Hawkes D, et al. The CD94/NKG2A inhibitory receptor educates uterine NK cells to optimize pregnancy outcomes in humans and mice. *Immunity*, 2021, 54: 1231–1244.e4
- 85 Reister F, Frank H G, Heyl W, et al. The distribution of macrophages in spiral arteries of the placental bed in pre-eclampsia differs from that in healthy patients. *Placenta*, 1999, 20: 229–233
- 86 Hosseini A, Dolati S, Hashemi V, et al. Regulatory T and T helper 17 cells: their roles in preeclampsia. *J Cell Physiol*, 2018, 233: 6561–6573
- 87 Charlier C, Disson O, Lecuit M. Maternal-neonatal listeriosis. *Virulence*, 2020, 11: 391–397
- 88 Crespo Â C, Mulik S, Dotiwala F, et al. Decidual NK cells transfer granulysin to selectively kill bacteria in trophoblasts. *Cell*, 2020, 182: 1125–1139.e18
- 89 Fang X, Zhou Y, Chen S, et al. Natural killer cells promote intra-cellular-infected trophoblasts survival via APOD-LRP1 axis. *Immunol*, 2023
- 90 Megli C, Morosky S, Rajasundaram D, et al. Inflammasome signaling in human placental trophoblasts regulates immune defense against *Listeria monocytogenes* infection. *J Exp Med*, 2021, 218
- 91 Fisher S, Genbacev O, Maidji E, et al. Human cytomegalovirus infection of placental cytotrophoblasts *in vitro* and *in utero*: implications for transmission and pathogenesis. *J Virol*, 2000, 74: 6808–6820
- 92 Weisblum Y, Panet A, Zakay-Rones Z, et al. Modeling of human cytomegalovirus maternal-fetal transmission in a novel decidual organ culture. *J Virol*, 2011, 85: 13204–13213
- 93 Maidji E, Genbacev O, Chang H T, et al. Developmental regulation of human cytomegalovirus receptors in cytotrophoblasts correlates with distinct replication sites in the placenta. *J Virol*, 2007, 81: 4701–4712
- 94 Hemmings D G, Kilani R, Nykiforuk C, et al. Permissive cytomegalovirus infection of primary villous term and first trimester trophoblasts. *J Virol*, 1998, 72: 4970–4979
- 95 Siewiera J, El Costa H, Tabiasco J, et al. Human cytomegalovirus infection elicits new decidual natural killer cell effector functions. *PLoS Pathog*, 2013, 9: e1003257
- 96 Crespo Â C, Strominger J L, Tilburgs T. Expression of KIR2DS1 by decidual natural killer cells increases their ability to control placental HCMV infection. *Proc Natl Acad Sci USA*, 2016, 113: 15072–15077
- 97 de Mendonça Vieira R, Meagher A, Crespo Â C, et al. Human term pregnancy decidual NK cells generate distinct cytotoxic responses. *J Immunol*, 2020, 204: 3149–3159
- 98 Tabata T, Petitt M, Fang-Hoover J, et al. Survey of cellular immune responses to human cytomegalovirus infection in the microenvironment of the uterine-placental interface. *Med Microbiol Immunol*, 2019, 208: 475–485
- 99 Giraldo M I, Gonzalez-Orozco M, Rajsbaum R. Pathogenesis of Zika virus infection. *Annu Rev Pathol Mech Dis*, 2023, 18: 181–203
- 100 Male V, Sharkey A, Masters L, et al. The effect of pregnancy on the uterine NK cell KIR repertoire. *Eur J Immunol*, 2011, 41: 3017–3027

- 101 Sen Santara S, Crespo Â C, Mulik S, et al. Decidual NK cells kill Zika virus-infected trophoblasts. [Proc Natl Acad Sci USA](#), 2021, 118: e2115410118
- 102 Turco M Y, Gardner L, Hughes J, et al. Long-term, hormone-responsive organoid cultures of human endometrium in a chemically defined medium. [Nat Cell Biol](#), 2017, 19: 568–577
- 103 Turco M Y, Gardner L, Kay R G, et al. Trophoblast organoids as a model for maternal-fetal interactions during human placentation. [Nature](#), 2018, 564: 263–267
- 104 Mo S B, Guan R Y, Zhang L, et al. The application and research advances of organoids in clinical medicine (in Chinese). [Sci Sin Vitae](#), 2023, 53: 221–237 [莫少波, 管若羽, 张龙, 等. 类器官在临床医学中的应用和研究进展. [中国科学: 生命科学](#), 2023, 53: 221–237]
- 105 Pierce G B. The cancer cell and its control by the embryo. Rous-Whipple Award lecture. [Am J Pathol](#), 1983, 113: 117–124
- 106 Murray M, Lessey B. Embryo implantation and tumor metastasis: common pathways of invasion and angiogenesis. [Semin Reprod Med](#), 1999, 17: 275–290
- 107 Sharma A, Seow J J W, Dutertre C A, et al. Onco-fetal reprogramming of endothelial cells drives immunosuppressive macrophages in hepatocellular carcinoma. [Cell](#), 2020, 183: 377–394.e21
- 108 Chew S C, Choo S Y, Chow P K H. A new perspective on the immune escape mechanism in HCC: onco-foetal reprogramming. [Br J Cancer](#), 2021, 124: 1897–1899

Immune microenvironment at the maternal-fetal interface in early pregnancy and pregnancy-related diseases

DING XiaoYu & WEI HaiMing

Institute of Immunology, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230027, China

Fetal extravillous trophoblasts invade maternal decidual tissue during pregnancy. However, the maternal immune system recognizes the semi-allogeneic fetus and supports its growth and development in utero, which contradicts the classical theory of immune rejection. The maternal immune system must establish tolerance to the allogeneic fetus while maintaining the ability to defend against pathogens. Such tolerance requires the establishment of a well-coordinated maternal immune system to promote a successful pregnancy. In contrast, a high risk of adverse pregnancy outcomes has been shown in patients suffering from recurrent spontaneous abortion (RSA), preeclampsia (PE), or infection. This high risk of adverse pregnancy outcomes is closely related to immunological imbalance at the maternal-fetal interface. In this review, we illustrate the immune microenvironment at the maternal-fetal interface in early pregnancy, especially in understanding the function of decidual NK (dNK) cells. We also discuss the impact of an altered immune microenvironment at the maternal-fetal interface on the pregnancy outcome in patients with RSA, PE, or infection, and the effect of dNK cells is highlighted. The aim of this review is to: (i) summarize and understand the immune microenvironment at the maternal-fetal interface during normal and abnormal pregnancies; (ii) provide a theoretical basis for the treatment of pregnancy-related disorders.

immune microenvironment at the maternal-fetal interface, decidual NK cells, recurrent spontaneous abortion, preeclampsia, infection

doi: [10.1360/SSV-2023-0171](https://doi.org/10.1360/SSV-2023-0171)