

Why doesn't a pregnant woman reject her fetus?

母-胎免疫耐受研究进展

王松存, 杜美蓉, 李大金*

复旦大学上海医学院附属妇产科研究所, 上海 200011

* 联系人, E-mail: djli@shmu.edu.cn

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摘要 正常妊娠是一个复杂的生理过程. 胎儿虽携有遗传自父系的HLA抗原, 但却并未引发母体产生针对胎儿这种特殊半同种“天然移植物”的排斥. 妊娠期母-胎间必然存在着复杂的分子对话机制, 以维持胎儿胎盘正常发育. 母-胎交互对话异常, 将引起母体对胚胎的免疫排斥(母-胎免疫调节紊乱), 导致妊娠失败或妊娠并发症如自然流产、子痫前期等. 母-胎对话的关键是母-胎免疫适应, 而母-胎免疫适应的本质在于母体免疫系统对胚胎抗原的免疫耐受, 其核心部位在母-胎界面; 妊娠早期蜕膜局部出现免疫细胞亚群的富集和重分布, 母体免疫系统不仅不排斥携有父系抗原的胚胎, 反而形成母-胎免疫耐受, 至今免疫生物学仍无法解释母-胎免疫相容的生理性机制. 本文在总结既往研究成果的基础上, 围绕母-胎界面关键的功能细胞, 阐明基于母-胎交互对话的母-胎免疫耐受的建立和维持机制.

关键词 母-胎免疫耐受, 妊娠, 母-胎界面, 滋养细胞, 蜕膜基质细胞, 蜕膜免疫细胞

生理妊娠类似于同种异体移植, 作为自然的同种移植物的胚胎不被母体免疫系统排斥, 是免疫排斥现象的唯一例外, 实际上反映了母体对于胚胎的耐受. 有关母-胎免疫耐受的理論可以追溯到20世纪50年代, 诺贝尔奖获得者Medawar^[1]曾提出3种理论解释作为半同种移植物的胎儿如何逃逸母体免疫系统的攻击: (1) 胎盘屏障学说; (2) 胎儿的抗原不成熟学说; (3) 母体子宫的免疫特许. 这3种理论曾一度推动了生殖免疫学的发展, 至今对该领域的研究仍有重要的指导意义. 然而, 随着生殖免疫学的飞速发展, 后来的研究使得这些观点受到质疑和挑战.

母-胎界面是妊娠建立和维持的关键部位, 主要由3种细胞构成: 胚胎来源的滋养细胞(trophoblast, Tro), 母体来源的蜕膜基质细胞(decidual stromal cell, DSC)和蜕膜免疫细胞(decidual immune cell, DIC).

作为母-胎界面唯一携带有父系抗原的滋养细胞, 其侵袭与迁移是胚泡着床、胎盘发育, 并建立母-胎关系的关键步骤. 蜕膜基质细胞除参与蜕膜营养供应之外, 还分泌多种活性分子调节胚泡着床与胎盘发育, 并作为免疫潜能细胞, 参与抗原提呈和分泌细胞因子, 发挥重要的免疫调节作用. 蜕膜免疫细胞是母-胎免疫耐受的基础, 通过表达特殊的活化标记和分泌大量的细胞因子, 在母-胎界面局部发挥着不同于外周的免疫调节作用. 正常生理妊娠时母-胎界面呈现Th2型免疫优势和调节性T细胞(regulatory T cells, Treg)扩增现象, 一旦这种耐受状态被打破, Th1型免疫反应占优势, 将导致自然流产等不良妊娠结局.

1 滋养细胞在母-胎免疫耐受中的作用

来源于胚胎的滋养细胞沿两条通路分化, 合体

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滋养细胞主要参与营养物质和代谢物质的转运并执行胎盘的内分泌功能;而绒毛外滋养细胞(EVT)具有侵袭力,向子宫间质和螺旋动脉腔内呈侵袭性生长,取代螺旋动脉血管内皮并导致血管重塑,向胎儿提供氧和营养物质^[2]。滋养细胞是唯一与母体蜕膜免疫细胞直接接触的胚胎细胞,与母体免疫细胞直接接触并被其有效识别。胚胎着床后,功能失常的绒毛外滋养细胞会导致胚胎死亡及妊娠相关疾病,例如先兆子痫、胎儿宫内生长受限等^[3]。

EVT不表达经典的MHC I, II类分子^[4],从而逃逸了母体对胎儿同种异体移植物的排斥;但完全缺乏MHC I类分子的胚胎细胞易被NK细胞识别并杀伤。绒毛外细胞滋养细胞表面可特异性表达非经典的MHC I类抗原,如HLA-G, HLA-E及HLA-C^[5]。在早孕期蜕膜广泛分布的NK细胞特征性表达杀伤细胞抑制性受体KIR。KIR在滋养细胞表达的HLA-G, HLA-C启动下,向细胞内传导相应抑制性信号,使这些母-胎界面重要的杀伤细胞非但不能有效杀伤胚胎来源的细胞,相反对其行使免疫保护作用。一旦滋养细胞表面HLA分子或NK表面的抑制性受体表达异常,NK即可对滋养细胞进行攻击^[6],表现为自发流产、子痫前期等。EVT上表达的HLA-G,有助于滋养细胞的侵袭,蜕膜细胞的分化、胎盘血管的重铸,并促进母-胎界面免疫耐受状态的维持^[7]。EVT上表达的HLA-G可以增加蜕膜局部NK细胞(dNK)中IL-4和IL-10的表达,同时降低Th1型细胞因子TNF- α 的表达^[8]。有研究显示通过选择性表达不能被ILT2识别的HLA-G分子,可以限制NK细胞毒性并促进NK细胞分泌有利于妊娠维持的分子^[9]。滋养细胞同时可以受HLA-C限制性,通过直接接触的方式,上调母-胎界面T细胞上Tim-3/PD-1的表达,而Tim-3/PD-1信号可以调节T细胞功能,促进母-胎界面Th2型免疫优势^[10,11]。

滋养细胞是妊娠期妇女胸腺基质促淋巴细胞生成素(TSLP)的主要来源,而TSLPR主要表达于DC细胞而不是T细胞。通过分泌TSLP,滋养细胞可以训导DC细胞,促进其Th2型趋化因子CCL17与IL-10,进一步诱导蜕膜CD4⁺T细胞向Th2型细胞优势分化,形成母-胎界面独特的Th2型免疫优势;进一步研究发现,滋养细胞分泌的TSLP训导DC细胞通过TGF- β 1诱导CD4⁺CD25⁺T细胞转化为CD4⁺CD25⁺Foxp3⁺Treg,这种Treg反作用于滋养细胞,上调HLA-G表达并促进其侵袭能力,经Treg训导的滋养细胞能更强地抑

制dNK细胞杀伤活性,并诱导其产生Th2型细胞因子。而自发流产患者滋养细胞分泌TSLP水平降低,不能有效地训导蜕膜DC细胞,导致母-胎界面Th2型优势与Treg扩增的格局被打破,自然流产被诱发^[8,12]。此外,滋养细胞还可以分泌大量的细胞因子CXCL12,除了促进自身MMP-2/9的分泌与侵袭能力,还可以通过与DSC与DIC上CXCR4相互作用,促进共培养体系的Th2型优势,并且这种增加的Th2型细胞因子主要来源于滋养细胞,其次来源于DSC^[13]。EVT表达的CXCL16可以识别 $\gamma\delta$ T细胞上的CXCR6并促进其分泌IL-10^[14]。以上这些研究确定了滋养细胞在母-胎交互对话中的主导作用。

2 蜕膜基质细胞在母-胎免疫耐受中的作用

既往许多研究工作聚焦于母-胎界面胎儿来源的滋养细胞,而另一群特殊的母体来源的细胞DSC(蜕膜的主要组成细胞),具有广泛的生物学功能,除参与蜕膜营养供应外,尚能分泌活性激素、多种细胞因子和酶类,表达孕激素受体,参与抗原提呈及分泌细胞因子。作为母-胎界面的两种主要组成细胞,DSC与滋养细胞直接接触,它们之间的相互作用是母-胎免疫调节的重要组成部分^[15]。胎儿绒毛外滋养细胞能与母体DSC形成桥粒连接^[16],提示滋养细胞与DSC细胞之间确实存在对话与交流,而且这种对话与交流对于正常妊娠的维持至关重要。

通过分泌趋化因子CCL2, DSC促进蜕膜免疫活性细胞IL-4和IL-10的分泌,抑制IFN- γ 和TNF- α 的分泌,参与维持母-胎界面Th2型免疫优势^[17]。通过吡啶啉2,3-双加氧酶(IDO)和前列腺素E2(PGE2)的作用,DSC可以抑制NK细胞的增殖、毒性及产生IFN- γ 的能力,同时抑制DC细胞的分化及其诱导T细胞增殖的能力^[18]。DSC产生的巨噬细胞抑制因子-1(MIC-1)可以促进母-胎界面抑制性DC细胞的产生^[19]。DSC同样可以表达HLA-G而发挥重要的免疫调节功能^[20]。基因沉默DSC中的关键趋化因子基因会减少杀伤性T细胞进入母-胎界面进而促进母-胎免疫耐受^[21]。但同时,DSC又可以保护蜕膜局部T细胞免遭凋亡^[22]。而DSC发挥不同的免疫效应影响母-胎之间的免疫交互对话对妊娠结局至关重要^[23]。

3 蜕膜免疫细胞在母-胎免疫耐受中的作用

蜕膜免疫细胞是母-胎免疫耐受的基础,免疫细

胞在母-胎界面微环境训导下发生表型和功能改变,从而对胚胎抗原产生耐受,以维持正常妊娠.在胚胎着床后的早孕期,母体内大量的免疫细胞迁移至子宫蜕膜,参与维持母-胎耐受和抗感染免疫.蜕膜免疫细胞的构成极为特殊,主要由特殊类型的NK细胞(CD56^{bright}/CD16⁻)(~70%)、T细胞(~15%)和单核细胞(~15%)组成,它们通过表达特殊活化标志和产生大量的细胞因子,在母-胎界面局部发挥着不同于外周的免疫调控作用;并通过旁分泌作用调控滋养细胞的生长、分化和迁移,从而对妊娠的维持起重要的局部调节作用.

与非孕妇女相比,妊娠期妇女外周血NK细胞数量及产生INF- γ 的能力明显下降^[24].与外周NK相比,dNK细胞以其绝对组成优势(约占蜕膜免疫细胞的70%)与独特的表型(CD56^{bright}CD16^{dim}、抑制性受体和活化性受体库),在母-胎耐受中发挥至关重要的调节作用.蜕膜NK细胞表达 KIR 家族受体,保护胚胎来源的滋养细胞免遭NK的杀伤作用.有研究表明KIR表型与子痫前期的发展密切相关^[25].dNK细胞还可以通过分泌细胞因子,为滋养细胞的侵入创造合适的免疫耐受微环境.孕鼠蜕膜螺旋动脉重塑时间与dNK细胞分泌INF- γ 的峰值重合;敲除INF- γ 基因的孕鼠可以出现螺旋动脉重塑异常;螺旋动脉重塑依赖于活化的蜕膜NK细胞分泌大量的INF- γ .INF- γ 能够解离底蜕膜螺旋动脉血管壁的完整性,使得螺旋动脉内皮和平滑肌细胞结构松散,利于滋养细胞入侵并取代,完成子宫螺旋动脉重塑^[26].

在母-胎免疫耐受机制中,辅助性T细胞的功能至关重要.初始CD4⁺T细胞接受抗原刺激后,首先分化为Th0细胞,在不同细胞因子作用下,分化为Th1, Th2, Th17及Treg细胞,发挥不同生物学作用.在母-胎界面, Th1, Th2, Th17及Treg之间存在着平衡机制,共同维持正常妊娠^[27].在围着床期,子宫内膜局部分泌的细胞因子呈现Th2型免疫优势,从而起到维持妊娠的作用.尽管围着床期子宫局部炎症微环境利于胚泡的着床^[28], Th1型免疫应答及其相关细胞因子,如IL-2, INF- γ 和TNF- α 等对胚胎具有细胞毒作用,不利于妊娠维持;而以IL-4等为代表的Th2型相关细胞因子对妊娠具有免疫营养和保护作用^[29].正常妊娠时母-胎界面Treg亦明显高于外周血及自然流产患者局部, Treg数量过低和Th17优势会引起过度炎症反应及效应性T细胞活化的失调,从而引起自然流产和

子痫前期^[30].妊娠期间,接种父系来源的肿瘤细胞能够为母体接受,而不出现非孕期的免疫排斥反应,提示妊娠过程中,可能存在类似于Treg在移植免疫耐受中的系统性免疫调节作用^[31].以上这些研究提示母-胎界面Th2型免疫优势及Treg扩增是成功妊娠的关键.然而,有关母-胎界面Th2型免疫优势及Treg扩增产生的确切机制至今尚不甚清楚.

除了TCR识别抗原传递的第一信号, T细胞的活化还需要协同刺激信号.而母-胎界面辅助性T细胞的功能平衡还与协同共刺激分子、抑制性分子的作用相关.自然流产患者蜕膜CD86转录水平明显高于正常早孕期蜕膜;而CTLA-4转录水平则低于正常早孕期蜕膜^[32].复发性自然流产患者及流产小鼠模型Tim-3⁺PD-1⁺T的比例均要低于正常组, Tim-3联合PD-1信号可以促进T细胞产生Th2型细胞因子,阻断Tim-3/PD-1信号后, T细胞功能紊乱,促炎性细胞因子明显增多,母-胎界面耐受状态被打破,胚胎丢失增加^[10,11].Tim-3⁺NK细胞优势产生Th2型细胞因子,且在自然流产组Tim-3⁺NK细胞(而不是Tim-3⁻NK细胞)产生Th2/Th1细胞因子紊乱,表明Tim-3信号还可以通过调控NK细胞的功能,维持正常妊娠的进行^[33].母-胎界面还表达IDO、L-精氨酸酶、PDL-1及CD95L等抑制母体T细胞的过度活化,避免母体对胚胎的排斥,促进母-胎免疫耐受^[34~36].

蜕膜巨噬细胞(dM ϕ)参与蜕膜化的进程,促进螺旋动脉重塑,利于妊娠的维持^[37].在母-胎界面,巨噬细胞主要为产生抗炎细胞因子(如IL-10)为主的M2细胞,而不是以分泌促炎细胞因子(如TNF, IL-12)为主的M1细胞^[38].M2细胞高表达清道夫受体、甘露糖受体等,精氨酸酶活性增强,从而具有较高的组织修复能力^[39].dM ϕ 亚群失调将导致复发性流产的发生^[40].

DC在母-胎界面局部具有双重作用:一方面,通过诱导效应性T细胞凋亡和调节性T细胞(Treg)扩增进而促进母-胎免疫耐受;另一方面,又作为抗原提呈细胞活化引流淋巴结的T细胞促进T细胞免疫应答^[41].正常妊娠时,母-胎界面DC抗原提呈效力减弱,协同共刺激分子表达减少, IL-12产生减低,而IL-10表达增加,从而形成耐受表型,利于母体耐受作为同种移植物的胚胎^[19].

4 结语

母-胎免疫调节是生殖免疫学重点与热点研究方

向,即便是在辅助生育技术飞速发展的今天,仍不能克服因母-胎免疫调节功能紊乱造成的妊娠失败.母-胎免疫调节的核心科学问题是母体对同种异体胚胎抗原的特异性免疫耐受.随着分子生物学和分子免疫学等技术的应用,对生殖免疫学研究的重点已转入生殖道局部,尤其是胚胎抗原特异性的母-胎免疫调节.母

-胎免疫调节网络将为妊娠相关疾病诊断与治疗打开新的突破口,并将促进围产医学基础理论及技术进步.这一领域的研究成果将为自身免疫性疾病及肿瘤免疫学诊断与治疗开辟新的视野.母-胎免疫调节机制的研究对于移植免疫学、肿瘤免疫学及自身免疫性疾病防治新策略的研究具有重要的学术价值.

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复旦大学附属妇产科医院副院长，妇产科研究所所长，教授、研究员、博士研究生导师。“973”项目首席科学家。2015 年美洲生殖免疫学会授予生殖免疫学研究杰出成就奖。2008 年入选上海领军人才；2007~2008 年度卫生部有突出贡献中青年专家；2004~2006 年度上海市劳动模范。现任中国中西医结合学会妇产科专业委员会主任委员。中国免疫学会理事，及上海市免疫学会副理事长；中国免疫学会生殖免疫分会主任委员。

Research progress of maternal-fetal tolerance

WANG SongCun, DU MeiRong & LI DaJin

Hospital and Institute of Obstetrics and Gynecology, Shanghai Medical College, Fudan University, Shanghai 200011, China

Development of the allogeneic fetus in the maternal uterus represents an immunological paradox. Successful pregnancy requires the maternal immune system to tolerate the semi-allogeneic fetus. A failure in immune tolerance may result in abnormal pregnancies, such as recurrent spontaneous abortion. These call for a better understanding of the mechanisms leading to maternal-fetal tolerance. As the only exception to the traditional immunological principles, maternal-fetal tolerance has always been the focus of attention in the fields of reproductive immunology. Embryos express paternal antigens that are foreign to the mother, but the mother provides a special immune milieu at the fetal-maternal interface to permit rather than reject the embryo growth in the uterus until parturition by establishing precise crosstalk between the mother and the fetus. The formation of a functional synapse of the invading fetal trophoblasts, maternal immune cells and decidual stromal cells have now been identified. An improved mechanistic understanding of maternal-fetal tolerance is emerging during the last century. During early pregnancy, the developing decidua undergoes dramatic changes in response to invading trophoblasts. Extravillous trophoblast (EVT) cells do not express major histocompatibility complex (MHC) class I human leukocyte antigens (HLA)-A and HLA-B, which are the main causes of CD8⁺ T cell-mediated rejection. However, HLA-C and HLA-G, highly expressed on EVT cells, can elicit a direct tolerant response by NK cells in most cases. Furthermore, maternal immune cells could be educated by embryonic trophoblasts to develop a unique phenotype and tolerate the fetus. Decidual stromal cells (DSCs) are the predominant cell type of the maternal decidua and play a key role in embryo implantation and placentation. Apart from nutritive and endocrine functions, DSCs are believed to be involved in many immune activities, such as cytokine production and antigen presentation, and regulate the decidual immune responses that may lead to either a successful pregnancy or miscarriage. However, there are still unanswered questions in the maintenance of pregnancy, including the poorly understood phenomenon of maternal tolerance to the allogeneic conceptus, and the remarkable biological roles of placental trophoblasts that invade the uterine wall and decidual stromal cells which are the largest number of cells in the decidua. Here we review the previous research results in the field, with a special focus on the establishment and maintenance mechanism of maternal-fetal tolerance based on the maternal-fetal crosstalk. Nevertheless, recent advances in molecular biology have dramatically enhanced our knowledge of the immunobiology of the maternal-fetal interface. Insights into maternal-fetal tolerance will not only advance our understanding of normal pregnancy but also may be helpful on how immune tolerance can be applied in therapeutic strategies to prevent pregnancy loss. Further research in these areas will give us more avenues for preventing pregnancy complication related to faulty maternal-fetal immune interactions.

maternal-fetal tolerance, pregnancy, maternal-fetal interface, trophoblasts, decidual stromal cells, decidual immune cells

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