·综述·

T细胞代谢重编程在复发性流产中的研究进展

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摘要 复发性流产(RSA)病因复杂,涉及遗传、解剖、内分泌、感染、环境及免疫等多种因素。母胎界面免疫失衡是RSA的重要机制,T细胞功能异常与其密切相关。糖代谢、氨基酸代谢和脂质代谢重编程可改变T细胞增殖、分化和效应功能,进而影响Th17/Treg、Th1/Th2细胞平衡,破坏妊娠免疫耐受。mTOR、AMPK和GCN2等信号通路在上述过程中发挥关键调控作用。本文对T细胞代谢重编程在RSA中的研究进展进行综述,并探讨基于代谢调控的免疫治疗思路,以期为RSA机制研究和治疗策略提供参考。

关键词 复发性流产;T细胞;代谢重编程;免疫治疗
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Research progress on T cell metabolic reprogramming in recurrent spontaneous abortion

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Abstract Recurrent spontaneous abortion (RSA) has a multifactorial etiology involving genetic, anatomical, endocrine, infectious, environmental, and immunological factors. Immune imbalance at the maternal-fetal interface is a key mechanism underlying RSA, and T cell dysfunction is closely associated with this process. Reprogramming of glucose, amino acid, and lipid metabolism reshapes T cell proliferation, differentiation, and effector function, thereby disturbing the helper T (Th) 17/regulatory T (Treg) cell and Th1/Th2 cell balance and weakening maternal-fetal immune tolerance. Signaling pathways such as mTOR, AMPK, and GCN2 are central regulators of these metabolic-immune interactions. This review summarizes recent evidence regarding T cell metabolic reprogramming in RSA and discusses immunotherapeutic strategies based on metabolic regulation, thereby providing a reference for mechanistic studies and treatment development.
Keywords recurrent spontaneous abortion; T cell; metabolic reprogramming; immunotherapy

欧洲人类生殖与胚胎学学会2022年指南[1]将复发性流产(recurrent spontaneous abortion,RSA)定义为2次或以上妊娠丢失。我国《复发性流产诊治专家共识》[2]将RSA界定为与同一配偶连续发生2次及以上妊娠28周前的妊娠丢失。反复妊娠丢失会损伤子宫内膜,降低后续受孕机会,增加宫腔粘连及后续妊娠风险[3]。RSA既是生殖医学问题,也关系到家庭生活和社会生育健康[4-6]。RSA病因包括子宫结构异常、胚胎或亲代染色体异常、内分泌失衡、感染、年龄增长、环境暴露和药物因素等。免疫因素贯穿RSA发生、发展过程,其中母胎界面免疫失调最受关注[7]。母胎界面由胎盘滋养层、胎儿胎盘组织和母体蜕膜共同构成,是母体与胎儿交换信号并建立免疫耐受的关键部位。正常妊娠中,滋养细胞、蜕膜基质细胞及免疫细胞协同维持局部稳态,使母体免疫系统识别胎儿抗原而不发生排斥,该稳态被打破时,炎症反应和免疫攻击会削弱妊娠维持能力并增加流产风险[8]。

1 T细胞亚群与RSA

T细胞是适应性免疫系统的核心细胞。$CD4^+$ T细胞可分化为辅助性T(helper T,Th)细胞1、Th2细胞、Th17细胞、滤泡辅助性T(follicular helper T,Tfh)

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细胞和调节性T（regulatory T，Treg）细胞等亚群，并通过细胞因子和细胞间相互作用调控妊娠期免疫耐受[8-9]。RSA患者的外周血中常出现Th1、Th17细胞比例及Th1/Th2细胞比值升高，Th2、Treg细胞比例及Treg/Th17细胞比值降低[9-10]。T细胞的代谢状态直接影响其增殖、分化和效应功能，糖代谢、氨基酸代谢和脂质代谢改变会进一步塑造母胎界面免疫反应[11-12]。阐明T细胞代谢重编程与RSA免疫失衡之间的联系有助于明确RSA的免疫病理机制。

2　T细胞代谢重编程在RSA中的作用和机制

T细胞代谢重编程主要涉及糖代谢、氨基酸代谢和脂质代谢，哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路贯穿这3类代谢过程，是调控T细胞分化和功能的核心枢纽[11-12]。mTOR活化促进糖酵解和效应T细胞分化；腺苷酸活化蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）通过抑制mTOR、增强脂肪酸氧化和氧化磷酸化来支持Treg细胞功能[11]。妊娠期升高的孕激素和雌激素也会通过基因组和非基因组机制影响T细胞糖酵解、三羧酸循环和氧化磷酸化[13]。

2.1　T细胞糖代谢重编程在RSA中的作用和分子机制

葡萄糖在细胞内通过三羧酸循环、糖酵解和磷酸戊糖途径代谢。母胎界面低氧环境可促进乳酸积累。Quinn等[14]研究发现，乳酸通过改变NADH氧化还原状态，抑制GAPDH和PDH等关键酶活性，减少糖酵解中间产物及磷酸戊糖途径前体生成，从而限制T细胞增殖。低浓度乳酸或局部微环境中的乳酸梯度可能对T细胞亚群产生差异化调节，Th17细胞在糖酵解活跃时仍能维持增殖和功能。$CD4^+$ T细胞受刺激后会调整代谢模式，进一步决定其分化方向，并影响免疫耐受[15]。小鼠模型母体肠道菌群失调会扰乱胎盘碳水化合物代谢，并削弱免疫细胞糖酵解能力，葡萄糖补充可部分恢复免疫功能并降低胎儿吸收率，提示代谢底物可直接调节母胎界面免疫功能[16-17]。

mTOR通过调节$CD4^+$ T细胞糖酵解参与RSA免疫失衡。对不明原因RSA患者蜕膜组织的研究[18]显示，AMPK/mTOR信号通路参与糖酵解重编程。mTOR-HIF-1α-糖酵解轴可影响Th17与Treg细胞分化方向：mTORC1促进Th17细胞有氧糖酵解，而$Foxp3^+$ Treg细胞形成需要mTORC1和mTORC2活性受到限制[12]。AMPK活化后可抑制葡萄糖转运蛋白1和mTOR信号，促进Treg细胞分化及功能维持[12]。在细胞因子层面，白细胞介素（interleukin，IL）-6与转化生长因子β（transforming growth factor-β，TGF-β）共同驱动$CD4^+$ T细胞向Th17细胞分化，Th17细胞分泌IL-17，并与肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）协同诱导炎症反应[19]。妊娠早期胚胎着床需要适度的炎症反应，Th17细胞短暂活化有利于滋养层植入；健康孕妇妊娠期外周血Th17/Treg细胞比例呈动态变化[20]，但Th17/Treg细胞比例平衡持续偏移会破坏免疫耐受。Meta分析显示，RSA患者Th1、Th17细胞比例及Th1/Th2细胞比值升高，Th2、Treg细胞比例及Treg/Th17细胞比值降低，Th17与Treg细胞群呈负相关[9]。Th17及Th1细胞偏移可促使IL-1β、γ干扰素（interferon-γ，IFN-γ）等促炎性细胞因子升高，IL-4、IL-13和IL-10等抗炎细胞因子降低，最终破坏母胎界面稳态[9]。

2.2　T细胞氨基酸代谢重编程在RSA中的作用和分子机制

氨基酸既是蛋白质合成原料，也是T细胞代谢感应和分化调控信号。代谢组学研究[21]发现，妊娠丢失患者血浆中色氨酸代谢和支链氨基酸代谢紊乱，其中色氨酸代谢通路富集最显著。RSA患者蜕膜基质细胞诱导Treg细胞能力下降，进而削弱蜕膜局部抗炎和免疫耐受功能[22]。谷氨酰胺和精氨酸能维持T细胞增殖及效应功能，缺乏时会干扰T细胞反应[23]。氨基酸代谢可通过mTOR、AMPK和HIF-1α等信号通路影响T细胞代谢适应，进而调节Th1、Th17、Treg及$CD8^+$ T细胞等亚群的分化和功能[24]。mTOR信号将氨基酸供应状态与T细胞命运连接起来。mTOR活化支持初始$CD4^+$ T细胞向Th1、Th17细胞等效应亚群分化；mTOR受限并伴随线粒体代谢和脂质稳态调整时，Treg细胞分化更易建立[13-14]。

一般性控制阻遏蛋白激酶2（general control non-derepressible 2，GCN2）是另一类氨基酸感受器。氨基酸缺乏激活GCN2后，下游真核翻译起始因子2α（eukaryotic translation initiation factor 2α，eIF2α）磷酸化，细胞蛋白翻译和周期推进受到限制[25]。在免疫调节中，IDO介导的色氨酸代谢可通过氨基酸感应

途径影响T细胞启动和分化[26]。GCN2轴与mTOR轴共同决定T细胞在营养限制环境中的增殖、效应分化和Treg细胞形成，因此是连接氨基酸代谢与母胎免疫耐受的重要通路。

Th17/Treg细胞平衡是氨基酸代谢影响RSA的重要靶点。Th17细胞产生促炎性细胞因子IL-17，Treg细胞分泌IL-10和TGF-β等抗炎细胞因子。正常妊娠中，Treg细胞优势有助于抑制母体对胎儿的免疫排斥；RSA中Th17/Treg细胞偏移会削弱这种保护[27-28]。胎儿抗原特异性Treg细胞可在产后积累，并在后续妊娠中表现出记忆功能；部分记忆Treg细胞来源于Th17细胞转分化，说明Th17与Treg细胞之间存在可塑性[29]。Th17细胞向Treg细胞转化依赖从糖酵解向氧化代谢转换，代谢干预因此成为恢复免疫耐受的研究方向。

2.3　T细胞脂质代谢重编程在RSA中的作用和分子机制

脂质代谢异常主要表现为甘油三酯、低密度脂蛋白胆固醇和总胆固醇水平升高，以及高密度脂蛋白胆固醇水平降低。高脂饮食可削弱胎盘脂肪酸β氧化和代谢稳态[30]。在T细胞中，脂质代谢不仅提供膜结构和能量底物，还参与TCR信号、细胞因子产生和效应分化[31]。RSA患者血清甘油三酯和胆固醇水平升高，提示脂质代谢紊乱与RSA发生相关[32-33]。

脂质代谢产物对母胎界面免疫平衡具有双向调节作用。细胞膜磷脂中的花生四烯酸是类花生酸合成前体，经环氧合酶（cyclooxygenase，COX）作用生成前列腺素（prostaglandin，PG）。PGE2与E型前列腺素（E-type prostanoid，EP）2/EP4受体结合后可激活cAMP-PKA信号，抑制Th1细胞活化，促进Th2细胞分化，有利于妊娠免疫耐受；PGE2与EP1/EP3受体结合时则增强炎症反应[32-33]。PGF2α还可经MAPK和mTOR相关信号通路影响子宫内膜血管生成及胚胎细胞侵袭[33]。

脂肪酸氧化是Treg细胞维持抑制功能的重要能量来源。AMPK活化可促进脂肪酸氧化并支持Treg细胞存活和功能，从而限制母胎界面过度炎症反应[11]。Th17细胞的代谢状态也会影响其促炎功能，单细胞代谢研究[34]显示，Th17细胞代谢网络中存在调控自身免疫反应的关键节点。由此可见，脂质底物、脂质信号和氧化代谢共同影响T细胞亚群分化，并参与RSA相关免疫失衡。

脂质代谢紊乱还可诱导铁死亡和自噬异常。铁死亡源于铁代谢失衡和氧化应激，以谷胱甘肽过氧化物酶4功能受损和脂质过氧化物积累为特征。活化T细胞富含多不饱和脂肪酸并伴随铁积累，对铁死亡更敏感，进而可能激活炎症级联并损害蜕膜自然杀伤（natural killer，NK）细胞和T细胞功能。自噬可通过脂噬和线粒体自噬调控T细胞脂质代谢稳态，其异常会影响Treg细胞与效应T细胞平衡并诱发自然流产。

3　T细胞代谢重编程与RSA免疫疗法

免疫调节疗法通过免疫抑制剂或免疫调节剂来降低患者的异常炎症反应，减轻母体对胚胎的免疫攻击，尤其适用于合并自身免疫异常或免疫失衡明确的患者。

2–脱氧–D–葡萄糖（2-deoxy-D-glucose，2-DG）是常用的糖酵解抑制剂，可通过竞争性抑制葡萄糖利用，降低糖酵解水平，降低Th17细胞代谢活性和分化倾向，进而帮助恢复Th17/Treg细胞平衡。研究[35-36]发现，2-DG可降低糖酵解代谢物水平，并下调Wnt/β-catenin信号，限制糖酵解有望减轻过度的炎症反应并恢复免疫稳态。

mTOR抑制剂（如西罗莫司）可影响T细胞活化、糖酵解和效应分化，并在部分免疫异常疾病中显示出调节T细胞功能的作用。相关研究[37]显示，mTOR抑制可减轻T细胞慢性活化和Tfh细胞异常。结合前述机制，西罗莫司用于RSA时的理论基础在于抑制mTOR驱动的糖酵解和效应T细胞分化，促进Treg细胞相关免疫耐受；其临床适应证、剂量和安全性仍需基于RSA人群开展严格评估。

静脉输注免疫球蛋白（intravenous immunoglobulin，IVIG）是RSA免疫治疗方案之一。Han等[38]的回顾性研究显示，IVIG可改善细胞免疫异常RSA患者的妊娠结局。究其机制可能是IVIG通过调节Th1/Th2细胞比例，降低IFN-γ、TNF-α和IL-17等促炎性细胞因子水平，提高TGF-β和IL-10等抗炎细胞因子水平，并促进Treg细胞增殖、减少Treg细胞凋亡[32,38]。PPARs激动剂也可影响T细胞分化，如环格列酮促进初始$CD4^+$ T细胞向Treg细胞分化，吉非罗齐促进其向Th2细胞方向分化[31]。这些发现提示，糖酵解、

mTOR和脂质代谢干预值得进一步验证。

4　总结和展望

RSA病因复杂，免疫因素是其发生发展的核心环节之一。T细胞代谢状态与其功能密切相关，糖代谢、氨基酸代谢和脂质代谢重编程会改变Th17/Treg、Th1/Th2细胞比例，进而影响母胎界面免疫稳态。mTOR信号通路连接多种代谢途径，AMPK、GCN2等信号通路则共同参与T细胞能量感知、效应分化和免疫耐受维持。

T细胞代谢重编程参与RSA，但不同代谢通路之间的交互、外周血与蜕膜局部免疫状态的差异，以及代谢干预在临床人群中的安全性和有效性仍需系统验证。未来研究应结合单细胞组学、代谢组学、空间转录组学和功能实验，明确RSA不同病理类型中的代谢–免疫网络，为基于代谢调控的精准治疗提供依据。

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