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# 树突状细胞在肝移植免疫中的双重作用及其临床转化进展

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**摘 要**:肝移植(LT)是终末期肝病的有效治疗手段,但长期免疫抑制剂的应用仍带来感染、代谢紊乱等不良反应,限制了临床获益。树突状细胞(DCs)作为连接先天与适应性免疫的关键细胞,在LT中发挥免疫激活与免疫耐受的双重作用:一方面通过抗原呈递启动同种异体免疫反应,介导移植排斥;另一方面在特定微环境下诱导免疫耐受,参与移植物长期存活。本文围绕抗原识别通路、肝脏免疫微环境及免疫代谢重编程,系统综述DCs在LT中的功能调控机制。研究表明,糖酵解促进DCs向免疫原性表型分化,而脂肪酸氧化及氧化磷酸化有助于维持其耐受性表型(tolDCs)。在临床转化方面,基于tolDCs的细胞治疗及体内靶向调控策略已显示出诱导免疫耐受的潜力,但其表型稳定性及与现有免疫抑制治疗的协同机制仍有待进一步研究。未来,结合多组学技术构建DCs相关免疫评估体系,有望推动肝移植从非特异性免疫抑制向精准免疫调控转变。

**关键词**:肝移植;树突状细胞;免疫耐受
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# Dual roles of dendritic cells in liver transplantation immunity and their translational progress

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**Abstract:** Liver transplantation (LT) remains the definitive treatment for end-stage liver disease; however, its long-term success is limited by the lifelong dependence on immunosuppressive therapy and its associated complications. Dendritic cells (DCs), as key orchestrators bridging innate and adaptive immunity, play a dual and paradoxical role in LT by simultaneously

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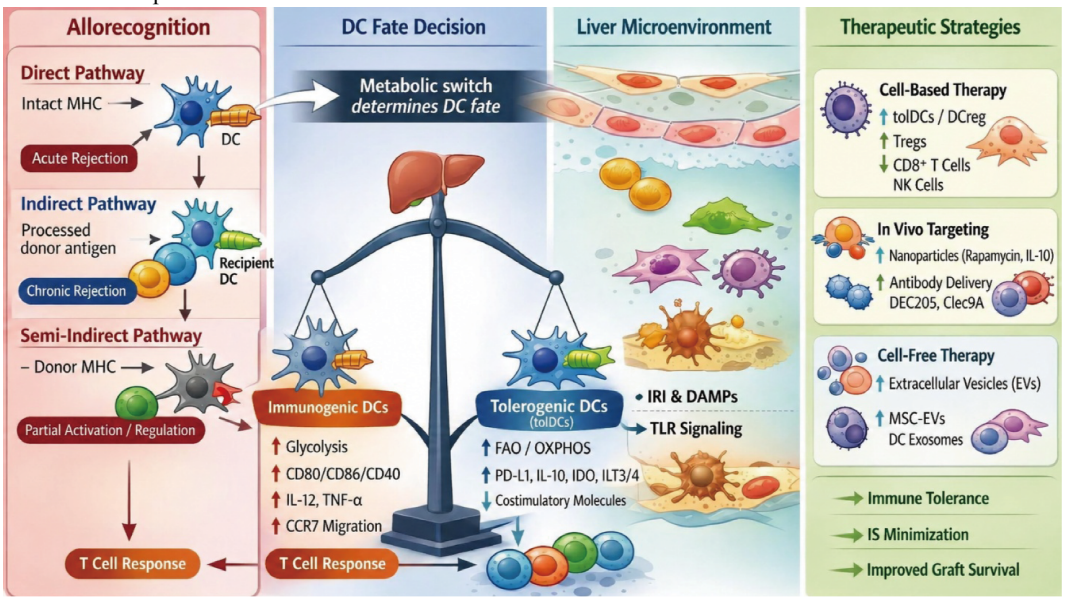
driving allograft rejection and promoting immune tolerance. This review provides a comprehensive synthesis of DCs immunobiology in LT, with a focus on their functional heterogeneity, spatial distribution, and dynamic fate determination. We first summarize the three principal DCs-mediated allorecognition pathways—direct, indirect, and semi-direct—and highlight their temporal interplay across different transplantation stages. Notably, the semi-direct pathway, characterized by "cross-dressing" of recipient DCs with intact donor MHC complexes, emerges as a critical mechanism for immune regulation and tolerance induction within the unique hepatic microenvironment. A central concept of this review is that immunometabolic reprogramming governs DCs functional fate. Immunogenic DCs predominantly rely on glycolysis to support rapid activation and pro-inflammatory responses, whereas tolerogenic DCs (tolDCs) preferentially utilize oxidative phosphorylation and fatty acid oxidation to maintain their regulatory phenotype. This metabolic dichotomy functions as a molecular switch that integrates environmental cues—including ischemia–reperfusion injury, damage-associated molecular patterns, and immunosuppressive signals—thereby shaping DCs-mediated immune outcomes. From a translational perspective, we discuss emerging DCs-targeted therapeutic strategies, including *ex vivo*–generated tolDCs therapy, *in vivo* DCs reprogramming via nanodelivery systems, and cell-free approaches such as extracellular vesicles. Early clinical studies indicate that tolDCs infusion is safe and capable of reshaping host immunity by promoting regulatory T cell expansion while suppressing effector $CD8^+$ T cells and natural killer cells. However, key challenges remain, including phenotypic stability, manufacturing standardization, and potential interactions with conventional immunosuppressive regimens. Finally, we propose that integrating single-cell and spatial transcriptomics with DCs-based biomarkers may enable the identification of "tolerance signatures" for real-time immune monitoring and personalized immunosuppression minimization. Collectively, targeting DCs biology represents a promising strategy to achieve antigen-specific immune tolerance and improve long-term outcomes in liver transplantation.




**Key words:** liver transplantation; dendritic cells; immune tolerance

## 1 引言

肝移植(LT)是终末期肝病最有效的治疗手段,其长期预后在很大程度上取决于供受体之间复杂而精细的免疫调控。肝脏作为具有独特"免疫特权"的器官,能够在持续暴露于肠源性抗原的条件下维持免疫耐受,同时保留对病原体的防御能力,这一特性使部分受者在停用免疫抑制剂(IS)后可实现"操作性耐受"。然而,排斥反应仍是影响移植物长期存活的关键因素,多数受者仍需长期依赖IS治疗,由此带来的感染、肾毒性及代谢紊乱等不良反应严重限制了临床获益[1,2]。因此,诱导抗原特异性免疫耐受、实现IS减量甚至停用,已成为移植免疫领域亟待解决的核心问题。

树突状细胞(DCs)作为连接先天免疫与适应性免疫的关键枢纽,在移植免疫中发挥决定性作用。供体来源的"过客DCs"与受体来源的浸润DCs共同参与同种异体抗原识别与T细胞极化,其功能状态在免疫原性与耐受性之间动态转换,直接影响移植结局。然而,不同DCs亚群在排斥与耐受中的主导作用及其相互调控关系仍缺乏系统认识。

近年来研究表明,肝脏特有的免疫微环境及代谢特征在塑造DCs功能命运中具有关键作用[3]。肝内非实质细胞(NPCs)通过分泌免疫调节因子及细胞间互作,维持DCs的耐受倾向;而缺血再灌注损伤及炎症刺激则可驱动DCs向免疫原性表型转化[4,5]。同时,糖酵解与脂肪酸氧化(FAO)/氧化磷酸化(OXPHOS)之间的代谢平衡,是决定DCs功能状态的重要分子基础[6,7]。基于此,本文围绕"抗原识别-微环境调控-代谢重编程"这一主线,系统综述DCs在LT排斥与免疫耐受中的作用机制,并探讨其临床转化策略。我们认为,DCs的双重功能本质上源于"抗原识别模式-微环境信号-代谢状态"的动态整合,该三维调控网络决定其向免疫原性或耐受性表型的分化方向。

## 2　肝脏DCs的来源与亚群特征

传统观点将DCs视为单一的抗原提呈细胞(APCs),但近年来单细胞多组学研究表明,肝脏内常规树突状细胞(cDCs)、浆细胞样DCs(pDCs)等亚群在表型、空间分布和功能上具有显著差异[4,8]。这些DCs与库普弗细胞(KCs)、肝星状细胞(HSCs)等NPCs协同作用,共同构建肝脏特有的免疫耐受微环境并参与免疫监视[9-11]。肝脏中主要DCs亚群核心特征见表1[12-22]。

### 2.1　cDC1/cDC2的表型特征与功能分化

肝脏中cDCs主要包括cDC1和cDC2两个亚群,二者在表型、发育来源及功能上存在显著差异[2,23,24]。cDC1通常高表达XCR1、CLEC9A等,依赖BATF3发育,在抗原交叉提呈方面具有独特优势,是激活$CD8^+$T细胞应答的关键细胞。cDC1可通过分泌白细胞介素(IL)-12激活肝驻留I型固有淋巴细胞,在急性肝损伤中发挥保护作用[13];在病理状态下则呈现促炎特性。如在原发性胆汁性胆管炎及非酒精性脂肪性肝炎(NASH)中,cDC1相关抗原呈递及肿瘤坏死因子(TNF)、干扰素(IFN)信号通路显著上调,其阻断或缺失可减轻肝脏炎症损伤[13,25]。在LT背景下,cDC1具有双向调控特征:既可通过直接抗原识别通路启动急性排斥反应,也可在耐受微环境中诱导$CD8^+$T细胞功能抑制或耗竭。

相比之下,cDC2亚群以CD1c(BDCA1)或CD11b为标志,依赖干扰素调节因子4发育,主要参与$CD4^+$T细胞激活及Th17等效应T细胞的极化。在原发性硬化性胆管炎患者及相关模型中,cDC2呈选择性扩增并表现为炎症性成熟表型[17]。然而,在LT中,单细胞RNA测序(scRNA-seq)提示,部分$CD11b^+$ DC可通过分泌IL-10抑制细胞毒性T细胞反应,参与免疫耐受建立[4],可能代表cDC2的功能性调节亚型;此外,在丙型肝炎病毒清除后,肝内$CD1c^+$ cDC2上调增殖相关基因,反映其在免疫重塑中的动态调节能力[18]。

总体而言,cDC1与cDC2在肝脏中分别以$CD8^+$与$CD4^+$ T细胞调控为核心,通过不同抗原识别路径及功能状态转换,共同塑造LT中排斥反应与免疫耐受的动态平衡。

### 2.2　pDCs的免疫调节特性

pDCs以BDCA2(CD303)、BDCA4(CD304)及

**表1　肝脏中主要树突状细胞亚群的核心特征**

**Table 1　Core characteristics of major dendritic cell subsets in the liver**

| DCs亚群 | 关键标志物(人) | 主要免疫功能 | 肝脏中分布/动态特征 | 参考文献 |
|---|---|---|---|---|
| cDC1 | $Lin^-$、$HLA\text{-}DR^+$、$CD141(BDCA3)^+$、$XCR1^+$、$CLEC9A^+$、$BTLA4^+$ | 高效交叉提呈抗原,激活$CD8^+$T细胞介导抗肿瘤免疫反应;诱导肝驻留记忆T细胞;在慢性肝病或损伤条件下促炎加剧肝损伤;在肝脏中还参与维持免疫耐受 | 在NASH及纤维化中数量增加且活化增强;在HCC免疫治疗响应者中富集;肝转移瘤中浸润不足 | [12-16] |
| cDC2 | $Lin^-$、$HLA\text{-}DR^+$、$CD1c(BDCA1)^+$、$SIRP\alpha^+$、$XCR1^-$、$CLEC9A^-$ | 激活$CD4^+$T细胞并驱动Th1/Th2/Th17分化;在炎症中分泌促炎因子;在移植中促进效应T细胞激活,耐受环境下可诱导$Foxp3^+$Tregs生成 | 在原发性硬化性胆管炎及小鼠胆管炎模型中显著扩增并处于炎症成熟状态 | [12,17] |
| pDCs | $Lin^-$、$HLA\text{-}DR^+$、$CD303(BDCA2)^+$、$CD304(BDCA4)^+$、$TLR7/9^+$ | 产生I型干扰素介导抗病毒免疫;在肿瘤中呈免疫抑制表型;在LT中具有双重作用:早期参与IRI炎症反应,稳态下通过PD-L1/IDO诱导Tregs并促进耐受 | 在HCC患者肿瘤组织、血液、腹水中累积;LT耐受中可能参与调节 | [12,18-22] |

注:LT,肝移植;NASH,非酒精性脂肪性肝炎;HCC,肝细胞癌;PD-L1,程序性死亡配体1;IDO,吲哚胺2,3-双加氧酶;Tregs,调节性T细胞;IRI,缺血-再灌注损伤

Toll样受体(TLR)7/9高表达为特征,传统上被认为是IFN-I的主要来源,在抗病毒免疫中发挥核心作用。在刀豆素A诱导的肝炎模型中,Ccr9$^{-/-}$小鼠pDCs肝内募集增强并呈现更强免疫抑制能力,从而减轻肝损伤,提示CCR9轴在调控免疫抑制性pDCs富集中的重要作用[22]。然而在肝细胞癌(HCC)中,pDCs浸润与免疫抑制及不良预后相关;在急性肝衰竭模型中,其又表现出一定治疗潜力[22]。

在LT背景下,pDCs同样呈现双重功能:在缺血-再灌注损伤(IRI)阶段,通过分泌IFN-I及炎症因子参与早期免疫激活;而在稳态或耐受环境中,则通过高表达程序性死亡配体(PD-L)1及吲哚胺2,3-双加氧酶(IDO)促进调节性T细胞(Tregs)分化并抑制效应T细胞反应,从而维持免疫耐受。因此,pDCs可能作为连接炎症激活与免疫抑制的关键枢纽,其功能具有明显的微环境依赖性,并与cDC亚群形成互补调控网络。

### 2.3 肝脏其他DCs 及其空间分布特征

除cDC1/cDC2与pDCs外,肝脏中还存在单核细胞来源DCs(moDCs)及新近鉴定的cDC3等亚群。moDCs在NASH等代谢性肝病中参与炎症调控,而cDC3兼具cDC与单核细胞特征,反映DCs发育与功能的连续谱[13,18,26,27]。单细胞转录组学进一步揭示,传统表面标志分型与功能状态之间存在动态对应关系。

在稳态条件下,肝内DCs数量较少(约占NPCs的1%),多处于低活化状态,有助于维持免疫耐受[9,28]。从空间分布看,肝脏DCs呈现明显的区域特异性,cDCs主要位于肝窦及中央静脉周围区域,而pDCs更多分布于肝实质内[29]。这种空间异质性与其功能分工密切相关:肝窦区DCs侧重循环抗原监视,实质内DCs则偏向局部免疫调节。

在LT及相关病理状态下,DCs的空间分布与功能状态发生动态重塑。炎症或损伤(如慢加急性肝衰竭(ACLF)或药物性肝损伤)可驱动DCs活化并向肝窦及炎症灶聚集,增强抗原提呈与免疫激活[12,30];而在慢性肝病(如乙型肝炎、酒精或代谢相关肝病)及肿瘤微环境中,DCs常呈功能受抑或免疫耗竭状态[13,31,32]。此外,肿瘤或纤维化微环境可通过IL-6等信号抑制cDC1发育[33],或诱导调节性DC(rDC)抑制CD8$^+$ T细胞功能。在LT受者中,供体来源及受体募集的DCs广泛分布于肝实质及门脉区,参与早期IRI及后续抗供体免疫反应[9];部分亚群(如CD1c$^+$ DC、CADM$^+$ DC)比例变化提示其在排斥或耐受中的潜在作用。值得注意的是,代谢重编程(如糖酵解异常)亦可进一步削弱DCs功能[34];而外源性干预(如TLR2激活的益生菌)可诱导具有免疫调节特征的DCs亚群在肝内积累[35]。

总体而言,肝内DCs在空间分布、亚群组成及功能状态上均具有显著异质性,并在稳态耐受与炎症免疫之间动态转换,这一特性构成其调控LT免疫结局及肝脏疾病进展的重要基础。

### 2.4 不同DCs亚群的抗原提呈能力比较

不同DCs亚群在抗原提呈能力上具有显著异质性。cDC1因高表达DNGR-1/CLEC9A、XCR1等交叉提呈相关分子,具有高效处理胞内抗原的能力,是启动CD8$^+$ T细胞应答的关键亚群[36]。相比之下,cDC2主要通过主要组织相容性复合体(MHC)-II途径提呈外源性抗原,激活CD4$^+$ T细胞并可驱动Th1、Th2或Th17等分化[37]。pDCs虽具备基础抗原提呈能力,但其MHC-II和共刺激分子(如CD80/86)表达水平较低,稳态下更倾向于诱导免疫耐受而非激活。临床研究显示,在肝硬化及ACLF等重症肝病中,DCs(包括moDCs)普遍表现为HLA-DR及CD86表达下调、IL-12生成减少,导致抗原提呈能力受损并与感染风险及预后不良相关[38,39]。在LT微环境中,供体来源DCs可通过“交叉着装”机制将完整供体MHC分子转移给宿主DCs,直接调控抗供体T细胞反应并促进T细胞耗竭[9];此外,肝内CD11b$^+$ DC通过分泌IL-10抑制细胞毒性T细胞,增强局部免疫抑制效应[4]。总体而言,肝内DCs的抗原提呈功能不仅由其固有亚群特性决定,还受到疾病状态及微环境信号的动态调控,从而在免疫激活与耐受之间实现精细平衡。

## 3 DCs介导的同种异体免疫识别:三通路

在LT中,受体T细胞通过三种经典途径识别供体同种异体抗原:直接、间接及半直接识别通路(图1),分别由供体来源DCs、受体来源DCs及“交叉着装”的受体DCs主导,共同决定排斥反应与免疫耐受的动态平衡。

### 3.1 直接识别通路

直接通路是急性细胞性排斥反应的主要启动机制。供体来源DCs迁移至脾脏及引流淋巴结,其表面的完整供体MHC-肽复合物可被受体T细胞直接

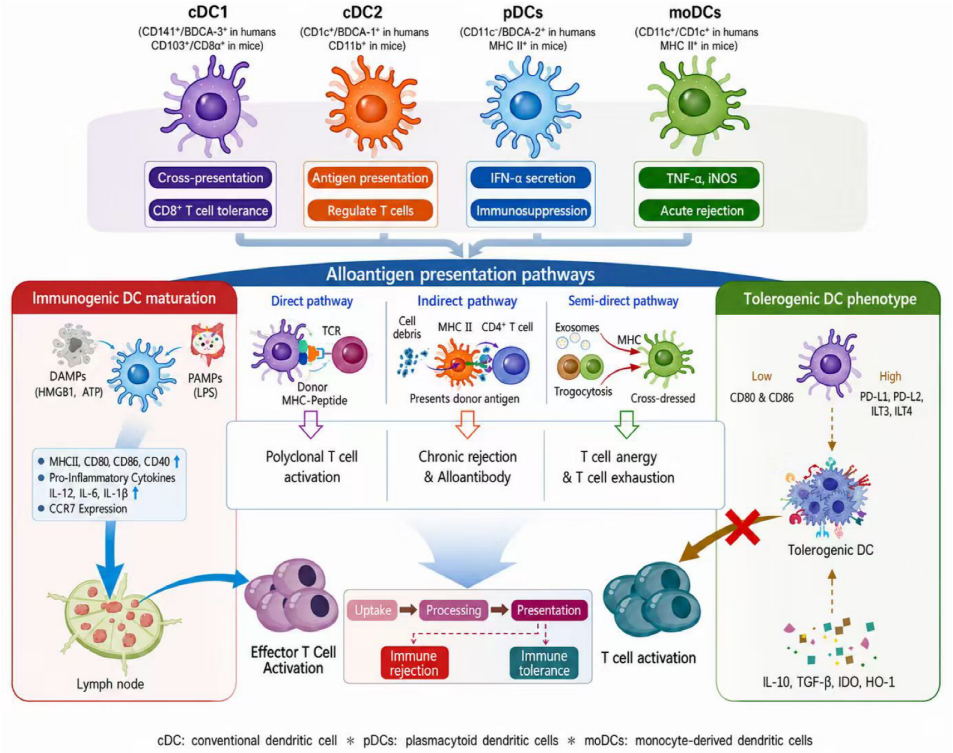



**图1 不同亚型DCs在同种异体移植中，通过三条抗原呈递通路调控免疫排斥或耐受的过程**

肝脏DCs主要可分为经典DCs(cDCs)、浆细胞样DCs(pDCs)以及炎症条件下募集的单核细胞来源DCs(moDCs)。cDCs是肝脏内执行抗原提呈功能的主要亚群，进一步细分为cDC1和cDC2两个亚群。cDC1参与交叉呈递，cDC2负责抗原呈递，pDCs 发挥免疫抑制，moDCs 关联急性排斥。①直接通路：供体DCs携带自身 MHC-肽复合物，直接激活受体多克隆T细胞，介导急性排斥；②间接通路：受体DCs摄取供体细胞碎片，以自身 MHC II 呈递抗原激活 $CD4^+$T 细胞，参与慢性排斥与抗体产生；③半直接通路：受体DCs通过胞啃/外泌体摄取供体 MHC(交叉着装)，但因缺乏共刺激分子，诱导T细胞无能/耗竭，促进免疫耐受。免疫原性DCs可被 DAMPs(如 HMGB1)或 PAMPs(如 LPS)激活，上调 MHCII/CD80等分子及促炎因子，迁移至淋巴结启动T细胞活化。tolDCs通过下调CD80/86、分泌IL-10等抑制因子，阻断T细胞活化，最终介导免疫耐受。整体体现 DCs 的“摄取-处理-呈递”过程对移植后“免疫排斥/耐受”结局的核心调控作用。

注：DAMPs：损伤相关分子模式；PAMPs：病原体相关分子模式；TCR：T细胞受体；HMGB1：高迁移率族蛋白 B1；ATP：三磷酸腺苷；LPS：脂多糖；MHC：主要组织相容性复合体；PD-L：程序性死亡配体； ILT：免疫球蛋白样转录物；IL：白细胞介素；TGF：转化生长因子；IDO：吲哚胺 2,3-双加氧酶；HO-1：血红素氧合酶-1。

**Figure 1 Different subtypes of DCs regulate the process of immune rejection or tolerance in allogeneic transplantation through three antigen presentation pathways**

DCs in the liver can be mainly classified into classical DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs) recruited under inflammatory conditions. cDCs are the main subpopulation in the liver that perform antigen presentation functions and are further divided into cDC1 and cDC2 subgroups. cDC1 is involved in cross-presentation, cDC2 is responsible for antigen presentation, pDCs exert immunosuppressive effects, and moDCs are associated with acute rejection. ① Direct pathway: Donor DCs carry self-MHC-peptide complexes and directly activate recipient polyclonal T cells, mediating acute rejection. ② Indirect pathway: Recipient DCs take up donor cell debris and present the antigen with their own MHC II to activate $CD4^+$ T cells, participating in chronic rejection and antibody production. ③ Semi-direct pathway: Recipient DCs take up donor MHC through phagocytosis/exosomes (cross-dressing), but due to the lack of co-stimulatory molecules, they induce T cell anergy/exhaustion, promoting immune tolerance. Immune-stimulatory DCs can be activated by DAMPs (such as HMGB1) or PAMPs (such as LPS), upregulating MHC II/CD80 and other molecules as well as pro-inflammatory factors, and migrate to lymph nodes to initiate T cell activation. tolDCs inhibit T cell activation by down-regulating CD80/86 and secreting inhibitory factors such as IL-10, ultimately mediating immune tolerance. Overall, this reflects the core regulatory role of the ″uptake - processing - presentation″ process of DCs in the outcome of ″immune rejection/tolerance″ after transplantation.

Note: DAMPs: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns; TCR: T cell receptor; HMGB1: High mobility group box 1 protein; ATP: Adenosine triphosphate; LPS: Lipopolysaccharide; MHC: Major histocompatibility complex; PD-L: Programmed death ligand; ILT: Immunoglobulin-like transcript; IL: Interleukin; TGF: Transforming growth factor; IDO: Indoleamine 2,3-dioxygenase; HO-1: Heme oxygenase-1.

识别,从而诱导高频、多克隆T细胞强烈活化[1]。随着时间推移,供体DCs逐渐被清除或被受体细胞替代,该通路作用逐步减弱[40]。在特定免疫抑制或耐受环境中,其亦可能诱导T细胞耗竭或功能抑制,呈现双重效应[41]。

### 3.2 间接识别通路

间接通路由受体来源DCs主导,其通过摄取供体来源抗原并经加工后以MHC II形式提呈给$CD4^+$ T细胞,进而促进B细胞产生同种异体抗体,与慢性排斥密切相关[1]。在LT微环境中,肝窦内皮细胞(LSECs)和HSCs等非专职APCs亦可参与该过程,扩展抗原呈递网络[11]。

### 3.3 半直接识别通路与交叉着装

半直接通路是一种非经典抗原识别模式,在急性与慢性排斥反应的起始阶段发挥关键作用。该通路的核心特征在于:受体APCs(如DCs)通过摄取供体来源的膜片段、外泌体或细胞碎片,获得并直接展示完整的供体MHC-肽复合物(即"交叉着装"),无需对抗原进行重新加工[40,42]。需要指出的是,半直接识别通路并非直接识别向间接识别的简单时间替代,而是二者之间的重要交汇机制:同一受者APCs既可通过自身MHC呈递加工后的供者抗原肽,激活间接识别反应,也可展示完整供者MHC-肽复合物,诱导直接识别样T细胞反应,从而协调$CD4^+$T细胞辅助、$CD8^+$T细胞激活及同种异体免疫反应的放大。在肿瘤免疫研究中,半同种异体DCs疫苗诱导的半直接通路可在肿瘤生长的早期及后期阶段发挥作用,提示该通路的时间动态可能因疾病模型而异[43]。不同于交叉呈递依赖抗原加工,"交叉着装"保留完整供体MHC结构,从而直接被受体T细胞识别[11]。功能上,此类DCs常表现为低共刺激、高共抑制表型,诱导T细胞无能、耗竭或Tregs分化,是促进免疫耐受的重要机制[11,29,44]。空间转录组学研究进一步提示,该通路可激活TIGIT–NECTIN2等抑制性信号轴,重塑局部免疫微环境[45]。因此,半直接识别通路的时间动态和免疫效应可能受移植物类型、炎症程度、APCs功能状态及局部微环境共同影响。

总体而言,三条通路在时间与空间上协同演替:移植早期以直接通路驱动急性排斥;随后间接及半直接通路逐渐占主导,其中半直接通路更倾向于诱导免疫耐受,而持续活跃的间接通路则推动慢性排斥(表2)[40,46]。因此,调控三通路的动态平衡(如增强"交叉着装"介导的耐受或抑制间接通路)已成为抗排斥治疗的重要策略方向[47,48]。

## 4 DCs的功能命运决定:免疫原性与耐受性的动态平衡

相较其他器官移植,LT更易实现操作性耐受(约5%~20%患者可停用IS),提示其具有独特的免疫调控优势[49]。在这一过程中,DCs作为关键枢纽,其功能并非固定,而是在免疫原性与耐受性之间动态转换,该"命运决策"由微环境信号、炎症刺激及代谢重编程共同决定。总体而言,稳态肝脏微环境倾向诱导耐受表型,而IRI、感染及组织损伤等炎症信号则驱动DCs向免疫原性成熟转换[35,50]。

### 4.1 免疫原性DCs的成熟与促排斥作用

在损伤相关分子模式/病原相关分子模式(DAMPs/PAMPs)等"危险信号"刺激下,DCs通过模式识别受体启动免疫原性成熟程序,主要由cDC2及炎症募集的moDCs介导。移植物中高迁移率族蛋白B1(HMGB1)等分子可激活核因子(NF)-κB通路,促进DCs成熟并驱动Th1/Th17反应,从而参与急性排斥[51];而在慢性肝病中,TLR信号受损则导致DCs功能低下,提示其具有情境依赖性[35]。此外,特定TLR配体亦可诱导rDC形成,如TLR2激活的益生菌可促进肝内rDC积累并抑制炎症反应[52]。

成熟免疫原性DCs表现为MHC分子及抗原呈递能力增强、共刺激分子(CD80/CD86/CD40)高表达、促炎细胞因子(IL-12、IL-6、TNF-α)分泌增加及CCR7表达增强,从而促进其向淋巴结迁移并激活

**表2 树突状细胞介导的同种异体免疫识别:三条通路**

**Table 2 Dendritic cell–mediated allogeneic immune recognition: three pathways**

| 通路 | 主导DCs类型 | 主导时间阶段 | 功能 |
|---|---|---|---|
| 直接通路 | 供体cDC1/cDC2 | 早期 | 激活初始T细胞,介导急性排斥 |
| 间接通路 | 受体cDC2/moDCs | 中后期 | 促进体液免疫反应,驱动慢性排斥 |
| 半直接通路 | 受体DCs(交叉着装) | 早期 | 兼具免疫激活与免疫调节作用 |

备注:DC,树突状细胞;moDCs,单核细胞来源DCs

初始T细胞,从而启动急性排斥反应[53]。在亚群层面,moDCs具有最强促炎潜能,是急性排斥的重要驱动者;cDC2倾向诱导Th1/Th17应答;cDC1则在特定条件下兼具免疫激活与调节功能。

### 4.2 tolDCs的形成及免疫抑制机制

在缺乏危险信号(如PAMPs/DAMPs)或富含IL-10、转化生长因子(TGF)-β等免疫抑制因子的环境中,DCs可维持未成熟/半成熟状态或进一步转化为tolDCs[54,55]。需强调,tolDCs并非独立谱系,而是多亚群在特定微环境下形成的功能状态。

tolDCs通过多重机制发挥免疫调节作用:①共刺激信号不足,诱导T细胞无反应;②共抑制信号增强(如PD-L1、免疫球蛋白样转录本3/4(ILT3/4)),抑制T细胞受体信号转导[56];③分泌IL-10、TGF-β等促进Tregs分化[57];(4)通过IDO、血红素氧合酶-1等代谢途径抑制效应T细胞增殖[58,59]。pDCs及"交叉着装"状态下的DCs因其低共刺激、高抑制表型,被认为是重要的耐受促进细胞。免疫检查点网络在其中发挥关键作用,包括PD-L1/PD-1、细胞毒性 T淋巴细胞相关蛋白4(CTLA-4)及TIGIT-NECTIN2等通路[45,60]。此外,肠道菌群状态可通过调控检查点分子表达影响耐受维持[61]。

### 4.3 "耐受印记"与tolDCs稳定性

"耐受印记"是指DCs在长期免疫抑制微环境中形成的相对稳定的免疫调节程序。其分子基础包括:表观遗传重塑(通过抑制促炎基因表达并维持免疫抑制相关基因(如IL-10、PD-L1)染色质开放状态)、转录调控(由信号转导及转录激活蛋白 3、芳香烃受体(AHR)及肌腱膜纤维肉瘤癌基因同源物B转录因子等关键转录因子协同驱动耐受程序)、代谢重编程(向FAO/OXPHOS的持续偏移)及免疫抑制分子(PD-L1、ILT3/4、IDO)的持续表达。其中,AHR通路通过促进IL-10表达并抑制炎症反应,在连接环境信号与免疫耐受中发挥重要作用。然而,这种耐受状态并非绝对稳定,在强烈炎症刺激(如IRI或感染)下,tolDCs仍可能发生功能逆转。因此,如何维持其稳定性是tolDCs临床转化面临的核心挑战。表3对免疫原性与耐受性DCs的特征进行了比较。

## 5 肝脏微环境与免疫代谢调控

DCs的免疫原性与耐受性由局部微环境、炎症刺激及细胞内代谢重编程共同决定。在LT背景下,肝脏固有的耐受性微环境与移植相关损伤信号相互作用,持续塑造DCs功能状态。其中,"微环境-代谢-功能"耦合轴构成调控DCs命运的核心机制。

### 5.1 肝脏免疫微环境特点

肝脏具有天然免疫耐受倾向,这与其解剖结构及NPCs的协同调控密切相关。在稳态下,LSECs、KCs及HSCs通过细胞接触及分泌可溶性因子共同构建抑制性环境。LSECs低表达共刺激分子而高表达PD-L1,并分泌IL-10和TGF-β;KCs持续释放低水平IL-10及前列腺素E2抑制T细胞过度活化;静息态HSCs则通过视黄酸抑制DCs成熟并促进Tregs分化[65,66]。在此背景下,肝内DCs多维持未成熟或耐

**表3　免疫原性与耐受性DCs的特征比较**

**Table 3　Comparison of immunogenic and tolerogenic dendritic cells**

| 特征 | 免疫原性 DCs (驱动排斥) | tolDCs (诱导耐受) | 参考文献 |
|---|---|---|---|
| 主要功能 | 提呈抗原并激活效应T细胞,促进Th1/Th17反应及排斥反应 | 提呈抗原但诱导Treg分化、T细胞无能、克隆删除,抑制效应T细胞反应 | [51,62] |
| 关键表面标志物 | 高表达 MHC II、CD80、CD86、CD40 | 低表达CD80/86,较高表达PD-L1、ILT3、ILT4等免疫调节分子 | [53] |
| 细胞因子/酶 | IL-12、IL-6、TNF-α、iNOS | IL-10、TGF-β、ILT3/ILT4、PD-L1、IDO | [53,56-59] |
| 代谢状态 | 糖酵解增强,HIF-1α/mTOR相关通路激活 | 相对依赖OXPHOS和FAO | [63] |
| 信号通路 | NF-κB、MAPK、PI3K/Akt/mTOR、HIF-1α | IL-10/STAT3、AMPK、β-catenin、AHR等 | [51] |
| 微环境诱因 | DAMPs、PAMPs、缺血再灌注损伤、炎症因子 | IL-10、TGF-β、视黄酸、凋亡细胞及肝脏局部免疫调节信号 | [51,54,55] |
| 临床策略 | 抑制其成熟、抗原提呈或共刺激信号 | 体外诱导tolDCs后过继回输 | [64] |

注:AMPK,腺苷酸活化蛋白激酶通路;AHR,芳香烃受体;NF-κB,核因子-κB;HIF-1α,缺氧诱导因子-1α;PI3K/Akt/mTORC1,磷脂酰肌醇3-激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白复合物1通路;STAT,信号转导和转录激活因子通路;β-catenin,β-连环蛋白通路;OXPHOS,氧化磷酸化;FAO,脂肪酸氧化;MHC,主要组织相容性复合体;PD-L1,程序性死亡配体1;IDO,吲哚胺2,3-双加氧酶;ILT,免疫球蛋白样转录本;TGF,转化生长因子;IL,白细胞介素;DAMPs,损伤相关分子模式;PAMPs,病原相关分子模式

受性表型[67]。

然而,IRI可打破这一稳态。DAMPs通过TLR等通路迅速激活驻留DCs及募集的moDCs,诱导其向免疫原性转化,表现为MHC II及共刺激分子上调、促炎因子分泌增加及CCR7表达增强,从而启动T细胞应答并推动急性排斥[68,69]。其中,moDCs被认为是关键促炎效应细胞[29]。

### 5.2 促炎DCs的糖酵解依赖性

促炎性DCs的激活与功能高度依赖糖酵解代谢。类似Warburg效应的代谢转换可为其成熟、细胞因子分泌及抗原提呈提供能量与生物合成底物。抑制糖酵解可显著削弱DCs的免疫刺激能力[70]。因此,糖酵解不仅是促炎DCs的重要代谢特征,也是其介导移植排斥反应的重要物质基础。

### 5.3 tolDCs的FAO/OXPHOS特征

与之相对,tolDCs主要依赖FAO/OXPHOS等代谢途径。该代谢模式与IL-10分泌、Tregs诱导及免疫抑制功能密切相关[63]。在稳态肝脏中,DCs倾向维持这一代谢状态;而在IRI等炎症刺激下,则发生向糖酵解主导的代谢切换,从而获得免疫原性功能。该“代谢开关”是连接微环境变化与免疫结局的关键枢纽[71]。阻断DCs向糖酵解转化、维持其FAO/OXPHOS优势状态,已成为tolDCs诱导及相关转化治疗的重要策略[72]。

### 5.4 代谢重编程决定DCs命运

DCs由耐受向促炎转化,本质上是细胞内代谢程序的系统性重构。OXPHOS、糖酵解、脂质及氨基酸代谢的动态重塑共同决定其免疫极化方向[72,73]。现有研究表明,HMGB1等炎症信号可促进DCs成熟并增强促炎功能,而脂质代谢异常亦可重塑肝脏免疫微环境并影响DCs功能[52,74]。此外,单细胞分析提示,在LT早期耐受状态下,巨噬细胞等细胞群的OXPHOS通路被协同激活,进一步支持代谢重编程在耐受形成中的关键作用[4]。

总体而言,肝脏稳态微环境通过维持DCs以FAO/OXPHOS为主的代谢模式促进免疫耐受,而炎症刺激则通过诱导糖酵解驱动其向促炎表型转化。代谢重编程不仅是功能改变的伴随现象,更是决定DCs免疫命运的核心机制。

## 6 LT临床场景中的DCs动态演变

在LT过程中,DCs呈现明显的时间依赖性演变:由早期促炎激活逐步转向免疫调节或耐受状态,这一动态变化贯穿IRI、急性排斥及长期耐受阶段,是决定移植结局的关键免疫基础。

### 6.1 IRI阶段的DCs激活特征

在IRI阶段,DCs迅速响应组织损伤信号,整体处于高度活化且偏向促炎的功能状态。scRNA-seq测序提示,XCR1高表达DCs亚群与$CD8^+$ T细胞密切互作,可能加重IRI相关损伤[13];而供体来源间质DCs在早期具有一定保护作用,其缺失可加重肝损伤并干扰后续耐受建立[9]。DAMPs是驱动DCs激活的核心因素,其中HMGB1通过NF-κB通路促进DCs成熟、增强促炎因子分泌并抑制抗原摄取功能[52]。靶向HMGB1或NF-κB可有效逆转DCs过度活化、减轻肝损伤并延长移植物存活[52]。总体而言,该阶段以促炎激活为主,但已存在向调节方向转化的潜在窗口。

### 6.2 急性排斥反应期DCs亚群比例变化

在急性排斥反应阶段,DCs亚群组成及功能进一步向促炎方向偏移。促炎DCs亚群(如$XCR1^+$ DC及moDCs)扩增,并与$CD8^+$ T细胞浸润及肝损伤密切相关[8]。动物模型研究显示,肝移植后第5~10天,HMGB1表达显著上调,伴随血清转氨酶升高及$CD3^+$、$CD86^+$炎症细胞浸润。HMGB1通过促进DCs成熟(如CD86等共刺激分子上调),驱动$CD4^+$ T细胞向Th1/Th17方向分化,并加剧Th17/Treg免疫失衡,从而推动急性排斥进程[52]。

scRNA-seq与高维成像质谱流式分析显示,DCs通过MIF-($CD74^+CD44$)轴促进单核细胞募集,并通过ICAM1-LFA1通路增强$CD8^+$ T细胞效应分化,从而放大局部炎症反应[75]。尽管如此,部分亚群(如CCR9相关pDCs及$CD11b^+$ DC)仍可通过IL-10等机制发挥负向调控作用,提示排斥过程中仍存在内源性耐受调节信号[22]。

### 6.3 长期耐受患者的DCs表型

在实现长期操作性耐受(操作性耐受指在无IS维持下移植物功能稳定)的受者中,DCs呈现明确的调节性/耐受性表型特征:IL-10与PD-L1显著上调,而MHC-II、CD86、CD40等共刺激分子表达降低,从而抑制效应T细胞活化[76,77]。特定亚群(如$CD141^+CD163^+$ DC)比例升高,与效应T细胞反应减弱相关[78]。在功能层面,cDC1可通过转录及代谢重编程参与Tregs诱导[24]。在自发耐受的小鼠模

型中,肝源性pDCs较脾脏pDCs高表达DNAX激活蛋白12及其共受体髓系细胞触发受体2,并呈现更高的PD-L比例,提示其参与耐受调控[79]。此外,$CD11b^+$ DC通过分泌IL-10抑制细胞毒性T细胞,其功能与OXPHOS及特定代谢通路激活相关[4]。促红细胞生成素受体信号可驱动cDC1向耐受相关成熟状态转化;TLR信号(如TLR2激活)亦可促进肝内调节性DCs积累[80]。这些tolDCs与KCs、LSECs等协同,通过细胞间通讯网络共同维持免疫抑制微环境[45]。

## 7 基于DCs的免疫耐受诱导策略与临床转化

基于DCs免疫调节特性的深入认识,通过诱导tolDCs以实现抗原特异性免疫耐受,已成为移植免疫干预的重要方向[72]。其核心在于构建具有免疫调节功能的"活体细胞药物"或通过原位重编程DCs,在体内主动重塑免疫反应,从而促进移植物长期耐受。

### 7.1 体外诱导tolDCs的细胞治疗策略

体外诱导tolDCs并回输受者,是目前最成熟的策略之一。临床前及早期研究表明,供者来源调节性DC(DCreg)输注可在不增加排斥风险的前提下重塑受体免疫状态,包括降低效应$CD8^+$T细胞及NK细胞数量、抑制抗供体T细胞增殖,并减少IL-12p40、IFN-γ等促炎因子,同时增加耐受相关DCs亚群,提示其有助于IS减量甚至撤药[78]。动物研究亦证实供体DCs可减轻IRI并促进耐受建立[9]。

#### 7.1.1 药理学诱导

以外周血单核细胞为起始,通过粒细胞巨噬细胞刺激因子和IL-4诱导分化,并联合免疫调节因子(如地塞米松、维生素D3、雷帕霉素或IL-10)维持其未成熟或耐受表型,是目前最成熟的制备方法[29,81-83]。该策略工艺稳定,已应用于早期临床研究[9]。

#### 7.1.2 基因工程修饰

通过病毒载体或CRISPR-Cas9技术对tolDCs进行基因改造,如过表达IL-10、PD-L1或FasL,或沉默RelB等促炎因子,从而"锁定"耐受表型[84,85]。尽管该策略可显著增强稳定性,但其潜在安全性及技术复杂性仍限制临床应用。

#### 7.1.3 代谢重编程

通过抑制糖酵解、增强FAO/OXPHOS诱导tolDCs形成[6],其中雷帕霉素靶蛋白/腺苷酸活化蛋白激酶(mTOR/AMPK)通路发挥关键调控作用[86];联合策略(如代谢调控+IL-10表达或线粒体靶向干预)可进一步增强其稳定性[56,87]。

### 7.2 靶向体内DCs的原位重编程策略

相较体外细胞治疗,体内靶向调控DCs具有更好的可扩展性。该策略通过精准递送免疫调节分子,实现DCs功能的原位重塑。

#### 7.2.1 纳米递送系统

纳米颗粒可通过被动富集或主动靶向(如DEC-205、甘露糖受体、DC-SIGN)实现DCs定向递送,提高摄取效率及亚群特异性[88-90]。

#### 7.2.2 抗体-药物偶联策略

通过靶向DCs表面特异性分子(如DEC205、Clec9A、CD11c),可将免疫调节剂精准递送至特定DCs亚群,从而实现高效且低毒性的功能调控。这一策略借鉴肿瘤靶向治疗经验,在调控DCs交叉提呈及T细胞应答方面具有重要潜力[90]。

#### 7.2.3 细胞外囊泡(EVs)介导的无细胞治疗策略

DCs来源外泌体可调控移植免疫微环境,诱导免疫耐受[5];MSC来源EVs通过调控巨噬细胞极化及抗炎反应,减轻IRI并促进肝再生[91,92]。工程化EVs(如维生素A修饰EVs)可实现特异性细胞靶向,提高治疗效率[93]。

### 7.3 联合IS的协同治疗

DCs靶向干预与传统IS联合应用,有望实现协同增效并降低毒性。供者DCreg联合标准免疫抑制方案具有良好安全性,并可促进耐受相关免疫重塑[78]。未来可基于DCs亚群特性优化组合策略,例如:mTOR抑制剂促进tolDCs形成,钙调磷酸酶抑制剂(CNIs)抑制DCs成熟,联合NF-κB抑制或IDO通路激活,有望进一步增强耐受诱导效果。在肿瘤领域中DCs疫苗联合靶向药物的成功经验为移植免疫提供了重要借鉴[94]。

总体而言,DCs靶向治疗正由体外细胞治疗向体内精准调控及联合治疗模式演进。结合LT易于诱导耐受的特性,在IS减量窗口期引入DCs干预,有望成为实现操作性耐受的重要策略路径。

## 8 DCs作为移植免疫状态监测的潜在生物标志物

作为连接抗原识别与免疫应答启动的关键"哨兵"细胞,DCs的外周血表型及功能状态在一定程度

上可反映移植物局部免疫微环境的变化。因此,基于外周血DCs的“液体活检”策略,有望实现对移植免疫状态的动态评估,为个体化免疫治疗提供依据。

然而,DCs相关指标易受IS干扰。例如,在CNIs治疗背景下,若仍观察到DCs共刺激分子(如CD86)显著上调,提示存在突破性免疫激活;而DCs低活化状态则难以区分真实耐受与药物抑制导致的“假阴性”。因此,单一指标解释力有限,需结合多参数综合评估。

### 8.1 排斥反应的早期免疫预警

DCs在LT后的动态变化为其作为排斥预警指标提供基础。在IRI及排斥过程中,DCs浸润增加并伴随炎症相关基因上调,且亚群比例失衡及共刺激分子表达增强均与排斥密切相关[95,96]。HMGB1可通过促进DCs表观遗传重编程增强抗原提呈能力,加速排斥进程[97];相反,耐受相关DCs亚群(如$CD141^+CD163^+$)的增加则与免疫抑制状态相关[78]。因此,DCs亚群构成、成熟状态及细胞因子谱的动态变化可作为早期免疫预警信号。

### 8.2 IS减量的决策支持

DCs功能状态亦可为IS减量提供参考。研究表明,tolDCs或DCreg干预后,受者可实现IS减量,并伴随$CD8^+$ T细胞活化降低及Treg相关指标上升[78,98]。体外光化疗亦可通过增加$BDCA1^+$/$BDCA4^+$ DCs促进Tregs扩增,提示免疫环境向耐受转变[99]。因此,动态监测DCs特征有助于识别接近免疫稳态或操作性耐受的患者,从而指导精准减药。

### 8.3 常规免疫抑制治疗对DCs功能的影响

常规IS可显著影响DCs的表型与功能,从而影响其作为生物标志物的判读。例如,CNIs及抗增殖药物(如吗替麦考酚酯)在抑制T细胞的同时,也可抑制DCs成熟及抗原提呈功能,降低促炎细胞因子分泌[100]。此外,PD-L1等共抑制信号可通过DCs来源外泌体传递,其表达亦可能受到免疫抑制治疗调控[101]。

## 9 临床转化面临的关键挑战与局限性

尽管DCs在移植免疫监测与干预中具有重要潜力,其临床应用仍面临多重限制。首先,免疫抑制治疗(如CNIs)可显著干扰DCs表型与功能,从而掩盖其真实免疫状态,影响生物标志物的判读准确性[102]。因此,基于DCs的监测体系需结合细胞亚群比例、转录组特征及功能性读出等多维指标进行综合评估,并建立标准化检测与分析流程。总体而言,DCs作为“动态免疫读出系统”的临床应用,仍依赖于多参数整合及规范化体系的完善。

### 9.1 临床研究进展与转化证据

现有研究已初步证实tolDCs疗法的安全性及免疫调节潜力。《The ONE Study》显示,在肾移植中tolDCs未增加感染或排斥风险,并具有促进IS减量的趋势,同时伴随Tregs比例上升[9,103]。在LT领域,I期临床试验(NCT03164265)验证了供者来源tolDCs的安全性及免疫调节作用,后续研究(NCT04208919)进一步提示其可改善预后并促进耐受相关免疫表型形成[63,78]。机制上,tolDCs通过抑制Th1炎症反应及限制$CD8^+$ T细胞和NK细胞活化,重塑免疫微环境[78]。其潜在优势在于支持IS精准减量,并可能恢复抗肿瘤免疫监视,从而降低肝癌复发风险[104]。

### 9.2 临床应用面临的关键挑战

尽管前景明确,DCs相关策略仍面临以下核心瓶颈:①标准化不足:tolDCs制备流程及质量控制尚未统一,个体差异导致细胞产品稳定性与效力波动,限制规模化应用[104,105]。②表型稳定性与体内行为不确定:tolDCs在炎症环境中可能发生表型逆转,其归巢、分布及存活时间尚缺乏系统研究[2,106]。③工程化与个体差异影响:基因编辑效率有限,且患者免疫状态、炎症水平及肠道菌群差异均可能影响疗效一致性[107]。④治疗策略整合不足:细胞治疗与传统免疫抑制方案之间存在潜在拮抗,且不同干预手段具有显著时序依赖性,如何实现精准联合仍待优化[108,109]。

## 10 总结与展望

本综述系统阐述了DCs在LT免疫调控中的核心作用。当前,移植免疫正由非特异性抑制逐步迈向抗原特异性的精准调控,而DCs的功能命运决定排斥与耐受的平衡。以tolDCs为代表的细胞治疗已在早期临床中显示安全性与潜在疗效,结合纳米递送与无细胞策略的体内调控,为其转化提供了更具可扩展性的路径。同时,多组学技术的发展正不断深化对DCs异质性及空间分布的认识,为靶向干预与生物标志物开发奠定基础[78,109]。未来发展可聚焦三方面:其一,建立人源DCs亚群与动物模型的可靠

对应关系,以提升研究的可转化性;其二,开发无创动态生物标志物,实现排斥预警与IS个体化调整;其三,整合代谢调控与微环境干预策略,构建多维度精准免疫调控体系。总体而言,随着多组学解析与精准递送技术的进步,基于DCs的免疫调控策略有望推动LT从经验性免疫抑制向机制导向的耐受诱导转变,并为实现长期低毒甚至无免疫抑制治疗提供新的可能。

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