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结核病免疫治疗的研究进展

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摘　要

结核病目前仍旧是全球性重要公共卫生难题，特别是耐药结核病的出现，使传统抗结核化疗面临疗效欠佳、毒副作用显著、治疗周期漫长及患者依从性不佳等多重挑战。宿主免疫状态直接决定结核病的发病进程、发展态势及最终转归，因此针对宿主的免疫疗法作为一种极具潜力的辅助治疗策略，正日益受到医学界的广泛关注。本文整合近年来的研究进展，从免疫活性物质、治疗性疫苗、化学药物、细胞疗法和免疫检查点抑制剂五个方面系统总结结核病免疫治疗的现状与未来方向，希望为结核病尤其是耐药结核的综合治疗提供一些新思路。

关键词

结核病，免疫治疗，细胞因子，治疗性疫苗，细胞疗法

Research Progress in Immunotherapy for Tuberculosis

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Abstract

Tuberculosis remains a major global public health challenge. The emergence of drug-resistant tuberculosis, in particular, has exposed the limitations of traditional anti-tuberculosis chemotherapy, including limited efficacy, significant toxicity, prolonged treatment duration, and poor patient adherence. Host immune status determines the occurrence, progression, and outcome of tuberculosis. Therefore, host-directed immunotherapy has emerged as a highly promising adjunctive therapeutic strategy. This article synthesizes recent research progress and systematically summarizes the

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current status and future directions of tuberculosis immunotherapy from five aspects: immunologically active substances, therapeutic vaccines, chemical drugs, cell-based therapies, and immune checkpoint inhibitors. The aim is to provide new insights for the comprehensive treatment of tuberculosis, especially drug-resistant tuberculosis.

Keywords

Tuberculosis, Immunotherapy, Cytokines, Therapeutic Vaccines, Cell-Based Therapy

1. 引言

结核病(tuberculosis, TB)是一种通过感染结核分枝杆菌(Mycobacterium tuberculosis, Mtb)引起的慢性传染病，是全球死亡率高的传染病之一。据世界卫生组织统计，2020 年全球新增结核病例约 990 万例，死亡人数达 128 万[1]。目前临床主要采用多种抗结核药物联合化疗的方案，虽然在一定程度上控制了疫情，但长期应用面临诸多瓶颈：治疗周期长(6~24 个月)、药物毒副作用大、患者依从性差，以及日益严峻的耐药问题(耐多药结核病和广泛耐药结核病) [2]。

近年来的研究表明，宿主对 Mtb 的免疫识别、免疫应答和免疫调节决定了结核病的发生、发展和转归[3]。Mtb 通过持续抗原刺激和免疫逃逸机制，诱导 T 细胞、巨噬细胞等免疫细胞出现功能耗竭，表现为增殖能力下降、细胞因子分泌减少、抑制性受体(如 PD-1、Tim-3)表达上调，从而削弱宿主防御能力[4] [5]。因此，通过免疫干预恢复宿主免疫平衡、增强保护性免疫应答，成为结核病治疗的重要突破口[6]。

本文整合近年来的研究进展，从免疫活性物质、治疗性疫苗、化学药物、细胞疗法和免疫检查点抑制剂五个方面系统总结结核病免疫治疗的现状与未来方向，希望能为结核病尤其是耐药结核的综合治疗提供一些新思路。

2. 免疫活性物质

免疫活性物质是一种由免疫细胞或者其他细胞产生的有免疫调节作用的分子，包括细胞因子、抗体等。

2.1. 细胞因子

细胞因子是调节免疫应答的关键分子，已在结核免疫治疗中得到广泛研究。白细胞介素-2 (interleukin-2, IL-2)能促进 CD4 T 细胞和 NK 细胞的增殖以及转化，部分临床研究显示其可提高痰菌阴转率，但对影像学改善不显著，疗效存在争议[7]。一项 Meta 分析显示，重组人 IL-2 (recombinant human IL-2, rhuIL-2)免疫辅助治疗对肺结核/耐多药结核病患者安全，能促进 CD4T 细胞和 NK 细胞的增殖和转化，提升痰菌阴转率，不过对影像学上的改善无明显效果[8]。

粒细胞－巨噬细胞集落刺激因子(Granulocyte-Macrophage Colony-Stimulating Factor, GM-CSF)能够抑制 Mtb 在单核巨噬细胞里的生长[9]。一项 II 期临床试验表明，rhuGM-CSF 联同抗结核化疗治疗活动性肺结核具有较好的安全性、耐受性，治疗到第 8 周时患者痰菌快速转阴[10]。在耐多药结核小鼠的模型中，IL-2 以及 GM-CSF 联合免疫治疗可增大小鼠存活率，降低肺、脾组织中的菌载量以及肺部病变严重

程度[11]。白细胞介素-24 (IL-24)是 IL-10 细胞因子的家族成员，Mtb 感染可降低人外周血单个核细胞(Peripheral Blood Mononuclear Cells, PBMCs)中 IL-24 的表达，降低结核患者血清 IL-24 水平，可能增加结核易感性并促进慢性结核发展[12]。IL-24 可通过激活 CD8 T 细胞的 IL-24 受体信号通路产生大量干扰素-γ (interferon-γ, IFN-γ)来抵抗 Mtb [12]。白细胞介素-32 (IL-32)通常是由 T 细胞、上皮细胞以及 NK 细胞产生，可诱导巨噬细胞产生关键的炎症因子(如 TNF-α、IL-1β、IL-6、MIP-2 和 IL-8)从而消除 Mtb [13] [14]。研究表明，热灭活 Mtb 刺激人 PBMCs 可诱导产生大量 IL-32，增强人单核－巨噬细胞清除 Mtb 的能力[15]。通过 siRNA 干扰下调人 THP-1 巨噬细胞内源性 IL-32 表达后，细胞内炎症因子(TNF-α、IL-1β 等)显著降低，细胞内 Mtb 增加[16]。

2.2. 抗体

传统观点认为人体感染结核杆菌后主要依赖细胞免疫，但近年多项研究表明，抗体同样也在抗结核中发挥保护作用。Meta 分析显示，部分抗体缺乏的宿主对结核病易感性增加[17]。针对不同 Mtb 表位的抗体保护功能各异。例如，结核患者体内抗 LAM 或 AM 抗体水平越低，结核进展越快、播散频率越高[18]；人抗 HBHA IgM 抗体可阻止 Mtb 进入结核患者上皮细胞[19]；抗 Ag85A IgG 可降低活动性结核风险、减少空洞形成和痰菌清除[20]。

被动注射针对 Mtb 抗原的多克隆/单克隆抗体或血清可改善吞噬作用，调节 CD8 T 细胞，减少小鼠组织损伤、肺部炎症和菌载量。例如，经气管内或鼻内接种抗 Acr IgA 抗体或经 hsIgA 预处理的 Mtb 感染小鼠，其肺部菌落计数减少，肉芽肿形成改善[21] [22]；抗 HBHA IgG3 McAb 4057D2 和 IgG2a McAb 3921E4 或抗 LAM IgG 可显著减少 Mtb 的肺外播散[23] [24]。

2.3. 小分子活性肽

抗菌肽(Antimicrobial Peptides, AMPs)是具有抗菌活性及趋化、自噬和免疫调节活性的小分子阳离子两亲性肽[25] [26]。许多 AMPs 对 Mtb 感染具有潜在免疫治疗效果，其对 Mtb 的杀菌作用不依赖于菌株是否耐药[27]。必需氨基酸 L-异亮氨酸及其类似物可通过激活转录因子 NF-κB 诱导 β-防御素表达，用 L-异亮氨酸治疗肺结核小鼠模型可增加 mBd-3 和-4 基因表达，减少菌载量和肺部炎症[28]；纳米封装合成的 Magainin-I 类似肽可减少活 Mtb 数量约 3.03-log CFU，通过避免细菌诱导的吞噬体－溶酶体融合和凋亡抑制来增强宿主防御机制[29]；重组人中性粒细胞肽-1 (HNP-1)、人 β 防御素-2 (HBD-2)、LL-37 衍生肽 HHC-10 或 LLKKK18、天然防御调节因子(IDR HH2 和 IDR-1018)用于治疗结核小鼠模型，可减少菌载量和肺部炎症[30]-[32]。

胸腺喷丁是一种具有免疫活性的合成五肽。在 BALB/c 小鼠模型中，胸腺喷丁治疗组外周血 Th1 和 Th17 细胞显著增加，而 Th2、Treg 反应和程序性死亡受体-1 (programmed cell death protein-1, PD-1)表达降低，与对照组相比无显著副作用[33]。此外，胸腺喷丁联合化疗治疗结核患者具有协同作用，可缓解临床症状、提高痰菌阴转率和病灶吸收[34]。

2.4. 免疫阻断剂

长期慢性炎症可造成 Th1/Th2 免疫失衡、免疫抑制以及 T 细胞耗竭等。使用免疫阻断剂阻断有害的某些免疫分子可达到免疫治疗目的。例如，用抗 IL-4 抗体处理过的小鼠结核模型可阻止 Th2 细胞因子 IL-4 的分泌，导致免疫平衡转向保护性 Th1 反应，从而降低小鼠脾脏、肺部的菌载量[35]。

在 Mtb 慢性感染的小鼠中，IL-10 受体被单抗阻断后，可解除其对巨噬细胞活化以及 Th1 免疫应答的抑制，刺激肺内 T 细胞募集和 IFN-γ 的产生，减少肺菌载量，提升小鼠存活率[36]。用抗 IL-17A 单抗

治疗小鼠结核模型可阻断 Th17 过度反应引起的大量中性粒细胞募集和组织损伤[37]。因此，在结核治疗过程中维持 Th1-Th17 平衡对促进抗结核免疫和避免炎症组织损伤至关重要。

3. 治疗性疫苗

治疗性疫苗通过调控或定向激发 Mtb 感染人群免疫系统的能力，重建免疫稳态，减轻免疫损害，增强免疫应答，进而抑制或清除 Mtb。

3.1. 灭活疫苗

在通过热灭活非结核分枝杆菌制备的灭活结核疫苗中，母牛分枝杆菌(*M. vaccae*, MV)疫苗和草分枝杆菌 F.U.36 (Utilins)已被认证用于结核治疗，在小鼠模型中，MV 疫苗对肺部 Mtb 感染具有保护作用[38]。Meta 分析显示，MV 疫苗能够明显增加痰菌阴转率，不过它对病灶吸收、空洞闭合以及死亡率的影响不一致，可能与 MV 应用的频率和间隔不统一有关。

MIP 疫苗(*M. indicus pranii*)由热灭活的非致病性印度普拉尼分枝杆菌制成，可诱导 Toll 样受体信号通路激活先天免疫，刺激 T 细胞免疫应答[39]。III期临床试验和 Meta 分析显示，MIP 疫苗可增加结核患者痰菌阴转率，并且没有不良反应[40]。然而，在结核性心包炎的III期临床试验中(约三分之二受试者为 TB-HIV 共感染)，MIP 无显著治疗效果，但出现严重副作用：15%患者注射部位出现脓肿，HIV 阳性患者卡波西肉瘤发生率较高[41]。

DAR-901 疫苗(Mk)由热灭活的 *M. kyogaense* sp. nov.制成。I 期和 II 期临床试验显示，皮内注射 DAR-901 易形成长期瘢痕，3~12 次 DAR-901 联合化疗可提高痰菌阴转率，促进病灶吸收，增强 Th1 细胞因子反应[42]。此外，DAR-901 片剂的 II 期临床试验显示，联合化疗一个月治疗结核和耐多药结核患者可提高痰菌阴转率，安全性高[43]。

RUTI 疫苗是在低 pH、低氧、营养不良环境中培养出 Mtb H37Rv，然后破碎解毒包埋于脂质体而制成的[44]。可诱导多种抗原的体液免疫应答和 Th1/Th2/Th3 混合细胞免疫应答，无局部或全身毒性[44]。在活动性结核动物模型中 RUTI 单独使用无效，甚至可能导致免疫损伤，但化疗后用 RUTI 治疗感染动物可获良好效果[45]。RUTI 联合化疗治疗潜伏结核感染的 I 期和 II 期临床试验结果显示，该疫苗能有效诱导潜伏结核感染志愿者产生细胞免疫应答，但不良反应与剂量正相关，注射部位易出现结节[46]。

3.2. 亚单位疫苗

亚单位疫苗可应用于潜伏结核感染的预防性干预和结核患者的辅助治疗。卡介菌多糖核酸注射液(BCG-PSN)是目前唯一获准用于结核的免疫治疗疫苗，但近年来主要用于非结核免疫缺陷疾病[47]。其他 4 种重组蛋白疫苗(Mtb72f/AS01E、H56/IC31、ID93/GLA-SE 和 AEC/BC02)目前已进入 I 期或 II 期临床试验阶段。

Mtb72f/AS01E 由重组嵌合蛋白 M72 (Mtb39 和 Mtb32)与 AS01E 佐剂配制而成[48]。I/IIa 期临床试验显示，Mtb72f/AS01E 临床耐受性可，诱导强烈的 M72 特异性体液免疫应答和 CD4T 细胞应答，不过 CD8T 细胞应答相对较弱[49]。随后 IIb 期临床试验显示，该疫苗可为 HIV 阴性潜伏结核感染成人提供 54%的保护，降低肺结核发病率[48]。

H56:IC31 是三种抗原(Mtb Ag85B、ESAT-6 和 Rv2660c)与 IC31 佐剂配制的重组融合蛋白[50]。研究表明，与对照组相比，H56/IC31 疫苗可预防潜伏结核或活动性结核小鼠或非人灵长类动物模型中细菌的再活化，显著降低菌载量[51]。I/II 期临床试验显示该疫苗安全，可诱导抗原特异性 IgG 和表达 Th1 型细胞因子的 CD4T 细胞应答，低剂量接种可在 Mtb 感染个体中检测到 TNF-*α*、IL-2、H56 特异性记忆 CD4T 细胞[50]。

ID93/GLA-SE 是四种抗原(Mtb Rv2608、Rv3619、Rv3620 和 Rv1813)与吡喃葡萄糖基 脂质佐剂配制的重组融合蛋白[52]。该疫苗联合化疗可诱导强烈且持久的 Th1 型细胞免疫应答，延长生存时间，减少器官菌载量和病理损伤，增强化疗效果[53] [54]。

3.3. DNA 疫苗

DNA 疫苗通过编码 Mtb 保护性抗原基因与真核表达载体构建而成，不仅能有效诱导体液免疫和 Th1 型细胞免疫应答，还能诱导特异性细胞毒性 T 淋巴细胞应答[55] [56]。GX-70 由四种 Mtb 抗原质粒(具体抗原未公开)和重组 Flt3 配体组成，是唯一可用于临床试验的结核 DNA 疫苗。该疫苗的 I 期临床试验原计划在治疗失败或复发高风险肺结核患者中进行评估，但因研究经费未确认而撤回[43]。

Ag85a/b 嵌合 DNA 疫苗已完成临床前研究和中试工艺，通过电诱导在结核小鼠模型中可诱导中等水平抗体、增强 Th1 细胞免疫应答、减少肺组织病变和器官菌落数，安全性评价未发现不良反应，正在准备申请临床试验[57]。

4. 化学药物

1α,25-二羟基维生素 D3 可抑制 Mtb 在 PBMCs 中的生长和促炎细胞因子分泌，诱导 LL-37 或自噬相关蛋白 Beclin-1 和 Atg5 介导杀伤效应[58]。然而，Bekele 等发现，维生素 D3 和苯丁酸联合化疗治疗肺结核可改善临床症状、减少并发症，但对痰菌清除无影响[59]。Meta 分析显示，维生素 D 临床研究结果不一致可能与临床试验设计、患者特征、剂量、时间和研究终点的巨大差异有关[60]。槲皮素和聚乙烯吡咯烷酮(QP)可促进内皮细胞生长，诱导炎症部位微循环活化，减少炎症和凝血[61]。对活动性肺结核患者进行 QP 联合化疗，能降低 IL-1β 和 TNF-α 表达，显著增加 IL-4，提高炎症部位一氧化氮水平，无副作用[61]。岩白菜素可激活 Mtb 感染巨噬细胞中的 MAPK、ERK1/2 和 SAPK/JNK 通路，选择性诱导 CD4 和 CD8 T 细胞表达 IFN-γ、TNF-α、IL-12、IL-17，促进 NO 产生清除 Mtb，与异烟肼联用可显著减少病理损伤和菌载量。大蒜素能够增强 MAPK 和 SAPK/JNK 通路的激活，选择性诱导 Th1 应答抵抗 Mtb 侵袭，抑制 p38-MAPK 磷酸化减少 TNF-α 和 IL-10 表达[62]。熊果酸和齐墩果酸通过产生 NO 和活性氧、抑制 TGF-β 表达、诱导 TNF-α 表达、激活巨噬细胞发挥抗结核免疫调节作用。

5. 细胞疗法

细胞疗法通过体外激活和扩增自体或异体免疫效应细胞，回输患者体内以纠正免疫失衡、增强免疫功能，杀灭 Mtb 和感染细胞[63]。

5.1. 间充质干细胞

间充质干细胞(Mesenchymal Stem Cells, MSCs)具有抗炎、免疫调节、促进组织再生修复及低免疫原性等多重特性，是治疗慢性 Mtb 感染引发的免疫系统紊乱和免疫组织损伤的一种前景广阔的免疫疗法。自体骨髓来源 MSC 辅助治疗既往化疗无应答的 MDR-TB 和 XDR-TB 患者的临床试验表明，宿主功能性免疫应答得到恢复，痰菌转阴，肺空洞缩小或闭合，治愈率明显提升，仅少数患者出现轻微不良反应[64]-[66]。但也有研究发现，MSCs 可能激活休眠 Mtb，协助 Mtb 免疫逃逸和在宿主体内长期潜伏，留下结核复发可能[67]。

5.2. $\gamma\delta$ T 细胞

$\gamma\delta$ T 细胞主要通过裂解细胞、产生细胞因子和调节免疫细胞参与免疫应答，具有非 MHC 限制性(可

异体使用)的优势[68]。作为主要的人外周 $\gamma\delta$ T 细胞亚群，Vγ9Vδ2 T 细胞在非人灵长类动物模型中可分化成多功能效应细胞，产生 IFN-γ、穿孔素和颗粒溶素等免疫因子，有效抵抗结核[69]。一项开放标签、单臂初步研究显示，同种异体 Vγ9Vδ2 T 细胞治疗 MDR-TB 患者可促进肺病灶修复，改善宿主免疫，减少 Mtb 负担，且安全性良好[70]。

5.3. 细胞因子诱导的杀伤细胞

细胞因子诱导的杀伤(Cytokine-Induced Killer, CIK)细胞是由人 PBMCs 经多种细胞因子刺激体外扩增获得的非限制性杀伤细胞[71]。中国一例播散性肺结核患者采用化疗联合 CIK 免疫治疗后，一个月后痰培养和涂片阴性，无肝损伤[72]。

5.4. 恒定自然杀伤 T 细胞

恒定自然杀伤 T (invariant Natural Killer T, iNKT)细胞是受 CD1d 限制的保守 T 细胞亚群，以 $CD4^{-}CD8^{-}$ NKT 细胞为主。结核分枝杆菌(Mtb)感染的巨噬细胞能够激活 iNKT 细胞，促使后者释放大量 IFN-γ，进而进一步激活巨噬细胞分泌 TNF-α 和 NO，从而增强吞噬体和溶酶体对 Mtb 的杀伤能力[73]。此外，Mtb 感染通过 CD1d 依赖性途径促进 iNKT 细胞分泌 GM-CSF，有效抑制 Mtb 的增殖[74]。

6. 免疫检查点抑制剂

免疫检查点是 T 细胞和其他免疫细胞表面的负调节因子。近年来研究发现，结核患者存在 T 细胞功能障碍和耗竭，提示免疫检查点抑制剂在抗结核治疗中的潜力。

6.1. PD-1 及其配体

PD-1 是表达于多种免疫细胞(尤其是耗竭 T 细胞)的 I 型跨膜蛋白[75]。PD-1/PD-L1 相互作用能够抑制 CD3 介导的 T 细胞增殖，而 PD-1/PD-L2 相互作用则显著抑制 TCR 介导的 CD4T 细胞增殖及细胞因子产生[76]。研究表明，PD-1 缺失导致调节性 T 细胞和 MSCs 丰度增加，Th1、Th2 和 Th17 细胞因子产生增强，但抑制 Mtb 抗原特异性 T 细胞增殖和巨噬细胞自噬，可能增加对 Mtb 感染的易感性[77]。然而，Kamboj 等报道了 PD-1 对宿主抗结核应答的负面影响，并证明 PD-1 抑制可恢复多能 T 细胞受抑制的保护功能，抗结核化疗联合 PD-1 抑制在感染小鼠中显示出降低肺和脾菌载量的良好效果[78]。

6.2. Tim-3

Tim-3 是一种表达于 T 细胞、单核细胞、巨噬细胞和树突状细胞等多种免疫细胞的 I 型跨膜蛋白，被视为 T 细胞耗竭的重要标志[79]。Tim-3 通过与配体半乳凝素-9 (galectin-9, Gal9)相结合，进而诱导 Th1 细胞发生凋亡，诱导巨噬细胞活化，促进 IL-1β 分泌和病原体清除[80] [81]。

7. 挑战与展望

尽管结核病免疫治疗在动物研究和部分临床试验中显示出前景，但仍面临重大挑战。

首先，免疫机制尚未完全阐明。机体对结核病的免疫反应是一把双刃剑。未来的方向在于有效利用免疫调节和免疫干预手段，促进有益的生理性反应，同时抑制病理性效应。目前对 T 细胞耗竭的理解主要归因于持续的结核分枝杆菌(Mtb)抗原暴露，但驱动抗原持续存在的因素以及诱导耗竭的其他替代途径仍不清楚。

其次，临床应用受限。大多数免疫治疗仍处于临床前或早期临床试验阶段，多项挑战阻碍了基础科学成果向临床实践的转化。目前仅有少数免疫治疗药物可供临床应用，且在药物选择、剂量确定、给药

时机、治疗方案设计、宿主免疫状态评估及免疫学影响等方面缺乏系统研究。标准化、安全有效的联合治疗策略尚未形成。

第三，缺乏免疫学标志物。亟需新型免疫诊断方法，以帮助临床医生清晰了解结核病进展、评估治疗反应、预测临床结局，并为免疫治疗的应用提供实验依据。

第四，特殊人群疗效存在差异。活动性结核病患者、潜伏性结核感染者及 HIV 合并感染者等不同人群的免疫状态各异，同一免疫治疗方案可能产生不同疗效。例如，MV 疫苗已被证实可改善 HIV 阴性结核病患者的临床症状并促进痰菌转阴，但在 HIV 阳性结核病患者中却未显示出疗效[82] [83]。

未来研究应聚焦于：阐明 Mtb 诱导免疫耗竭的分子机制；开发新型免疫治疗药物(如纳米递送系统、mRNA 疫苗)；建立标准化免疫治疗方案；开展高质量临床试验以验证疗效和安全性；以及针对不同患者群体开展个性化免疫治疗策略研究。

8. 结论

结核病免疫治疗通过调控宿主免疫应答，为传统化疗提供了重要补充，尤其在耐药结核、潜伏结核和免疫功能低下人群中展现出广阔应用前景。随着分子生物学和免疫学的不断进步，免疫治疗有望成为继化疗之后又一控制结核病的关键手段。

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