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Review 综述

结核分枝杆菌调控树突状细胞抗原提呈的分子机制研究进展

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摘　要：结核病是一种古老且严重危害全球人类和动物健康的人兽共患病，结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)是引起结核病的主要病原体。树突状细胞(dendritic cell, DC)作为连接机体固有免疫应答和适应性免疫应答的桥梁，凭借其强大的抗原提呈功能激活宿主适应性免疫反应，以抵御病原体的进一步感染，在控制 Mtb 感染中发挥重要作用。近年来，越来越多的研究表明 Mtb 可通过调控 DC 分化和成熟、干扰吞噬作用和自噬过程、抑制抗原提呈相关分子的表达等多种策略逃避宿主免疫杀伤，从而引起持续性感染。本文就目前 Mtb 调控 DC 抗原提呈分子机制的研究进展进行梳理，以期为进一步深入研究 Mtb-DC 互作机制及结核病防控策略提供参考。

关键词：结核分枝杆菌；树突状细胞；抗原提呈；分子机制

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Advances in the molecular mechanisms of *Mycobacterium tuberculosis* in regulating antigen presentation in dendritic cells

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Abstract: Tuberculosis is an ancient zoonotic disease that poses a serious threat to the health of humans and animals worldwide. *Mycobacterium tuberculosis* (Mtb) is the primary causative agent of tuberculosis. As a bridge between innate and adaptive immunity, dendritic cells (DCs) play a pivotal role in controlling Mtb infection by utilizing their potent antigen-presenting capacity to activate the adaptive immune response of the host and thus resist further infection. In recent years, more and more studies have shown that Mtb can evade host immune defenses by regulating DC differentiation and maturation, interfering with phagocytosis and autophagy, and inhibiting the expression of antigen presentation-related molecules, thus causing persistent infection. This review summarizes the current research on the molecular mechanisms of Mtb in regulating DC antigen presentation, aiming to provide insights for further study of Mtb-DC interaction mechanism and development of prevention and control strategies for tuberculosis.

Keywords: *Mycobacterium tuberculosis*; dendritic cells; antigen presentation; molecular mechanisms

结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)是一种胞内病原体，主要通过呼吸道感染，引起人和动物的结核病。世界卫生组织发布的《2024 年全球结核病报告》显示，2023 年全球约有 1 080 万新发结核病患者，因结核病死亡的人数为 125 万，结核病重返导致人类死亡的单一传染病之首[1]。在全球 30 个结核病高负担国家中，我国结核病新发患者数位列第 3，2023 年估算的结核病新发患者数为 74.1 万，表明我国结核病的防控仍任重道远[2]。作为引起结核病的主要病原体，Mtb 最初特异性地感染肺脏驻留的肺泡巨噬细胞，并通过逃避宿主的免疫应答进行增殖以在细胞内存活[3-4]。

树突状细胞(dendritic cell, DC)最初由加拿大学者 Steinman 等于 1973 年在小鼠脾脏中发现，因成熟时有许多树枝状或伪足样突起而得名[5]。目前，人们广泛认为 DC 是机体功能最强的专职抗原提呈细胞，它能高效地摄取、加工、处理和提呈抗原。因此，DC 被认为是机体适应性免疫应答的启动者，是连接固有免疫应答和适应性免疫应答的桥梁[6]。

综上所述，DC 在宿主抵御病原体感染中扮演着重要的角色，同时，病原体也可通过多种途径调控 DC 的抗原提呈功能，从而逃避宿主免疫杀伤[7]。因此，本文就 Mtb 调控 DC 功能相关的研究进行总结梳理，旨在为后续相关研究提供理论参考。

1 树突状细胞

DC 存在于所有哺乳动物组织中，在适应性免疫反应的启动和调节以及先天免疫中起关键作用[8]。未成熟的 DC 存在于外周组织中，具有

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较强的迁移能力，通过其表达的受体识别病变细胞和病原体[9]；而成熟的 DC 主要存在于次级淋巴器官中，加工自身和非自身抗原并提呈给初始 T 淋巴细胞，处于启动、调控并维持免疫应答的中心环节[9]。

1.1 DC 亚群与功能

由于 DC 在生理和病理条件下对于控制免疫反应具有重要作用，因此其亚群和发育起源得到了广泛的研究，并被认为是潜在的治疗靶点。DC 起源于造血干细胞，广泛分布于血液、组织和淋巴器官中[10]。按照发育过程和所需转录因子，DC 可分为传统树突状细胞(conventional DC, cDC)和浆细胞样树突状细胞(plasmacytoid DC, pDC)，其中 cDC 又分为传统 I 型树突状细胞(cDC1)和传统 II 型树突状细胞(cDC2)[11]。不同 DC 亚群的表面标记物及功能由相关转录因子调控(表 1)。

在稳态条件下，cDC1 在血液和组织中的出现频率约为 cDC2 的 1/10[22]。cDC1 广泛分布于血液、皮肤和淋巴器官中，是一种高效的交叉提呈细胞，在坏死细胞相关成分的交叉提呈方面具有较强能力[23]。在体外实验中，cDC1 能促进细胞毒性 $CD8^+$ T 细胞的分化[13]。

cDC2 广泛存在于外周组织和淋巴器官中，尤其在 T 细胞与 B 细胞(T-B)的边界富集[22]。来自血液、淋巴器官、皮肤和肺的 cDC2 可诱导 $CD4^+$ T 细胞在体外极化为辅助性 T 细胞 1 (T helper cell 1, Th1)和 Th2 细胞[23-25]。在细胞因子分泌方面，cDC2 除能高效产生白介素 12 (IL-12p70)外，还可分泌白介素 23 (IL-23)和激活素 A[13,26]。

对于 pDC 的描述最早出现在 20 世纪 50 年代对人类淋巴结的研究中[27]。这些细胞能够分泌大量 I 型干扰素(type I interferon, IFN-I)，从而抵抗病原体[28-29]，而这一功能与 pDC 的分化密切相关[30]。pDC 通过 Toll 样受体(Toll-like receptor, TLR) 7 和 TLR9 识别病原体或自身核酸后，产生 I 型干扰素，在病毒防御中发挥关键作用[31-32]。

1.2 DC 的抗原提呈机制

DC 是机体调节免疫反应的关键细胞[9]。作为组织哨兵，DC 不断从其局部环境中摄取、加工并通过主要组织相容性复合物(major histocompatibility complex, MHC)提呈抗原，诱导固有和适应性免疫细胞的激活，以清除病原体[33-34]。DC 提呈抗原的方式主要包括蛋白酶体途径和溶酶体途径，此外，DC 还可以通过交叉提呈的方式提呈抗原，虽然这不是主要方式，但能更广泛地激活 T 细胞，有利于机体免疫应答(图 1)。

1.2.1 内源性抗原的提呈——蛋白酶体途径

对于内源性抗原，如胞内蛋白、核蛋白、病毒蛋白等，DC 通过蛋白酶体将其降解为多肽，随后由抗原加工相关转运蛋白(transporter associated with antigen processing, TAP)将其转运至内质网，在内质网中与 MHC-I 分子结合，形

表1 树突状细胞亚群的差异性

Table 1 Differences in dendritic cell subpopulations

Type	Distribution	Transcription factor	Phenotype	Function	References
cDC1	Blood, lymph nodes, tonsils, spleen, bone marrow	*Ret3*, *Csf2ra*, *Irf8*, *Batf3*, *Bcl6*, *Id2*	XCR1, DNGR-1, CD205, CD207	Cross-presentation of the antigen to $CD8^+$ T cells, producing high levels of IL-12p70, and promoting activation of cytotoxic T lymphocytes and Th1	[12-17]
cDC2	Blood, lymp, organs, skin, Lungs	*Sfpi1*, *Zbtb46*, *Irf4*	CD11b, CD11c, SIRPα	Presenting MHC class II antigens and promoting the differentiation of Th1, Th2, and Th17	[16,18-19]
pDC	lymph nodes, tonsils, peripheral blood	*Tcf4*, *Bcl11a*, *Runx2*, *SpiB*	CD304, CD303, CD123, BDCA2	The first line of defense against viral infection, initiating IFN-induced antiviral response, and recruiting cytotoxic NK cells	[10,16,20-21]

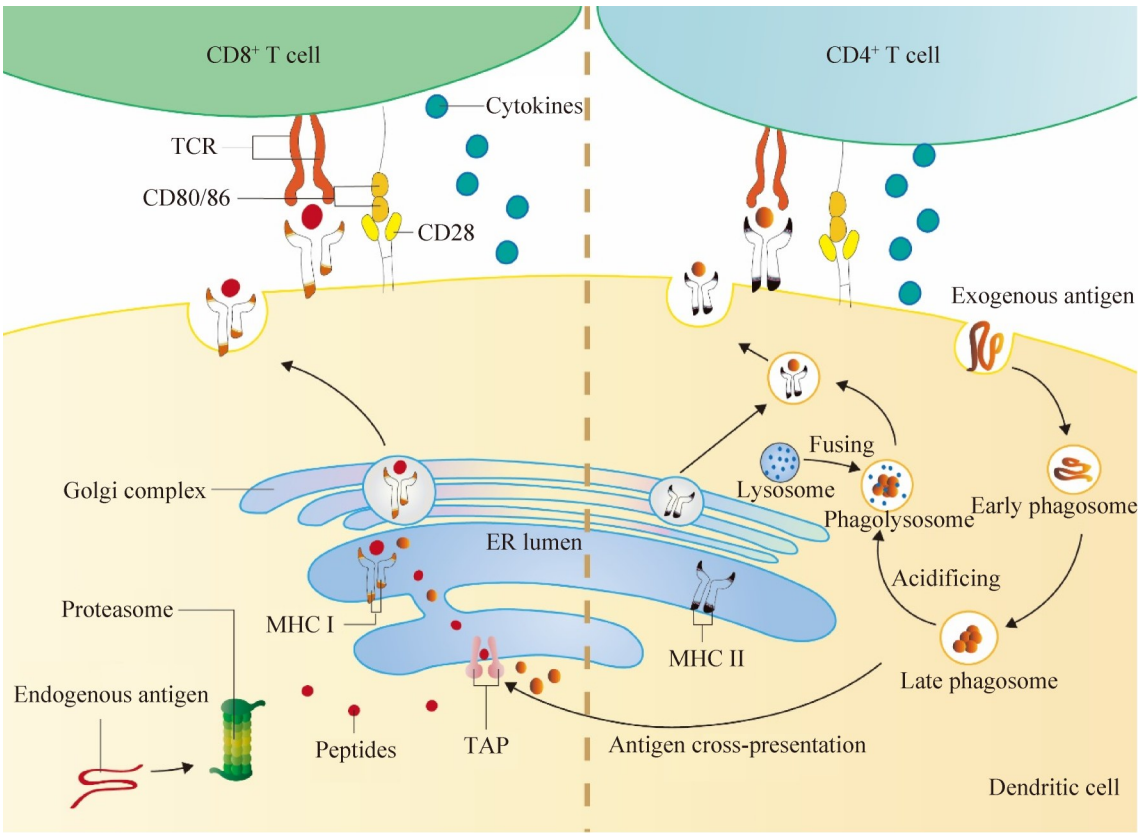

图1　树突状细胞提呈抗原的经典途径

Figure 1　The classical pathways of antigen presentation by dendritic cells. Dendritic cells present antigens to T cells through the proteasome pathway, lysosomal pathway, and cross-presentation.

成 MHC-I-抗原肽复合物，提呈给细胞毒性 T 淋巴细胞(cytotoxic T-lymphocyte, CTL)[34]。该途径在激活抗肿瘤 $CD8^+$ T 细胞反应中发挥重要作用[35]。

1.2.2　外源性抗原的提呈——溶酶体途径

MHC-Ⅰ类分子几乎在所有细胞表面表达，而 MHC-Ⅱ类分子主要在免疫细胞上表达。抗原首先通过吞噬作用或受体介导的内吞作用被细胞捕获。DC 通过其丰富的 C 型凝集素受体和 Fc 受体(Fc receptor, FcR)摄取外周组织环境中的抗原并将其内化，内化后大多数抗原被消化成肽段，通过肽-MHC-II 与 TCR 的相互作用及共刺激信号传导，引发 $CD4^+$ T 细胞的抗原特异性激活和扩增[36]。因此，在 DC 成熟过程中，MHC-II 分子表达量会增加数倍，并伴随着其定位的变化：未成熟 DC 的 MHC-II 分子主要存在于内体中，而成熟 DC 的 MHC-II 分子主要位于质膜上[37]。

1.2.3　抗原交叉提呈

除了上述 2 种途径外，DC 还可以通过交叉提呈的方式，利用 MHC-I 分子提呈细胞外环境中的抗原。外源抗原被吞噬入细胞后可从内体进入胞质，随后被蛋白酶体加工，并加载到内质网中的 MHC-I 类分子上[38-39]。

2　结核分枝杆菌调控树突状细胞抗原提呈的机制

当 Mtb 通过呼吸道被摄入体内时，首先会面临 DC 等固有免疫细胞的防御，其表达的 Toll

样受体、Nod 样受体和 C 型凝集素受体能够有效识别 Mtb 的多种成分，如脂蛋白 LprG 和磷脂酰肌醇甘露糖苷(phosphatidylinositol mannosides, PIMs)等，从而激活宿主细胞的自噬、炎性反应和凋亡等免疫防御信号通路[40] (图 2)。在与宿主免疫系统的长期对抗中，Mtb 进化出了多种保守策略以逃逸免疫杀伤，进而促进其生长和传播，例如抑制细胞抗菌肽的生成、阻碍吞噬体的成熟以及调控细胞自噬等，这些机制构成了感染相关研究中的一个复杂过程[41]。Mtb 与宿主的相互作用结果是决定疾病是否发生的关键[42]。近年来，越来越多的研究表明，Mtb 主要通过抑制抗原提呈细胞(antigen-presenting cells, APC)的吞噬作用、自噬过程、抑制 DC 的成熟以及调控 APC 的分化等多种策略操纵 DC 的抗原提呈功能[40,43-47]。

2.1 受体介导的识别与入侵

如前所述，DC 表达一系列病原体识别受体(pattern recognition receptors, PRR)，包括 TLR 和 C 型凝集素受体，它们可以识别病原体表达的分子模式[48]。每个 TLR 可识别特定的抗原，例如脂蛋白、脂多糖(lipopolysaccharides, LPS)或细菌 DNA[49]。LPS 是革兰氏阴性细菌细胞壁的一个组成部分，可被 TLR4 识别，而肽聚糖(peptidoglycan, PGN)是另一种细菌细胞壁的成分，可刺激 TLR2[50]。Su 等[51]研究发现，Rv1016c 脂蛋白是一种新型 TLR2 配体，在分枝杆菌感染过程中，Rv1016c 一方面可诱导依赖于 TLR2 的细胞凋亡，另一方面也会通过依赖于 TLR2 和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路的方式抑制 MHC-II 的表达和抗原加工，从而降低 $CD4^+$ T 细胞的识别

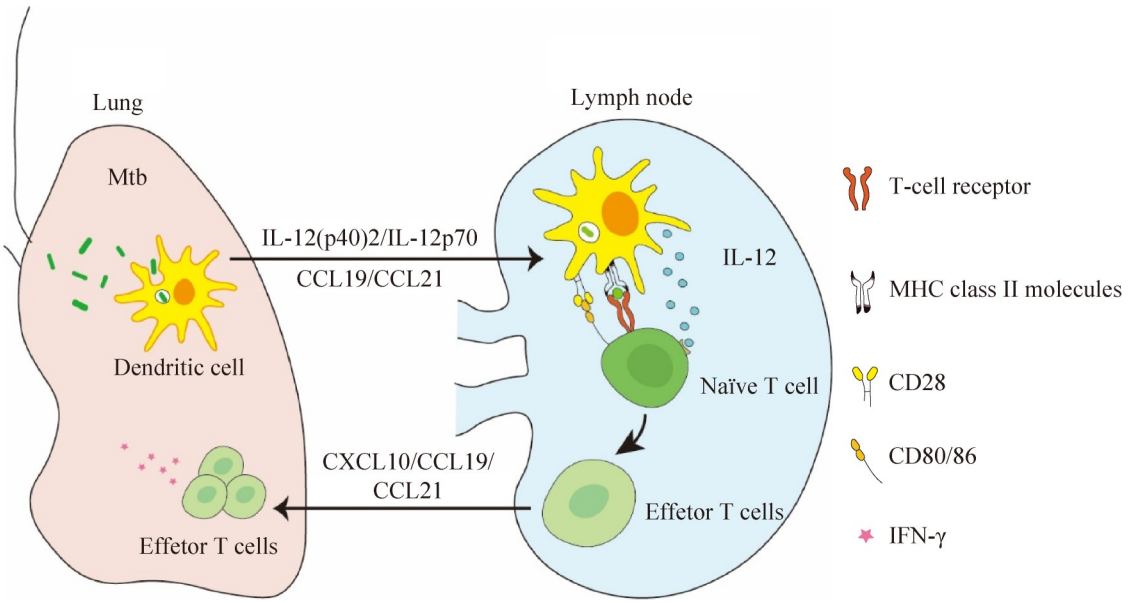

图2 结核分枝杆菌感染的树突状细胞免疫反应

Figure 2 The dendritic cell immune response to *Mycobacterium tuberculosis*. *Mycobacterium tuberculosis* infected DC migrates to the local lung-draining lymph nodes post infection. DC migrates to the lymph nodes under the influence of IL-12(p40)2, IL-12p70, and the chemokines CCL19 and CCL21. This migration facilitates the differentiation of naive T cells into a Th1 phenotype. Subsequently, protective antigen-specific Th1 cells migrate back to the lungs in a chemokine-dependent manner following the initial infection/exposure, where they produce IFN-γ.

能力，从而允许细胞内分枝杆菌的持续存活。

2.2 Mtb 对 DC 分化和成熟的调控

Balboa 等[52]发现，经伽马射线处理的 Mtb 可影响单核细胞衍生的 DC 的分化，进而减少特异性 T 细胞的增殖，这与 IL-10 的分泌和 TLR2 的激活有关。尽管 IL-10 会抑制单核细胞分化为 DC，但它会促进其成熟为巨噬细胞[53]。相比之下，巨噬细胞在抑制 Mtb 生长方面优于 DC，这有助于机体清除 Mtb[54]。

Mtb 的某些蛋白可促进 DC 的成熟。例如，早期分泌性抗原 6 (early secreted antigenic target of 6 kDa, ESAT-6) 和复苏促进因子 E (resuscitation-promoting factor E, RpfE) 可通过 TLR2 和 TLR4 依赖的方式诱导 DC 的成熟，并促进 Th1 和 Th17 型 T 细胞免疫[55-56]。此外，Mtb 通过 TLR 依赖的方式特异性结合树突状细胞特异性黏附分子-3-结合非整合素分子(dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, DC-SIGN)，诱导活性氧(reactive oxygen species, ROS)的产生，进而促进 DC 的成熟[57]。PPE60 可通过 MAPK 和核因子激活的 B 细胞的 κ-轻链增强(nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB)通路诱导 DC 成熟，增强 DC 的 MHC-II 表达和抗原加工[58]。Mtb 的 Rv1509 蛋白通过增加 CD80 和 MHC-II 的表达，并与 TLR2 相互作用下调 DC-SIGN 的表达，从而促进 DC 成熟，诱导小鼠抗原特异性 $CD4^+$ T 细胞和 $CD8^+$ T 细胞数量的增加[59]。此外，HSP70、Rv0462、PstS1 和 Rv3812 均被证明能够诱导 DC 成熟，并在引发针对 Mtb 的保护性免疫反应中发挥作用[60-63]。

然而，更多 Mtb 抗原通过抑制 DC 分化和成熟来逃避免疫反应。Mtb 在潜伏感染期间上调其 α 晶状体蛋白 1 (alpha-crystallin 1, Acr1)的表达，从而抑制 DC 的成熟[64]。Chen 等[65]研究发现，Mtb 蛋白复合物 PE25/PPE41 在体外可诱导小鼠骨髓来源的树突状细胞(bone marrow-derived dendritic cell, BMDC)成熟，增加共刺激分子 CD80、CD86 和 MHC-II 的表达，进而通过分泌促炎细胞因子 IL-4 和 IL-10 促进 Th2 极化。Mtb 细胞壁成分脂阿拉伯甘露聚糖(mannose-capped lipoarabinomannan, ManLAM) 与 DC-SIGN 结合破坏 TLR 信号通路[44]，导致 IL-10 的过度产生，进而抑制 DC 成熟[66]。Mtb 丝氨酸水解酶 1 (hydrolase important for pathogenesis 1, Hip1)可抑制促炎反应并损害 DC 功能，研究发现全长 GroEL2 蛋白具有诱导 DC 中促炎细胞因子产生的能力，并促进 DC 成熟和抗原提呈，但 Hip1 介导的 GroEL2 剪切体免疫刺激性差，无法促进 DC 成熟和抗原提呈[67]。Mtb 的 Rv1016c 通过与 TLR2、信号传导及转录激活蛋白(signal transducer and activator of transcription, STAT) 和细胞因子信号抑制物 3 (suppressor of cytokine signaling 3, SOCS3)通路相互作用抑制 DC 分化，从而损害初始 T 淋巴细胞向 Th1 和 Th17 细胞的分化[44,68]。此外，研究发现，Mtb 在活动性结核病患者中大量释放 MPT64 蛋白，能够将未成熟的 DC 转化为髓系抑制性细胞(myeloid-derived suppressor cells, MDSC)，进而促进调节性 T 细胞(regulatory T cells, Treg)的产生，抑制 Th1 细胞和 Th17 细胞的分化，从而促进 Mtb 的存活[69]。

2.3 Mtb 抑制吞噬体的酸化、成熟及其与溶酶体的融合

DC 通过吞噬作用将 Mtb 内化后，吞噬体逐步酸化、成熟，并与溶酶体融合，发育为吞噬溶酶体，从而降解病原体。随后，DC 将抗原提呈给 T 细胞，启动适应性免疫反应[70]。然而，Mtb 已进化出多种策略抑制这一过程，以实现胞内存活[71]。Mtb 的蛋白激酶 G (protein kinase G, PknG)通过降低甘油激酶(glycerol kinase, GlpK)的表达，增强 Ag85A 和 Ag85C 的表达，从而抑制溶酶体的成熟[72]；此外，PknG 还可通过增强宿主细胞内的信号转导来抑制吞噬体与溶酶体

的融合[43,70]。蛋白酪氨酸磷酸酶 A (protein tyrosine phosphatase, PtpA) 可与液泡 ATP 酶 (vacuolar ATPases, V-ATPases)的亚基 H 相互作用，阻止 V-ATPases 在吞噬体膜上打孔，进而抑制吞噬体的酸化[70,73]。Portal-Celhay 等[74]的研究发现，Mtb 通过分泌 EsxH 抑制宿主细胞的内体分选复合物(endosomal sorting complex required for transport, ESCRT)，而 ESCRT 是抗原加工所必需的；细胞实验表明，敲除 EsxH 后，Mtb 激活的 ESCRT 依赖性 T 细胞增加，表明 EsxH 可通过抑制 DC 加工抗原的能力来阻碍 $CD4^+$ T 细胞的激活和抗原提呈。近些年，关于 Mtb 的主要毒力因子磷酸二甲酯 (phthiocerol dimycocerosates, PDIM)的研究较为热门，主要因为 PDIM 可在 Mtb 感染的多种细胞中发挥作用。Augenstreich 等[75]研究表明，Mtb 通过差异区域 1 (region of difference 1, RD1)编码的 ESX-1 和 PDIM 协同作用诱导受感染巨噬细胞的吞噬体膜损伤和破裂。PDIM 还可导致人淋巴内皮细胞中的溶酶体破裂，最终引发宿主细胞凋亡[76]。然而这种机制是否存在于 DC 中仍有待研究。

2.4 Mtb 抑制自噬

Feng 等[77]研究通过高剂量 Mtb 感染自噬缺陷型小鼠，首次发现 $CD11c^+$细胞的自噬受损时，会导致 MDSC 的过度积累。这些过度积累的 MDSC 携带大量细菌，进而导致抗原呈递细胞数量减少和肺部 T 细胞增殖降低，从而阻碍了持续的 T 细胞反应并破坏了对 Mtb 感染的控制。此外，Mittal 等[78]研究揭示 PDIM 可保护 Mtb 免受 LC3 相关吞噬作用和经典自噬的影响。Hu 等[79]研究发现，Mtb 蛋白 SapM 可靶向宿主 Rab7，从而抑制自噬体-溶酶体融合。2016 年，一项研究通过对 Mtb 感染 DC 后抑制其 MHC-II 类限制性抗原提呈的基因位点进行全基因组筛选，鉴定出 PE_PGRS47 是 Mtb 的一种重要毒力因子[80]。进一步研究发现，编码 PE_PGRS47 蛋白的基因 *Rv2741* 发生靶向突变后，Mtb 在体外和体内的生长速度减慢，同时 PE_PGRS47 突变体在感染小鼠后显著增强了 DC 的 MHC-II 类限制性抗原提呈，表明 PE_PGRS47 蛋白可抑制 DC 的抗原提呈功能，且与抑制受感染宿主吞噬细胞的自噬有关[80]。此外，通过 Mtb 感染的 DC 转录组基因分析发现与自噬相关的基因显著上调，进而发现 Mtb 可通过操纵宿主细胞 microRNA-155 的表达来调节 Atg3，从而实现胞内存活[81]。Mtb 的毒力因子 Rv3416 和 Rv2463 也可抑制 DC 的自噬，以建立长期感染[82-83]。本研究组在前期研究中发现，牛分枝杆菌可通过“劫持”巨噬细胞的线粒体自噬来抑制异源自噬，从而有利于其胞内存活[84]。DC 中是否存在类似的机制仍有待进一步研究。

2.5 Mtb 抑制抗原提呈相关分子的表达

Satchidanandam 等[85]研究发现，通过卡介苗(*Bacillus* Calmette-Guérin, BCG)过表达 Mtb 的甘露糖基化蛋白 Rv1860，可显著下调共刺激分子 MHC-II、CD40、CD54、CD80 和 CD86 的分泌，从而抑制 DC 的抗原提呈及其对 T 细胞的激活。Dolasia 等[86]2021 年的研究发现，Mtb 的 PPE18 蛋白可抑制小鼠 MHC II 类抗原提呈；通过巨噬细胞与 T 细胞共培养实验发现，PPE18 以剂量依赖性方式抑制巨噬细胞 MHC-II 类介导的抗原提呈，导致 $CD4^+$ T 细胞活化较差；因此，Mtb 可能利用 PPE18 来抑制 MHC-II 类抗原提呈，从而削弱适应性免疫反应的激活。DC 中是否存在类似的机制仍有待进一步研究。

2.6 Mtb 调控抗原提呈的其他机制

Srivastava 等[87]研究发现，当 Mtb 入侵宿主后，若宿主固有免疫无法将其清除，招募到肺脏的 DC 也会被 Mtb 感染，进一步受感染的 DC 将 Mtb 运输到局部淋巴结，但激活 $CD4^+$ T 细胞的效果不佳，主要是因为 Mtb 为了提高胞内存活的概率，通过抗原输出途径减少了抗原提呈，虽然抗原输出后其他细胞仍可提呈，但这并不能补偿受感染细胞抗原提呈的减少。这代表了细菌逃避抗原提呈的另一种策略。

综上所述，Mtb 通过抑制自噬过程、吞噬作用、抑制 DC 的成熟以及抑制 APC 的分化等多种策略调控 DC 的抗原提呈过程(图 3)。然而，Mtb 是否存在某种成分能够抑制 DC 对包裹其成分的囊泡的降解或能够阻止 DC 表达 MHC 分子等机制尚不清楚。因此，研究 Mtb 操纵 DC 抗原提呈的分子机制具有重要的科学意义，可拓展和加深人类对 Mtb 免疫逃逸机制的认识，为结核病防控新策略的研发提供新的思路和理论依据。

3 基于促进抗原提呈的结核病新疫苗研制策略

目前唯一注册用于控制人类结核病的疫苗是 BCG，其免疫保护力只能维持 10−15 年[88]。Mtb 的复杂性及其免疫保护标志物的不确定性阻碍了结核病疫苗的开发。作为胞内菌，Mtb 入侵机体后主要引起细胞免疫反应，DC 通过抗原提呈激活 T 细胞免疫反应[89]。因此，研究 Mtb 调控 DC 抗原提呈的机制可为新疫苗的开发提供靶标。

近年来，Mtb 亚单位疫苗、重组 BCG 和减毒活疫苗的研究进展迅速[90]，主要通过不同组合的抗原提呈系统和亚单位疫苗，激活 T 细胞免疫反应以持续抵抗 Mtb 感染。研究表明，ESAT-6 可激活受体，促进抗原提呈细胞的成熟[91]，并且能以 TLR2 和 MyD88 依赖性方式在 DC 中诱导 IL-6 和 TGF-β，从而指导 Th17 细胞分化[92]。基于此，Kirk 等[93]制备了 ESAT-6/EsxA 与 Ag85B 和 EsxH 的组合疫苗，结果表明，这种疫苗可增强长期记忆免疫应答。VPM1002 是一种重组 BCG，可分泌李斯特菌溶血素 O，增加单核细胞增生李斯特菌的吞噬体逃逸[94]。通过敲除抑制吞噬体-溶酶体融合的脲酶 C (urease C, ureC)，该疫苗能够增强李斯特菌溶血素 O 的活性，诱导吞噬细胞凋亡，使 DC 能够通过摄取凋亡囊泡有效地提呈抗原[94]。MTBVAC 是一种

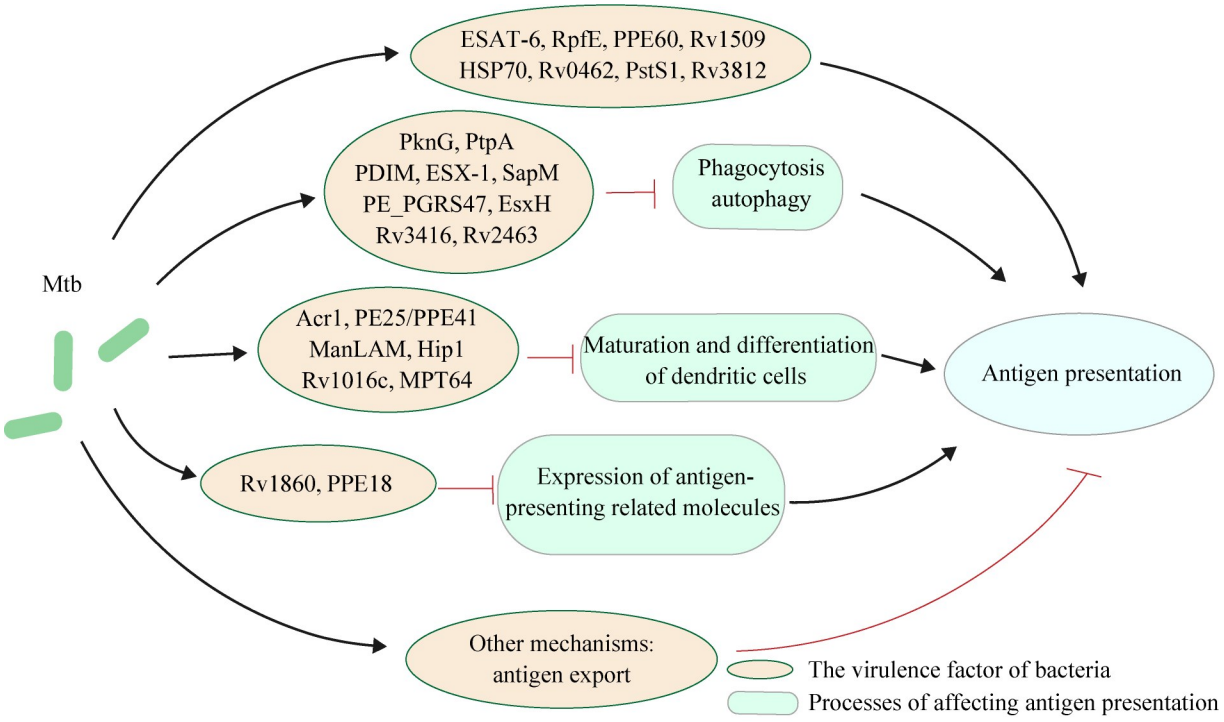

图3 结核分枝杆菌调控树突状细胞抗原提呈的机制

Figure 3 The mechanism by which *Mycobacterium tuberculosis* regulates antigen presentation in dendritic cells.

减毒活疫苗，通过突变毒力基因 *phoP* 和 *fadD26* 抑制了 DIM 和海藻糖衍生脂质的合成[95]。与 BCG 相比，MTBVAC 更能提高 $CD4^+$ T 细胞的 Th1 和 Th17 活性，这可能是由于 DC 抗原提呈水平的提高有助于机体对病原体的清除[96]。

4 总结与展望

尽管在过去几十年中人类对结核病的研究已经取得了巨大进展，但随着抗生素耐药性的增加[97]，要实现世界卫生组织设定的 2035 年终结结核病的目标，只能通过重大防控技术突破来实现，例如新型结核病疫苗的研制成功并得以广泛应用。然而，结核病防控技术的有效突破需要以深入理解 Mtb-DC 互作机制为基础。如前所述，大量研究表明 Mtb 在感染后抑制 DC 的成熟，选择合适的能够提高 DC 抗原提呈水平的抗原或 TLR 激动剂以激发更强的特异性免疫应答可能是有效的策略之一。因此，深入阐明 Mtb 如何调控 DC 的抗原处理与提呈过程是未来一个非常重要的研究方向。阐明 Mtb-DC 的互作机制，不仅可拓展对 Mtb 致病机制的认识，也有助于为新型长效结核病疫苗的研制提供理论基础和科学依据。

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作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

参考文献

[1] World Health Organization. Global tuberculosis report 2024[R]. [2024-10-31]. https://www. who. int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024.

[2] FENG QS, ZHANG GL, CHEN L, WU HZ, YANG YZ, GAO Q, ASAKAWA T, ZHAO YL, LU SH, ZHOU L, LU HZ. Roadmap for ending TB in China by 2035: the challenges and strategies[J]. Bioscience Trends, 2024, 18(1): 11-20.

[3] RAVESLOOT-CHÁVEZ MM, van DIS E, STANLEY SA. The innate immune response to *Mycobacterium tuberculosis* infection[J]. Annual Review of Immunology, 2021, 39: 611-637.

[4] VU A, GLASSMAN I, CAMPBELL G, YEGANYAN S, NGUYEN J, SHIN A, VENKETARAMAN V. Host cell death and modulation of immune response against *Mycobacterium tuberculosis* infection[J]. International Journal of Molecular Sciences, 2024, 25(11): 6255.

[5] STEINMAN RM, COHN ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution[J]. Journal of Experimental Medicine, 1973, 137(5): 1142-1162.

[6] BALAN S, SAXENA M, BHARDWAJ N. Dendritic cell subsets and locations[J]. International Review of Cell and Molecular Biology, 2019, 348: 1-68.

[7] RESCIGNO M. Dendritic cell functions: learning from microbial evasion strategies[J]. Seminars in Immunology, 2015, 27(2): 119-124.

[8] CABEZA-CABRERIZO M, CARDOSO A, MINUTTI CM, PEREIRA Da COSTA M, REIS E SOUSA C. Dendritic cells revisited[J]. Annual Review of Immunology, 2021, 39: 131-166.

[9] TIBERIO L, del PRETE A, SCHIOPPA T, SOZIO F, BOSISIO D, SOZZANI S. Chemokine and chemotactic signals in dendritic cell migration[J]. Cellular & Molecular Immunology, 2018, 15(4): 346-352.

[10] MUSUMECI A, LUTZ K, WINHEIM E, KRUG AB. What makes a pDC: recent advances in understanding plasmacytoid DC development and heterogeneity[J]. Frontiers in Immunology, 2019, 10: 1222.

[11] SICHIEN D, LAMBRECHT BN, GUILLIAMS M, SCOTT CL. Development of conventional dendritic cells: from common bone marrow progenitors to multiple subsets in peripheral tissues[J]. Mucosal Immunology, 2017, 10(4): 831-844.

[12] SEGURA E, AMIGORENA S. Cross-presentation by human dendritic cell subsets[J]. Immunology Letters, 2014, 158(1/2): 73-78.

[13] NIZZOLI G, KRIETSCH J, WEICK A, STEINFELDER S, FACCIOTTI F, GRUARIN P, BIANCO A, STECKEL B, MORO M, CROSTI M, ROMAGNANI C, STÖLZEL K, TORRETTA S, PIGNATARO L, SCHEIBENBOGEN C, NEDDERMANN P, de FRANCESCO R, ABRIGNANI S, GEGINAT J. Human $CD1c^+$ dendritic cells secrete high levels of IL-12 and potently prime cytotoxic T-cell responses[J]. Blood, 2013, 122(6): 932-942.

[14] SHORTMAN K. Dendritic cell development: a personal historical perspective[J]. Molecular Immunology, 2020, 119: 64-68.

[15] MERAD M, SATHE P, HELFT J, MILLER J, MORTHA A. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting[J]. Annual Review of Immunology, 2013, 31: 563-604.

[16] MURPHY TL, GRAJALES-REYES GE, WU XD,

TUSSIWAND R, BRISEÑO CG, IWATA A, KRETZER NM, DURAI V, MURPHY KM. Transcriptional control of dendritic cell development[J]. Annual Review of Immunology, 2016, 34: 93-119.
[17] PATEL VI, LELAND BOOTH J, DUGGAN ES, CATE S, WHITE VL, HUTCHINGS D, KOVATS S, BURIAN DM, DOZMOROV M, METCALF JP. Transcriptional classification and functional characterization of human airway macrophage and dendritic cell subsets[J]. Journal of Immunology, 2017, 198(3): 1183-1201.
[18] DUDZIAK D, KAMPHORST AO, HEIDKAMP GF, BUCHHOLZ VR, TRUMPFHELLER C, YAMAZAKI S, CHEONG C, LIU K, LEE HW, PARK CG, STEINMAN RM, NUSSENZWEIG MC. Differential antigen processing by dendritic cell subsets *in vivo*[J]. Science, 2007, 315(5808): 107-111.
[19] VREMEC D, POOLEY J, HOCHREIN H, WU L, SHORTMAN K. CD4 and CD8 expression by dendritic cell subtypes in mouse thymus and spleen[J]. Journal of Immunology, 2000, 164(6): 2978-2986.
[20] SWIECKI M, GILFILLAN S, VERMI W, WANG YM, COLONNA M. Plasmacytoid dendritic cell ablation impacts early interferon responses and antiviral NK and $CD8^+$ T cell accrual[J]. Immunity, 2010, 33(6): 955-966.
[21] WU J, LI S, LI TT, LV XP, ZHANG MY, ZANG GX, QI C, LIU YJ, XU L, CHEN JT. pDC activation by TLR7/8 ligand CL097 compared to TLR7 ligand IMQ or TLR9 ligand CpG[J]. Journal of Immunology Research, 2019, 2019: 1749803.
[22] GRANOT T, SENDA T, CARPENTER DJ, MATSUOKA N, WEINER J, GORDON CL, MIRON M, KUMAR BV, GRIESEMER A, HO SH, LERNER H, THOME JJC, CONNORS T, REIZIS B, FARBER DL. Dendritic cells display subset and tissue-specific maturation dynamics over human life[J]. Immunity, 2017, 46(3): 504-515.
[23] SEGURA E, VALLADEAU-GUILEMOND J, DONNADIEU MH, SASTRE-GARAU X, SOUMELIS V, AMIGORENA S. Characterization of resident and migratory dendritic cells in human lymph nodes[J]. Journal of Experimental Medicine, 2012, 209(4): 653-660.
[24] SEGURA E, DURAND M, AMIGORENA S. Similar antigen cross-presentation capacity and phagocytic functions in all freshly isolated human lymphoid organ-resident dendritic cells[J]. Journal of Experimental Medicine, 2013, 210(5): 1035-1047.
[25] CHIANG MC, TULLETT KM, LEE YS, IDRIS A, DING YT, McDONALD KJ, KASSIANOS A, LEAL ROJAS IM, JEET V, LAHOUD MH, RADFORD KJ. Differential uptake and cross-presentation of soluble and necrotic cell antigen by human DC subsets[J]. European Journal of Immunology, 2016, 46(2): 329-339.
[26] MITTAG D, PROIETTO AI, LOUDOVARIS T, MANNERING SI, VREMEC D, SHORTMAN K, WU L, HARRISON LC. Human dendritic cell subsets from spleen and blood are similar in phenotype and function but modified by donor health status[J]. Journal of Immunology, 2011, 186(11): 6207-6217.
[27] LENNERT K, REMMELE W. Karyometric research on lymph node cells in man. I. Germinoblasts, lymphoblasts & lymphocytes[J]. Acta Haematologica, 1958, 19(2): 99-113.
[28] CELLA M, JARROSSAY D, FACCHETTI F, ALEBARDI O, NAKAJIMA H, LANZAVECCHIA A, COLONNA M. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon[J]. Nature Medicine, 1999, 5(8): 919-923.
[29] SIEGAL FP, KADOWAKI N, SHODELL M, FITZGERALD-BOCARSLY PA, SHAH K, HO S, ANTONENKO S, LIU YJ. The nature of the principal type 1 interferon-producing cells in human blood[J]. Science, 1999, 284(5421): 1835-1837.
[30] SHORTMAN K, SATHE P, VREMEC D, NAIK S, O'KEEFFE M. Plasmacytoid dendritic cell development[J]. Advances in Immunology, 2013, 120: 105-126.
[31] SWIECKI M, COLONNA M. The multifaceted biology of plasmacytoid dendritic cells[J]. Nature Reviews Immunology, 2015, 15(8): 471-485.
[32] WU LL, YAN ZQ, JIANG YY, CHEN YY, DU J, GUO LJ, XU JJ, LUO ZH, LIU Y. Metabolic regulation of dendritic cell activation and immune function during inflammation[J]. Frontiers in Immunology, 2023, 14: 1140749.
[33] LEBLANC-HOTTE A, AUDIGER C, CHABOT-ROY G, LOMBARD-VADNAIS F, DELISLE JS, PETER YA, LESAGE S. Immature and mature bone marrow-derived dendritic cells exhibit distinct intracellular mechanical properties[J]. Scientific Reports, 2023, 13(1): 1967.
[34] VILLADANGOS JA, SCHNORRER P. Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets *in vivo*[J]. Nature Reviews Immunology, 2007, 7(7): 543-555.
[35] LEE SP, BROOKS JM, AL-JARRAH H, THOMAS WA, HAIGH TA, TAYLOR GS, HUMME S, SCHEPERS A, HAMMERSCHMIDT W, YATES JL, RICKINSON AB, BLAKE NW. CD8 T cell recognition of endogenously expressed Epstein-Barr virus nuclear antigen 1[J]. Journal of Experimental Medicine, 2004, 199(10): 1409-1420.
[36] ITANO AA, JENKINS MK. Antigen presentation to naive CD4 T cells in the lymph node[J]. Nature Immunology, 2003, 4(8): 733-739.
[37] VILLADANGOS JA, SCHNORRER P, WILSON NS. Control of MHC class II antigen presentation in dendritic cells: a balance between creative and destructive forces[J]. Immunological Reviews, 2005, 207: 191-205.
[38] CRUZ FM, COLBERT JD, MERINO E, KRIEGSMAN BA, ROCK KL. The biology and underlying mechanisms of cross-presentation of exogenous antigens on MHC-I molecules[J]. Annual Review of Immunology, 2017, 35: 149-176.
[39] JOFFRE OP, SEGURA E, SAVINA A, AMIGORENA S. Cross-presentation by dendritic cells[J]. Nature Reviews Immunology, 2012, 12(8): 557-569.
[40] LIU CH, LIU HY, GE BX. Innate immunity in tuberculosis: host defense *vs* pathogen evasion[J]. Cellular & Molecular Immunology, 2017, 14(12): 963-975.
[41] RAMON-LUING LA, PALACIOS Y, RUIZ A, TÉLLEZ-NAVARRETE NA, CHAVEZ-GALAN L. Virulence factors of *Mycobacterium tuberculosis* as

modulators of cell death mechanisms[J]. Pathogens, 2023, 12(6): 839.
[42] HOPE JC, THOM ML, McCORMICK PA, HOWARD CJ. Interaction of antigen presenting cells with mycobacteria[J]. Veterinary Immunology and Immunopathology, 2004, 100(3/4): 187-195.
[43] ZHAI WJ, WU FJ, ZHANG YY, FU YR, LIU ZJ. The immune escape mechanisms of *Mycobacterium tuberculosis*[J]. International Journal of Molecular Sciences, 2019, 20(2): 340.
[44] KOUL A, HERGET T, KLEBL B, ULLRICH A. Interplay between mycobacteria and host signalling pathways[J]. Nature Reviews Microbiology, 2004, 2(3): 189-202.
[45] WORBS T, HAMMERSCHMIDT SI, FÖRSTER R. Dendritic cell migration in health and disease[J]. Nature Reviews Immunology, 2017, 17(1): 30-48.
[46] VÁZQUEZ-FLORES L, CASTAÑEDA-CASIMIRO J, VALLEJO-CASTILLO L, ÁLVAREZ-JIMÉNEZ VD, PEREGRINO ES, GARCÍA-MARTÍNEZ M, BARREDA D, ROSALES-GARCÍA VH, SEGOVIA-GARCÍA CD, SANTOS-MENDOZA T, WONG-BAEZA C, SERAFÍN-LÓPEZ J, CHACÓN-SALINAS R, ESTRADA-PARRA S, ESTRADA-GARCÍA I, WONG-BAEZA I. Extracellular vesicles from *Mycobacterium tuberculosis*-infected neutrophils induce maturation of monocyte-derived dendritic cells and activation of antigen-specific Th1 cells[J]. Journal of Leukocyte Biology, 2023, 113(6): 588-603.
[47] CHAI QY, WANG L, LIU CH, GE BX. New insights into the evasion of host innate immunity by *Mycobacterium tuberculosis*[J]. Cellular & Molecular Immunology, 2020, 17(9): 901-913.
[48] Van KOOYK Y, GEIJTENBEEK TBH. DC-SIGN: escape mechanism for pathogens[J]. Nature Reviews Immunology, 2003, 3(9): 697-709.
[49] ADEREM A, ULEVITCH RJ. Toll-like receptors in the induction of the innate immune response[J]. Nature, 2000, 406(6797): 782-787.
[50] UNDERHILL DM, OZINSKY A, SMITH KD, ADEREM A. Toll-like receptor-2 mediates mycobacteria-induced proinflammatory signaling in macrophages[J]. Proceedings of the National Academy of Sciences of the United States of America, 1999, 96(25): 14459-14463.
[51] SU HB, ZHU SL, ZHU L, HUANG W, WANG HH, ZHANG Z, XU Y. Recombinant lipoprotein Rv1016c derived from *Mycobacterium tuberculosis* is a TLR-2 ligand that induces macrophages apoptosis and inhibits MHC II antigen processing[J]. Frontiers in Cellular and Infection Microbiology, 2016, 6: 147.
[52] BALBOA L, ROMERO MM, YOKOBORI N, SCHIERLOH P, GEFFNER L, BASILE JI, MUSELLA RM, ABBATE E, deLa BARRERA S, SASIAIN MC, ALEMÁN M. *Mycobacterium tuberculosis* impairs dendritic cell response by altering CD1b, DC-SIGN and MR profile[J]. Immunology and Cell Biology, 2010, 88(7): 716-726.
[53] REMOLI ME, GIACOMINI E, PETRUCCIOLI E, GAFA V, SEVERA M, GAGLIARDI MC, IONA E, PINE R, NISINI R, COCCIA EM. Bystander inhibition of dendritic cell differentiation by *Mycobacterium tuberculosis*-induced IL-10[J]. Immunology and Cell Biology, 2011, 89(3): 437-446.
[54] FÖRTSCH D, RÖLLINGHOFF M, STENGER S. IL-10 converts human dendritic cells into macrophage-like cells with increased antibacterial activity against virulent *Mycobacterium tuberculosis*[J]. Journal of Immunology, 2000, 165(2): 978-987.
[55] CHOI HG, KIM WS, BACK YW, KIM H, KWON KW, KIM JS, SHIN SJ, KIM HJ. *Mycobacterium tuberculosis* RpfE promotes simultaneous Th1- and Th17-type T-cell immunity *via* TLR4-dependent maturation of dendritic cells[J]. European Journal of Immunology, 2015, 45(7): 1957-1971.
[56] WANG XS, BARNES PF, HUANG FF, ALVAREZ IB, NEUENSCHWANDER PF, SHERMAN DR, SAMTEN B. Early secreted antigenic target of 6-kDa protein of *Mycobacterium tuberculosis* primes dendritic cells to stimulate Th17 and inhibit Th1 immune responses[J]. Journal of Immunology, 2012, 189(6): 3092-3103.
[57] ROMERO MM, BASILE JI, CORRA FEO L, LÓPEZ B, RITACCO V, ALEMÁN M. Reactive oxygen species production by human dendritic cells involves TLR2 and dectin-1 and is essential for efficient immune response against Mycobacteria[J]. Cellular Microbiology, 2016, 18(6): 875-886.
[58] SU HB, ZHANG Z, LIU ZJ, PENG BZ, KONG C, WANG HH, ZHANG Z, XU Y. *Mycobacterium tuberculosis* PPE60 antigen drives Th1/Th17 responses *via* Toll-like receptor 2-dependent maturation of dendritic cells[J]. The Journal of Biological Chemistry, 2018, 293(26): 10287-10302.
[59] P M, AHMAD J, SAMAL J, SHEIKH JA, ARORA SK, KHUBAIB M, AGGARWAL H, KUMARI I, LUTHRA K, RAHMAN SA, HASNAIN SE, EHTESHAM NZ. *Mycobacterium tuberculosis* specific protein Rv1509 evokes efficient innate and adaptive immune response indicative of protective Th1 immune signature[J]. Frontiers in Immunology, 2021, 12: 706081.
[60] LEHNER T, WANG Y, WHITTALL T, McGOWAN E, KELLY CG, SINGH M. Functional domains of HSP70 stimulate generation of cytokines and chemokines, maturation of dendritic cells and adjuvanticity[J]. Biochemical Society Transactions, 2004, 32(Pt 4): 629-632.
[61] HEO DR, SHIN SJ, KIM WS, NOH KT, PARK JW, SON KH, PARK WS, LEE MG, KIM D, SHIN YK, JUNG ID, PARK YM. *Mycobacterium tuberculosis* lpdC, Rv0462, induces dendritic cell maturation and Th1 polarization[J]. Biochemical and Biophysical Research Communications, 2011, 411(3): 642-647.
[62] PALMA C, SCHIAVONI G, ABALSAMO L, MATTEI F, PICCARO G, SANCHEZ M, FERNANDEZ C, SINGH M, GABRIELE L. *Mycobacterium tuberculosis* PstS1 amplifies IFN-γ and induces IL-17/IL-22 responses by unrelated memory $CD4^+$ T cells *via* dendritic cell activation[J]. European Journal of Immunology, 2013, 43(9): 2386-2397.
[63] VANI J, SHAILA MS, TRINATH J, BALAJI KN, KAVERI SV, BAYRY J. *Mycobacterium tuberculosis* cell

wall-associated Rv3812 protein induces strong dendritic cell-mediated interferon γ responses and exhibits vaccine potential[J]. The Journal of Infectious Diseases, 2013, 208(6): 1034-1036.

[64] AMIR M, AQDAS M, NADEEM S, SIDDIQUI KF, KHAN N, SHEIKH JA, AGREWALA JN. Diametric role of the latency-associated protein Acr1 of *Mycobacterium tuberculosis* in modulating the functionality of pre- and post-maturational stages of dendritic cells[J]. Frontiers in Immunology, 2017, 8: 624.

[65] CHEN W, BAO YG, CHEN XR, BURTON J, GONG XL, GU DQ, MI YJ, BAO L. *Mycobacterium tuberculosis* PE25/PPE41 protein complex induces activation and maturation of dendritic cells and drives Th2-biased immune responses[J]. Medical Microbiology and Immunology, 2016, 205(2): 119-131.

[66] GRINGHUIS SI, den DUNNEN J, LITJENS M, van HET HOF B, van KOOYK Y, GEIJTENBEEK TBH. C-type lectin DC-SIGN modulates Toll-like receptor signaling *via* raf-1 kinase-dependent acetylation of transcription factor NF- κB[J]. Immunity, 2007, 26(5): 605-616.

[67] NAFFIN-OLIVOS JL, GEORGIEVA M, GOLDFARB N, MADAN-LALA R, DONG L, BIZZELL E, VALINETZ E, BRANDT GS, YU S, SHABASHVILI DE, RINGE D, DUNN BM, PETSKO GA, RENGARAJAN J. *Mycobacterium tuberculosis* Hip1modulates macrophage responses through proteolysis of GroEL2[J]. PLoS Pathogens, 2014, 10(5): e1004132.

[68] SU HB, PENG BZ, ZHANG Z, LIU ZJ, ZHANG Z. The *Mycobacterium tuberculosis* glycoprotein Rv1016c protein inhibits dendritic cell maturation, and impairs Th1/Th17 responses during mycobacteria infection[J]. Molecular Immunology, 2019, 109: 58-70.

[69] SINGH S, MAURYA SK, AQDAS M, BASHIR H, ARORA A, BHALLA V, AGREWALA JN. *Mycobacterium tuberculosis* exploits MPT64 to generate myeloid-derived suppressor cells to evade the immune system[J]. Cellular and Molecular Life Sciences, 2022, 79(11): 567.

[70] LEE HJ, WOO Y, HAHN TW, JUNG YM, JUNG YJ. Formation and maturation of the phagosome: a key mechanism in innate immunity against intracellular bacterial infection[J]. Microorganisms, 2020, 8(9): 1298.

[71] van der WEL N, HAVA D, HOUBEN DE, FLUITSMA D, van ZON M, PIERSON J, BRENNER M, PETERS PJ. *M. tuberculosis* and *M. leprae* translocate from the phagolysosome to the cytosol in myeloid cells[J]. Cell, 2007, 129(7): 1287-1298.

[72] SAJID A, ARORA G, SINGHAL A, KALIA VC, SINGH Y. Protein phosphatases of pathogenic bacteria: role in physiology and virulence[J]. Annual Review of Microbiology, 2015, 69: 527-547.

[73] WONG D, BACH H, SUN J, HMAMA Z, AV-GAY Y. *Mycobacterium tuberculosis* protein tyrosine phosphatase (PtpA) excludes host vacuolar-H^+-ATPase to inhibit phagosome acidification[J]. Proceedings of the National Academy of Sciences of the United States of America, 2011, 108(48): 19371-19376.

[74] PORTAL-CELHAY C, TUFARIELLO JM, SRIVASTAVA S, ZAHRA A, KLEVORN T, GRACE PS, MEHRA A, PARK HS, ERNST JD, JACOBS WR Jr, PHILIPS JA. *Mycobacterium tuberculosis* Es_xH inhibits ESCRT-dependent $CD4^+$ T-cell activation[J]. Nature Microbiology, 2016, 2: 16232.

[75] AUGENSTREICH J, ARBUES A, SIMEONE R, HAANAPPEL E, WEGENER A, SAYES F, le CHEVALIER F, CHALUT C, MALAGA W, GUILHOT C, BROSCH R, ASTARIE-DEQUEKER C. ESX-1 and phthiocerol dimycocerosates of *Mycobacterium tuberculosis* act in concert to cause phagosomal rupture and host cell apoptosis[J]. Cellular Microbiology, 2017, 19(7): e12726.

[76] LERNER TR, QUEVAL CJ, FEARNS A, REPNIK U, GRIFFITHS G, GUTIERREZ MG. Phthiocerol dimycocerosates promote access to the cytosol and intracellular burden of *Mycobacterium tuberculosis* in lymphatic endothelial cells[J]. BMC Biology, 2018, 16(1): 1.

[77] FENG SW, McNEHLAN ME, KINSELLA RL, SUR CHOWDHURY C, CHAVEZ SM, NAIK SK, McKEE SR, van WINKLE JA, DUBEY N, SAMUELS A, SWAIN A, CUI XY, HENDRIX SV, WOODSON R, KREAMALMEYER D, SMIRNOV A, ARTYOMOV MN, VIRGIN HW, WANG YT, STALLINGS CL. Autophagy promotes efficient T cell responses to restrict high-dose *Mycobacterium tuberculosis* infection in mice[J]. Nature Microbiology, 2024, 9(3): 684-697.

[78] MITTAL E, KRISHNA PRASAD GR, UPADHYAY S, SADADIWALA J, OLIVE AJ, YANG GZ, SASSETTI CM, PHILIPS JA. *Mycobacterium tuberculosis* virulence lipid PDIM inhibits autophagy in mice[J]. Nature Microbiology, 2024, 9(11): 2970-2984.

[79] HU D, WU J, WANG W, MU M, ZHAO RP, XU XW, CHEN ZQ, XIAO J, HU FY, YANG YB, ZHANG RB. Autophagy regulation revealed by SapM-induced block of autophagosome-lysosome fusion *via* binding RAB7[J]. Biochemical and Biophysical Research Communications, 2015, 461(2): 401-407.

[80] SAINI NK, BAENA A, NG TW, VENKATASWAMY MM, KENNEDY SC, KUNNATH-VELAYUDHAN S, CARREÑO LJ, XU JY, CHAN J, LARSEN MH, JACOBS WR Jr, PORCELLI SA. Suppression of autophagy and antigen presentation by *Mycobacterium tuberculosis* PE_PGRS47[J]. Nature Microbiology, 2016, 1(9): 16133.

[81] ETNA MP, SINIGAGLIA A, GRASSI A, GIACOMINI E, ROMAGNOLI A, PARDINI M, SEVERA M, CRUCIANI M, RIZZO F, ANASTASIADOU E, Di CAMILLO B, BARZON L, FIMIA GM, MANGANELLI R, COCCIA EM. *Mycobacterium tuberculosis*-induced miR-155 subverts autophagy by targeting ATG3 in human dendritic cells[J]. PLoS Pathogens, 2018, 14(1): e1006790.

[82] SINGHAL J, AGRAWAL N, VASHISHTA M, GAYATRI PRIYA N, TIWARI BK, SINGH Y, RAMAN R, NATARAJAN K. Suppression of dendritic cell-mediated responses by genes in calcium and cysteine protease pathways during *Mycobacterium tuberculosis* infection[J]. The Journal of Biological Chemistry, 2012, 287(14):

11108-11121.
[83] ANANG V, SINGH A, KUMAR RANA A, SARASWATI SSK, BANDYOPADHYAY U, VERMA C, CHADHA A, NATARAJAN K. Mycobacteria modulate SUMOylation to suppresses protective responses in dendritic cells[J]. PLoS One, 2023, 18(9): e0283448.
[84] SONG YJ, GE X, CHEN YL, HUSSAIN T, LIANG ZM, DONG YH, WANG YZ, TANG CY, ZHOU XM. *Mycobacterium bovis* induces mitophagy to suppress host xenophagy for its intracellular survival[J]. Autophagy, 2022, 18(6): 1401-1415.
[85] SATCHIDANANDAM V, KUMAR N, JUMANI RS, CHALLU V, ELANGOVAN S, KHAN NA. The glycosylated Rv1860 protein of *Mycobacterium tuberculosis* inhibits dendritic cell mediated TH1 and TH17 polarization of T cells and abrogates protective immunity conferred by BCG[J]. PLoS Pathogens, 2014, 10(6): e1004176.
[86] DOLASIA K, NAZAR F, MUKHOPADHYAY S. *Mycobacterium tuberculosis* PPE18 protein inhibits MHC class II antigen presentation and B cell response in mice[J]. European Journal of Immunology, 2021, 51(3): 603-619.
[87] SRIVASTAVA S, GRACE PS, ERNST JD. Antigen export reduces antigen presentation and limits T cell control of *M. tuberculosis*[J]. Cell Host & Microbe, 2016, 19(1): 44-54.
[88] MANCUSO JD, MODY RM, OLSEN CH, HARRISON LH, SANTOSHAM M, ARONSON NE. The long-term effect of bacille calmette-guérin vaccination on tuberculin skin testing A 55-year follow-up study[J]. Chest, 2017, 152(2): 282-294.
[89] DIELI F, IVANYI J. Role of antibodies in vaccine-mediated protection against tuberculosis[J]. Cellular & Molecular Immunology, 2022, 19(7): 758-760.
[90] AN Y, NI R, ZHUANG L, YANG L, YE Z, LI L, PARKKILA S, ASPATWAR A, GONG W. Tuberculosis vaccines and therapeutic drug: challenges and future directions[J]. Molecular Biomedicine, 2025, 6(1): 4.
[91] PASSOS BBS, ARAÚJO-PEREIRA M, VINHAES CL, AMARAL EP, ANDRADE BB. The role of ESAT-6 in tuberculosis immunopathology[J]. Frontiers in Immunology, 2024, 15: 1383098.
[92] NETEA MG, DOMÍNGUEZ-ANDRÉS J, BARREIRO LB, CHAVAKIS T, DIVANGAHI M, FUCHS E, JOOSTEN LAB, van der MEER JWM, MHLANGA MM, MULDER WJM, RIKSEN NP, SCHLITZER A, SCHULTZE JL, STABELL BENN C, SUN JC, XAVIER RJ, LATZ E. Defining trained immunity and its role in health and disease[J]. Nature Reviews Immunology, 2020, 20(6): 375-388.
[93] KIRK NM, HUANG QF, VRBA S, RAHMAN M, BLOCK AM, MURPHY H, WHITE DW, NAMUGENYI SB, LY H, TISCHLER AD, LIANG YY. Recombinant Pichinde viral vector expressing tuberculosis antigens elicits strong T cell responses and protection in mice[J]. Frontiers in Immunology, 2023, 14: 1127515.
[94] GRODE L, GANOZA CA, BROHM C, WEINER J, EISELE B, KAUFMANN SHE. Safety and immunogenicity of the recombinant BCG vaccine $VPM_{10}02$ in a phase 1 open-label randomized clinical trial[J]. Vaccine, 2013, 31(9): 1340-1348.
[95] FRIGUI W, BOTTAI D, MAJLESSI L, MONOT M, JOSSELIN E, BRODIN P, GARNIER T, GICQUEL B, MARTIN C, LECLERC C, COLE ST, BROSCH R. Control of *M. tuberculosis* ESAT-6 secretion and specific T cell recognition by PhoP[J]. PLoS Pathogens, 2008, 4(2): e33.
[96] DIJKMAN K, AGUILO N, BOOT C, HOFMAN SO, SOMBROEK CC, VERVENNE RAW, KOCKEN CHM, MARINOVA D, THOLE J, RODRÍGUEZ E, VIERBOOM MPM, HAANSTRA KG, PUENTES E, MARTIN C, VERRECK FAW. Pulmonary MTBVAC vaccination induces immune signatures previously correlated with prevention of tuberculosis infection[J]. Cell Reports Medicine, 2021, 2(1): 100187.
[97] RAHMAN F. Characterizing the immune response to *Mycobacterium tuberculosis*: a comprehensive narrative review and implications in disease relapse[J]. Frontiers in Immunology, 2024, 15: 1437901.