ApoA-I在结核病形成中的潜在作用及机制研究

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摘要 结核病(tuberculosis, TB)主要是由结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)引起的免疫病理损伤并以干酪样肉芽肿为特征性病变的传染性疾病, 其病理发生机制较为复杂。载脂蛋白A1(Apolipoprotein A1, ApoA-I)是血浆中运载脂质的非糖基化蛋白质, 具有抗炎、抗氧化、调节胆固醇运输和调节细胞自噬等功能, 参与多种疾病形成。近年来, ApoA-I与结核病的关联受到广泛关注, 该文将对ApoA-I在结核病形成中的作用及其生物学机制加以综述, 为完善结核病的发病机理以及探索治疗结核病的新方向提供科学依据。

关键词 载脂蛋白 A1; 结核病; 分子机制

The Potential Role and Mechanism of ApoA-I in the Formation of Tuberculosis

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Abstract Tuberculosis, induced by Mtb (*Mycobacterium tuberculosis*), is characterized by caseating granuloma formation in response of immunopathological damages. The molecular mechanism underlying the tuberculosis is complex. ApoA-I (Apolipoprotein A1), as a non-glycosylated plasma protein, is anti-inflammatory and antioxidant, able to regulate cholesterol transport, and autophagy, to be involved in various other diseases. The association between ApoA-I and pathogenesis of tuberculosis has attracted extensive attention lately. This article will review the role of ApoA-1 in the tuberculosis development and related biological signaling pathway, which will complete the pathogenesis of tuberculosis and provide a clue for possible strategy of treatment for tuberculosis.

Keywords Apolipoprotein A1; tuberculosis; molecular mechanism

结核病是由结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)感染引起的严重威胁人类健康的传染性疾病之一。 2023年全球结核病报告显示2022年共有750万人确诊患有结核病, 这是世界卫生组织自1995年开始监测全球结核病以来的最高记录[1]。作为结核病的高发国家之一, 我国2022年的结核病新发病例为74.8万, 死亡人数约为3万[1]。随着人口流动增强、结核分枝杆菌耐药株变异及耐多药和广泛耐药结核病的出现, 结核病发病率近年来呈明显上升趋势[2], 全球结核病防控形势十分严峻。

载脂蛋白A1(Apolipoprotein A1, ApoA-I)是血浆中载送脂类的蛋白质, 主要功能是与胆固醇结合形成高密度脂蛋白(high density lipoprotein, HDL)以调控胆固醇代谢[3]。ApoA-I还可以发挥抗炎、抗氧化和调节细胞自噬等作用[4]。近年来ApoA-I抑制病原体感染的作用受到广泛关注。血浆中ApoA-I/HDL参与的体液免疫具有抗病毒活性, 可防止病毒渗透, 促进补体介导的细菌杀伤[5]。例如ApoA-I的两亲性

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螺旋可与人类免疫缺陷病毒的N-端肽结合, 防止病毒融合结构域插入细胞膜, 进而抑制其进入宿主细胞, 防止体内细菌感染和对人体免疫系统的破坏[6-7]; ApoA-I可中和登革热病毒非结构蛋白1诱导的细胞活化作用, 防止登革热病毒感染能力增强, 并介导细胞膜中脂筏耗竭以控制病毒感染, 减弱其对人体的危害[8]。

机体感染Mtb后胆固醇代谢和免疫功能均发生异常变化[9], ApoA-I作为脂质代谢的重要组分可参与机体抗感染过程。本文将论述ApoA-I与结核病发生发展、诊断和治疗方面关联的研究进展及可能的机制, 并总结其应用前景, 以期为揭示ApoA-I在结核病形成中的作用及探索治疗结核病的新方向提供参考。

1 ApoA-I的分子结构及功能

1.1 ApoA-I的分子结构

ApoA-I是由243个氨基酸残基组成的非糖基化蛋白质[3], 其基因位于第11号染色体长臂末端ql1→q13ter区域内, 长约1 863 bp, 包含4个外显子和3个内含子。成熟的ApoA-I是由267个氨基酸残基组成的前蛋白原(preproapo A-I)在分泌过程中被水解去除18个氨基酸残基的信号肽后, 在血浆中再由蛋白酶水解6个氨基酸残基后形成的。ApoA-I的二级结构包含6~8个由22个氨基酸重复序列和2个由11个氨基酸重复序列构成的两性α螺旋; 此种两性α螺旋的疏水部分与脂质分子相互作用, 其亲水部分则与水相作用, 有助于HDL的合成和稳定[10-11]。在新生盘状HDL分子中, ApoA-I的三级结构主要包括“双带”模型, 即α螺旋对在脂质盘周围形成光滑且基本平面的双环结构, 和“太阳耀斑”、“环带”等结构模型, 四级结构尚不清楚[12]。

1.2 ApoA-I的功能

*ApoA-I*基因在不同组织中均有表达, 其中在肝脏组织中的表达量最高[13]。ApoA-I的主要功能是调控胆固醇代谢, 包括介导胆固醇外流和胆固醇向肝脏的逆转运(reverse cholesterol transport, RCT)[14]。这些功能需要ApoA-I/HDL受体ATP结合盒转运蛋白A1(ATP-binding cassette transporter A1, ABCA1)和B类I型清道夫受体(scavenger receptor class B type I, SR-BI)的帮助。

细胞膜上ABCA1捕获胞内游离胆固醇(free cholesterol, FC)并传递给ApoA-I, ApoA-I结合FC形成盘状的初生HDL(nascent HDL, nHDL)。nHDL在卵磷脂–胆固醇酰基转移酶(lecithin-cholesterol acyl transferase, LCAT)的促进作用下形成球形的成熟HDL(mature HDL, mHDL)。血浆中的mHDL与肝细胞膜上SR-B1结合, 进入肝脏, 代谢为胆汁酸排出体外, 即为RCT[14](图1)。

ApoA-I/HDL除介导胆固醇外流、调节胆固醇代谢外, 还具有抗炎、抗氧化、促进细胞自噬和凋亡等作用[15]。这些作用在某种程度上与其介导胆固醇外流密不可分。

2 ApoA-I在结核病感染中的作用

2.1 ApoA-I与结核病的发生发展

Mtb可侵犯全身器官, 但常见于肺部[17]。Mtb感染机体后, 其表面病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)与免疫细胞膜上的模式识别受体(pattern recognition receptors, PRRs)结合而被识别。固有免疫系统是防御Mtb等病原体的第一道防线, 相继通过分泌炎症因子、招募新的固有免疫细胞、激活适应性免疫细胞以及启动自噬等过程清除病原体[18]。根据机体的免疫应答状态, 病原体可能被完全清除, 以及形成潜伏感染或活动性结核。Mtb感染组织后形成由大量巨噬细胞、泡沫细胞、T细胞、B细胞以及细胞外基质所组成的典型病理组织学特征结构——肉芽肿[19]。肉芽肿的形成使Mtb复制被暂时控制, 炎症反应消退, 结核转为潜伏状态。当遇到免疫应答降低或出现其他病毒等诱因时, 肉芽肿内的Mtb重新被激活并开始增殖, 病变进程由潜伏期转变为活动期。当细菌载量达到最大值时, 肉芽肿破裂, 内含的Mtb通过血液和淋巴系统扩散到其他器官[20]。

近年来研究发现ApoA-I蛋白水平下降时机体抗结核的免疫应答能力更容易受损[21]。ApoA-I调控的胆固醇是Mtb在细胞内增殖的主要营养来源。Mtb感染巨噬细胞后, 细胞内正常脂代谢平衡出现异常, 如脂质摄入增加、胞内脂质外排受阻。脂质的大量累积, 诱导巨噬细胞向泡沫细胞转化。大量研究证实富含胆固醇的泡沫细胞为Mtb逃逸机体的免疫监视和清除提供了“保护伞”, 并为其生长和繁殖提供了营养成分, 保障了Mtb在肉芽肿内的稳定生长[22-23]。这都提示了ApoA-I通过促进胆固醇外排

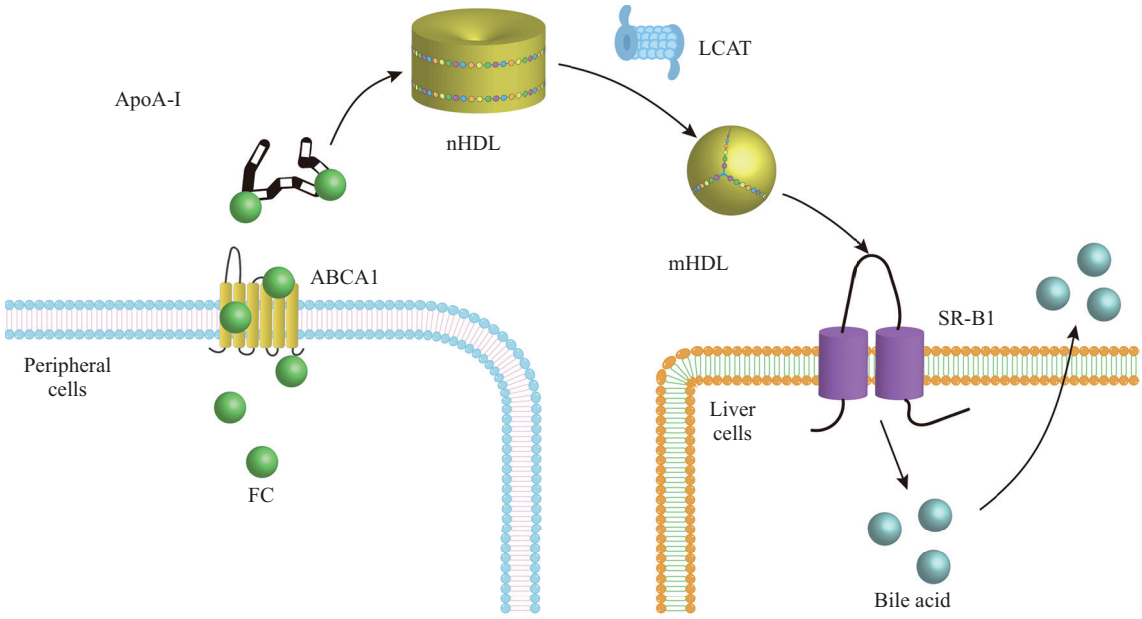


图1 ApoA-I在ABCA1和SR-BI的帮助下介导胆固醇外流, HDL和RCT的形成(根据参考文献[16]修改)

Fig.1 ApoA-I mediates cholesterol efflux, HDL formation, and RCT formation with the help of ABCA1 and SR-BI (modified from the reference [16])

而在结核病的形成中发挥重要作用。

此外, 结核病患者病灶局部及循环系统均存在氧化微环境, 机体中Mtb持续感染引起组织中蛋白质及脂质的氧化损伤[24]。WIID等[25]对结核感染患者和抗结核药物治疗后的血浆样本进行检测, 发现活动性肺结核患者血浆水平总氧化能力显著高于健康对照组及潜伏感染组, 而抗氧化能力则显著降低, 但经过抗结核药物治疗之后, 各氧化指标趋于正常。因此, 氧化应激水平与结核病的严重程度相关, 而ApoA-I可以通过降低整合素表达水平来降低免疫细胞的跨内皮迁移能力, 进而抑制T细胞接触诱导的单核细胞活化和促炎因子的产生, 抑制脂质过氧化[26], 提示ApoA-I具有降低细胞内活性氧水平和氧化应激水平进而抑制结核病的发生发展的功能[27]。此外, 有研究显示ApoA-I的过表达可以增加细胞自噬水平[28], 可能促进病原菌Mtb的降解和清除, 有助于机体抵抗结核病的发生发展的作用。因此, ApoA-I也可发挥抗炎抗氧化作用和促进细胞自噬来抑制结核病的发生发展。

2.2 ApoA-I与结核病的诊断

现有对结核病的诊断主要依据临床表现结合肺部影像(X-射线胸透和CT扫描)、病原学观察(痰涂片和痰培养物观察)。这些辅助手段有不同程度的局限性, 如胸透和CT扫描依赖于图像的清晰度和病灶的位置和大小, 痰涂片不能区分Mtb的死活、培养物需要较长的培养时间(4~8周)[29]。找寻有效的结核病标志物以便于快速诊断和评价结核病的预后仍然是结核病诊断领域的瓶颈问题。

脂质组学和蛋白质组学有助于分析结核病患者血清中差异脂质和蛋白标志物[21,30-31]。有研究发现, 与密切接触且未感染者相比, 活动性肺结核患者血浆中ApoA-I水平下降, 尽管潜伏感染者和密切接触且未感染者之间ApoA-I含量未见区别[21]。孟祥红课题组[30]比较了82例中青年结核病患者和85例体检健康者ApoA-I的表达水平, 评价其联合检测对中青年肺结核的临床应用价值。结果显示, 结核病患者血清总胆固醇、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)和ApoA-I的水平均低于对照组。FRANCO等[31]比较了97例典型肺结核患者和32例对照组(非结核病但芽孢杆菌感染)的血清总胆固醇、HDC-C和ApoA-I的表达情况, 与对照组相比, 结核病患者血清中总胆固醇、HDC-C和ApoA-I的含量明显降低。这些研究提示, 血清中ApoA-I的水平与结核病感染严重程度呈负相关, ApoA-I水平是Mtb感染状态的潜在标志物。

2.3 ApoA-I与结核病的治疗

ApoA-I蛋白通常以游离形式存在于血浆中, 也

可以以外泌体包裹形式存在于体液中。有研究发现其含量可指示结核病药物敏感性以及病程康复的状态，而且ApoA-I模拟肽或全长ApoA-I形式可用于结核病等肺部疾病的治疗。治疗2个月的结核病患者和治愈的结核病患者ApoA-I水平明显高于未治疗的结核病患者[32]。WANG等[33]以潜伏感染患者为研究对象，开展了多中心随机利福平治疗试验。结果显示，患者治疗1个月后其ApoA-I水平也显著增加。CHONG团队[32]基于相对和绝对定量iTRAQ标记结合2D-LC-MS/MS技术分析了结核病未治疗组、治疗2个月组和治疗6个月组患者血清中85种差异蛋白的表达水平变化，结果显示，治疗2个月组和6个月组血清中ApoA-I水平明显升高。最近有研究者利用Label-free蛋白质组学的定量分析发现，耐药性结核患者血浆外泌体中ApoA-I蛋白水平低于药性敏感型结核病患者[34]。结核病治疗好转中ApoA-I蛋白的伴随变化进一步证实ApoA-I参与结核病的形成，该指标可用于结核病疗效的动态监测。

ApoA-I蛋白治疗结核病等肺部疾病的形式包括模拟肽和全长蛋白。有研究发现ApoA-I模拟肽4F可通过减少促炎细胞因子如白细胞介素6(interleukin-6, IL-6)、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)和肿瘤坏死因子α(tumor necrosis factor α, TNF-α)的分泌水平来减缓结核病的进展[35]。ApoA-I模拟肽ELK-2A2K2E也可促进胆固醇外排、减少泡沫细胞的产生，从而抑制结核病的发生[36]。此外，ApoA-I模拟肽被尝试用于治疗嗜中性细胞性气管炎、肺气肿以及肺癌等其他肺部疾病(表1)。

3 ApoA-I调控结核病发生发展的潜在分子机制

ApoA-I能够调控脂质代谢且与结核病的发生发展和治疗进程密切相关(图2)。一方面，ApoA-I通过与细胞表面或胞内受体结合作用于下游信号通路，减少炎症因子生成和促进细胞自噬，在结核病形成中发挥重要抗炎和促自噬作用。另一方面，ApoA-I促进胆固醇外流，而胆固醇外流异常和胞内累积会诱导巨噬细胞变成泡沫细胞，后者为结核分枝杆菌的生长提供了碳源[10,23]。

3.1 ApoA-I调控cAMP-PKA通路抑制泡沫细胞的生成

环磷酸腺苷(cyclic adenosine monophosphate, cAMP)作为机体信号转导的第二信使，在响应外界刺激中起关键作用。当信号分子与受体结合后，三聚体G蛋白α亚基的释放，进而激活腺苷酸环化酶(adenylyl cyclase, AC)，AC水解腺苷三磷酸(adenosine triphosphate, ATP)产生cAMP。胞内cAMP水平增加会激活蛋白激酶A(protein kinase A, PKA)。PKA是一种多蛋白复合物，具有I型PKA(PKA RI)和II型PKA(PKA RII) 2种主要亚型。PKA RI可结合过度激活的cAMP，导致PKA RI构象变化，促使催化G蛋白α亚基释放并转移进入细胞核，与基因调控蛋白相互作用，阻止转录因子与IFN-γ近端启动子结合，从而抑制促炎因子基因*IFN-γ*的转录[56]。IFN-γ在Mtb感染时可促进机体引发T细胞免疫反应，故促炎因子基因*IFN-γ*的转录受到抑制时，结核病的发生会加重。

Mtb细胞壁中的脂阿拉伯甘露聚糖(lipoarabinomanan, LAM)[57]可与所处微环境中的ApoA-I结合，使游离环境中ApoA-I浓度降低，进而降低ApoA-I与下游G蛋白偶联受体ABCA1结合的机会，使得Gα激活AC的过程受阻，从而降低cAMP的浓度。WILBURN等[58]研究发现，体内低浓度cAMP水平无法有效抑制Mtb对胆固醇的吸收和利用，会加剧泡沫细胞的形成，进一步加重结核病的严重程度。因此，适当刺激ApoA-I和cAMP的产生有助于抑制Mtb吸收利用胆固醇的进程和促进免疫炎性因子的转录，进而抑制结核病的发展。

3.2 ApoA-I抑制TLRs/NF-κB通路防止过度炎性损伤

TLRs/NF-κB信号通路是抵御病原菌、诱发炎症反应的主要途径。Toll样受体(Toll-like receptors, TLRs)是一类PRRs，聚集于细胞膜上富含胆固醇和鞘脂的微区脂筏(lipid raft)内[59-61]，可识别Mtb等PAMPs[62-63]。TLRs识别Mtb并使TLRs胞内结构域募集接头蛋白MyD88[61]，进而激活下游的κB抑制因子激酶(inhibitor of kappa B kinase, IKK)，致使IKK催化核因子κB(nuclear factor kappa-B, NF-κB)与其结合的抑制蛋白解离[64-66]。活化的NF-κB进入细胞核内，与下游靶基因结合，启动炎症因子基因如*IL-1β*、*IL-6*和*TNF-a*的转录，促进其分泌[67-68]。

白细胞介素-1(分为IL-1α和IL-1β两种蛋白)在机体感染Mtb后通过刺激各种免疫和炎症细胞合成TNF-α和IL-6等促炎因子，或将中性粒细胞等免疫细

表1 ApoA-I模拟肽或ApoA-I蛋白治疗小鼠肺部疾病的效果(根据参考文献[37]修改)

Table 1 The effect of ApoA-I mimetic peptide or ApoA-I protein in the treatment of lung disease in mice (modified from reference [37])

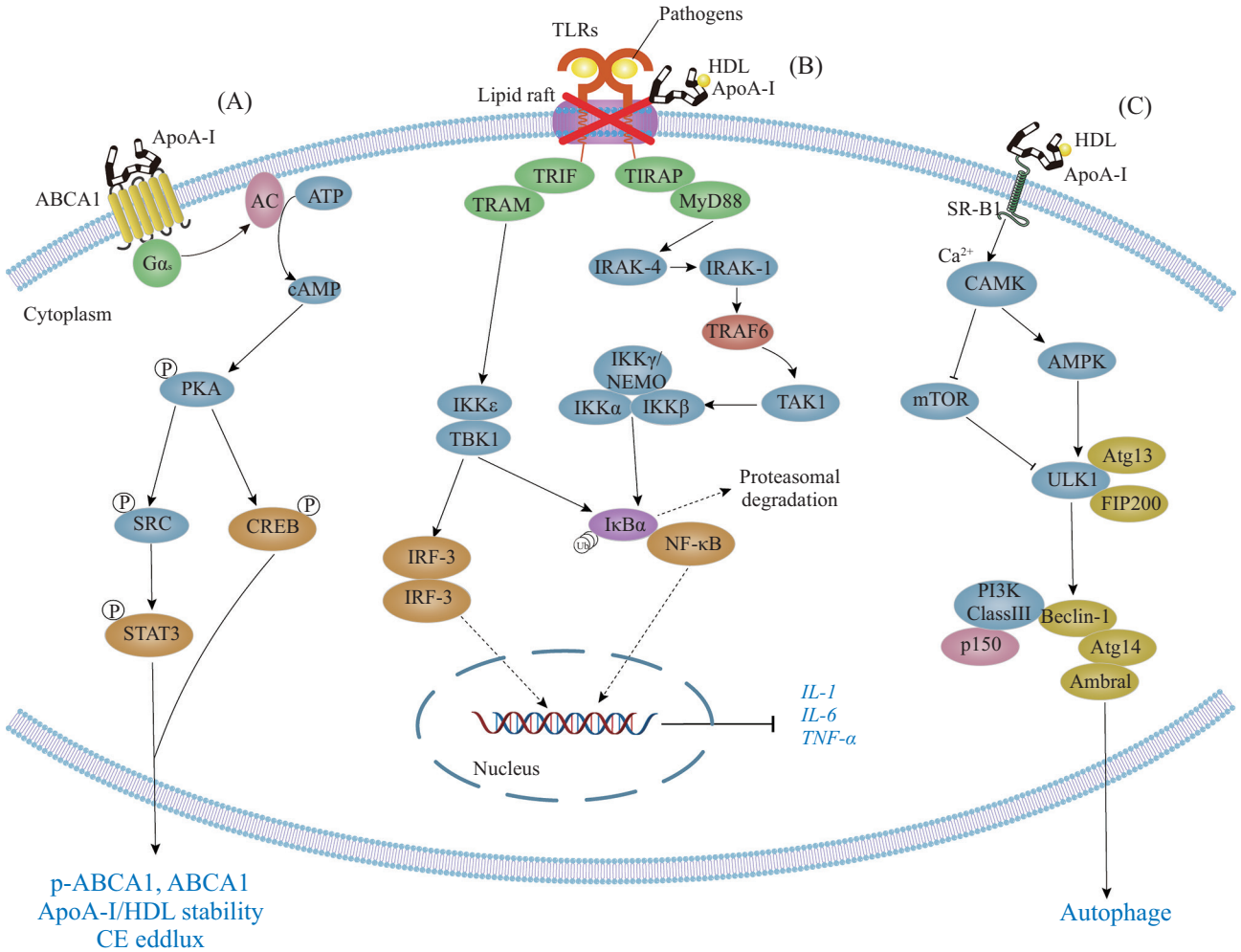
疾病模型 Disease model	多肽/蛋白 Peptides/proteins	来源或组成 Source or composition	治疗效果 Therapeutic effects
Asthma induced by ovalbumin	5A	Double helix amphiphilic peptide (replacing one helix with five alanines to reduce its hydrophobicity)	Reduce G-CSF expression and inhibit neutrophilic tracheitis in ApoA-I knockout mice [38]
	D-4F	ApoA-I modified 18 amino acid peptides (hydrophobic composed of D-type amino acids) α spiral	Reduce AHR, BALF eosinophils, and TGF in wild-type mice- β1. Secretion, collagen deposition, and oxidative stress [39]
Asthma induced by mite dust	5A	Double helix amphiphilic peptide (replacing one helix with five alanines to reduce its hydrophobicity)	Reduce AHR inflammatory cells, mucus cell metaplasia, collagen expression, and AHR in wild-type mice [40]
	Human ApoA-I protein	Serum purification	Inhibit the existing respiratory inflammation, AHR, and allergen inhalation caused by lung dendritic cells in wild-type mice; promote the production of lipoxygen-A and repair of epithelial tight junction protein (Zo-1, closure protein) in wild-type mice [41]
Smoking induced emphysema	Human ApoA-I protein	Transgenic mice (expressing human ApoA-I in alveolar epithelial cells)	Alleviate emphysema, pulmonary inflammation, oxidative stress, and activation of matrix metalloproteinases [42]
Neutrophilic pneumonia induced by LPS, CXCL1, or CXCL2	L-4F	ApoA-I modified 18 amino acid peptides (hydrophobic composed of L-type amino acids) α spiral	Inhibition of neutrophil invasion in wild-type mouse BALF [43]
Lung injury and sepsis induced by LPS and LTA	ApoA-I protein expressed by human ApoA-I or adenovirus	Purification of serum or supernatant	Reduce acute lung, kidney, and liver injury and mortality in wild-type mice [44-50]
Influenza pneumonia	D-4F	ApoA-I modified 18 amino acid peptides (hydrophobic composed of D-type amino acids) α spiral	Reduce inflammatory response, IL-6 levels, and pulmonary viral titer; maintain body temperature [51]
Lung cancer	Human ApoA-I protein	Transgenic mice expressing human ApoA-I (regulated by the human ApoA-I promoter)	Tumor volume reduction [52]
Pulmonary arterial hypertension	L-4F	ApoA-I modified 18 amino acid peptides (hydrophobic composed of L-type amino acids) α spiral	Reduce pulmonary hypertension and serum oxidized lipoprotein levels [53]
Bleomycin induced pulmonary fibrosis	Human ApoA-I protein	Serum purification	Inhibition of wild-type mouse BALF inflammatory cells and pulmonary fibrosis [54]
Silicosis	Human ApoA-I protein	Transgenic mice expressing human ApoA-I (regulated by surfactant protein C promoter)	Reduce pulmonary fibrosis, silicon nodules, BALF inflammatory cells, and TGF- β1. Secretion [55]

G-CSF: 粒细胞集落刺激因子; AHR: 气道高反应; LTA: 脂磷壁酸; BALF: 支气管肺泡灌洗液; TGF-β1: 转化生长因子-β1; IL-6: 白细胞介素-6。
G-CSF: granulocyte colony stimulating factor; AHR: airway hyperresponsiveness; LTA: lipoteichioic acid; BALF: bronchoalveolar lavage fluid; TGF-β1: transforming growth factor-β1; IL-6: interleukin-6.

胞吸引到感染部位, 启动炎症级联反应, 导致宿主组织炎性病理学损伤[69]。因此, 严格控制结核病期间过度或不受控制的炎性免疫应答, 可以最大限度地减少对机体造成的损伤。而ApoA-I/HDL能降低细胞膜上胆固醇含量、干扰脂筏结构和TLRs在脂筏内的聚集, 进而抑制TLRs/NF-κB通路和炎症因子分泌[70], 降低炎症反应的强度, 防止机体自身防御反应在抗Mtb过程中对宿主组织造成的损害[69]。因此, 适当增加ApoA-I含量有助于机体抑制TLRs/NF-κB信号通路进而防止过度炎性损伤。

3.3 ApoA-I结合SR-BI触发AMPK-mTOR-ULK1通路促进细胞自噬

结核病期间的免疫反应可能会导致器官损伤，SR-BI触发的细胞自噬被认为在这一过程中发挥主要保护作用。SR-BI是一类独特的脂质内吞受体，可结合Mtb表面的脂质和糖蛋白。病原菌Mtb当进入机体后，可被肉芽肿周边的间充质干细胞表达的SR-B1捕获，细胞将其吞噬，Mtb繁殖被抑制[71]。同时，体内的ApoA-I与SR-BI相互作用使SR-BI二聚化，进而诱导钙调蛋白依赖性蛋白激酶(calmodulin kinase, CAMK)的激活，CAMK可激活AMP依赖的蛋白激酶[adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK]来调节自噬[72]。AMPK是一种关键的能量传感器，调节细胞代谢以维持能量稳态。当AMPK被激活时，mTOR复合体1(mechanistic target of rapamycin complex 1, mTORC1)的磷酸化被抑制，随后UNC-51样激酶1(threonine-protein kinase, ULK1)可以与AMPK相互作用而磷酸化，活化的ULK1启动自噬。mTOR激酶则是ULK1的负调节因子，mTORC1磷酸化使形成的自噬调节复合物(由ULK1和其互作蛋白Atg13、FIP200、Atg101等形成)失活，从而影响自噬小体的生物发生，抑制细胞自噬[28,73]。而AMPK和mTOR激酶共同协调的细胞自噬是抗Mtb的免疫防御基础。AMPK调节的信号转导可增强细胞自噬和抗Mtb感染的活性，mTOR激活促进炎症，并在感染早期诱导肉芽肿形成和



A: ApoA-I结合ABCA1活化Gα，从而使cAMP激活，调控PKA作用于靶基因；B: ApoA-I/HDL干扰了TLRs在脂筏内的聚集，抑制了TLRs/NF-κB通路，进而抑制了炎症因子分泌；C: ApoA-I结合ABCA1使Ca^{2+}内流，活化AMPK并抑制mTOR，进而作用于ULK1促进细胞自噬。

A: ApoA-I binds to ABCA1 to activate Gα, thereby activating PKA, resulting in ABCA1 phosphorylation and increased esterification of ApoA-I; B: ApoA-I/HDL interfers with the aggregation of TLRs in lipid rafts, inhibits the TLRs/NF-κB pathway, and then inhibits the secretion of inflammatory factors; C: ApoA-I binds to ABCA1 to influx Ca^{2+}, activates AMPK and inhibits mTOR, which in turn acts on ULK1 to promote autophagy.

图2 ApoA-I参与调控炎症的分子机制示意图

Fig.2 Schematic diagram of the molecular mechanism of ApoA-I regulating the inflammatory

宿主先天防御[74]。然而, 持续的炎症反应会使感染Mtb的宿主细胞受损。因此, ApoA-I可能通过调节细胞自噬并利用SR-BI促进AMPK-mTOR-ULK1通路的激活, 有助于细胞内Mtb的控制和清除, 并在感染期间促进宿主保护性免疫反应。

4 总结和展望

ApoA-I作为一种载脂蛋白, 主要通过与SR-BI和ABCA1结合来激活相应的下游通路, 抑制泡沫细胞的形成和炎症级联反应中促炎因子的分泌, 促进细胞自噬清除凋亡免疫细胞和死细菌来抑制结核病的发生和发展。ApoA-I所属载脂蛋白家族中有些与ApoA-I功能一致, 如: ApoA-I和ApoC-II都可作为脂蛋白脂肪有关酶类的激活剂; ApoA-I和ApoE则是重要的脂质转运蛋白和代谢调节剂[75-76]。而有些如ApoB-48可作为细胞膜受体的配体, ApoE可在阿尔茨海默病等退行性疾病中发挥促进神经组织修复等重要作用[76-78], 从而区别于ApoA-I。

ApoA-I在血管疾病、癌症和肺部其他疾病中被广泛应用, 但ApoA-I在结核病方面的研究仍较为缺乏。在结核病作用机制方面, 从分子水平和动物模型上系统地验证和探究ApoA-I参与结核病的作用机制的研究有待开展; 在结核病诊断方面, 虽有研究提示血清中ApoA-I的水平与结核病感染程度呈负相关[21,30], 但将其作为结核病诊疗的标志物仍需要进一步研究证实; 在结核病治疗方面, 尽管ApoA-I模拟肽已被用于治疗多种肺部疾病, 但在结核病治疗方面的研究尚待开展。最新包载ApoA-I的纳米颗粒已被证实可抑制促炎巨噬细胞的激活, 靶向治疗模型小鼠的动脉粥样硬化[79]。未来开展上述工作, 在分子水平和转基因动物模型上明确ApoA-I参与结核病发生发展和治疗的机制, 分析结核病与患者血清ApoA-I自身抗体水平的关系, 以及探究ApoA-I及其模拟肽结合纳米递药系统治疗结核病的可行性, 无疑会为完善结核病的发病机制和找寻诊断及治疗新策略提供新的依据。

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贾晨曦负责阅读整理文献、起草编撰论文、修改论文; 刘麒苗负责提供写作思路、协助编撰论文; 武琛佳负责绘制信号通路图; 王昕负责协助修改论文格式、整理参考文献; 郝明媛负责指导、提供相关支持与资助; 董丽负责指导、修改论文及提供相关支持与资助。

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