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结核病易感因素及相关机制研究

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摘　要

结核病作为一种慢性传染病，其发病是由遗传易感性、环境、社会经济状况等综合作用的结果。目前，多项研究探讨结核病发病危险因素，包括老年、糖尿病、吸烟、饮酒、营养不良、手机依赖、睡眠障碍等，但关于这些危险因素如何增加结核分枝杆菌易感性机制，与机体免疫学具体关联是什么，相关报道较少。因此，本文主要从特定人群、不良生活方式两方面入手，就以上易感因素与结核病之间的关联作一综述，总结不同人群对结核分枝杆菌易感性相关机制，为结核病个体精准化防治提供理论依据。

关键词

结核，易感因素，机制

Study on Susceptible Factors and Related Mechanisms of Tuberculosis

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Abstract

As a chronic infectious disease, the incidence of tuberculosis is the result of genetic susceptibility, environment, socio-economic status and other comprehensive effects. At present, a number of

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studies have explored the risk factors of tuberculosis, including old age, diabetes, smoking, drinking, malnutrition, cell phone dependence, sleep disorders and so on, but there are few reports on how these risk factors increase the susceptibility mechanism of *Mycobacterium tuberculosis* and what is specifically related to immunology. Therefore, this paper mainly reviews the relationship between the above susceptible factors and tuberculosis from the two aspects of specific population and bad life style, and summarizes the mechanism of susceptibility to *Mycobacterium tuberculosis* in different populations, to provide theoretical basis for individual accurate prevention and treatment of tuberculosis.

Keywords

Tuberculosis, Susceptible Factors, Mechanism

1. 引言

近年来，结核病已成为由单一感染性病原体引起的主要死亡原因[1]。2016 年，全球结核病发病率为 1042 万，与结核病相关的死亡人数为 145 万[2]。鉴于这种疾病的严重性，联合国通过其可持续发展目标(2016~2030 年)和世界卫生组织(WHO)通过其结束结核病战略(2016~2035 年)分别设定了结束这一流行病的目标[3]。在大多数国家，结核病的诊疗条件都有所改善，但降低患病率、控制传染源仍旧是结核病防治工作的重要部分。现有研究证实结核病发病与多种因素相关[4]。我国作为结核病高负担国家之一，探究结核病高危人群易感机制及如何进行早期干预，对我国结核病防治具有重大意义。因此，本文着重从特定人群、不良生活方式与结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)易感相关机制研究作一综述，旨在为结核病的合理化诊治及预防提供循证学依据。

2. 特定人群与 Mtb 易感相关机制研究

2.1. 老年

免疫功能的衰退被认为是老年人易受 Mtb 感染的原因之一。感染 Mtb 时的肺环境状况是决定疾病严重程度的重要因素[5]。动物实验证实，老年小鼠的肺泡内衬液(alveolar lining fluid, ALF)具有高水平的促炎细胞因子，使得肺部粘膜环境长期处于低度炎症状态，并增加宿主对 Mtb 感染的敏感性[6]。Moliva 等[7]研究发现，在老年小鼠和老年受试者 ALF 中，表面活性蛋白 A (surfactant protein A, SP-A)、表面活性蛋白 D (surfactant protein D, SP-D)以及补体系统的组成部分(特别是 C3b)增加，而肺泡水解酶活性降低。人类肺泡内衬液成分，包括 SP-A、SP-D、补体蛋白 C3 和肺泡水解酶等，在控制 Mtb 感染中起着重要的先天免疫作用。肺泡水解酶能够改变 Mtb 细胞壁，继而改变巨噬细胞和中性粒细胞对 Mtb 的吞噬作用，显著地控制 Mtb 的细胞内生长，将炎症和随后的组织损伤降至最低[8]。SP-A 通过与巨噬细胞受体的直接相互作用，调节凋亡细胞的清除，增加巨噬细胞对 Mtb 的吞噬作用，调节炎症和氧化反应，并调节人巨噬细胞中 Toll 样受体和甘露糖受体的表达。而 SP-D 则减少了 Mtb 与巨噬细胞的联系，并推动吞噬小体–溶酶体融合。Hall-Stoodley 等[9]认为，SP-A 与 SP-D 可通过增强 Mtb 与肺上皮细胞的联系来提高 Mtb 的毒力。此外，通过激活经典的和替代的补体系统，C3 可以调理 Mtb，通过与巨噬细胞上的 CR3

相互作用启动吞噬作用[10]。基于以上机理，老年机体肺泡内环境为 Mtb 创造了良好的条件。

2.2. 糖尿病

据估计，全球每年有 960 万新的活动性结核病患者，其中 100 万人同时患有结核病和糖尿病[11]。糖尿病是活动性和潜伏性结核发生的主要危险因素。免疫功能障碍增加了糖尿病患者对 Mtb 的易感性。Lopez-Lopez 等[12]研究证实 2 型糖尿病可改变人类巨噬细胞的基本表型，并降低其应对，内化和控制 Mtb 的能力。糖尿病患者在细菌识别，吞噬活性和细胞活化方面的缺陷，导致趋化因子和细胞因子的产生受损。因高血糖宿主中抗原呈递细胞募集和功能受损而致使适应性免疫的启动延迟，Th1、Th2 和 Th17 细胞的频率降低(其分泌的细胞因子在巨噬细胞的激活中起着重要作用) [13]。作为连接肥胖症和 2 型糖尿病的关键分子，抵抗素被认为是促进胰岛素抵抗的一种蛋白质，患有 2 型糖尿病的受试者血清中的抵抗素水平较高，从而降低了人类巨噬细胞针对 Mtb 的免疫应答[14]。此外，Larsen 等[15]研究表明，糖尿病患者肠道微生物群发生了改变，随后影响了宿主体内的短链脂肪酸(Short-chain fatty acids, SCFAs)水平，然后 SCFAs 通过激活 G 蛋白偶联受体和抑制组蛋白脱乙酰化酶等作用于免疫和内皮细胞，从而发挥免疫活性，影响宿主对 Mtb 的易感性。

2.3. 营养不良

全球近 8 亿人口长期营养不良，其中 98%位于结核病流行的中低收入国家[16]。营养不良会导致蛋白质能量摄入不足和微量营养素缺乏，并通过削弱控制 Mtb 感染所需的先天性和适应性免疫反应，影响对卡介苗的反应，在破坏免疫系统和重新激活潜在的 Mtb 感染方面起着重要作用[16]。抗菌肽(Anti-microbial peptides, AMPs)是一种多功能分子，也称为阳离子宿主防御肽，被认为是先天免疫防御的第一道防线，在宿主抵御细菌、病毒和真菌的防御机制中发挥关键作用[17]。在 AMP 家族中，一些重要的 AMP 是人中性粒细胞多肽 1-3 (Human neutrophil peptide 1-3, HNP1-3)、人 β 防御素-2 (Human beta defensin-2, HBD-2)、颗粒溶素和肠溶素(LL-37)。研究表明，先天免疫反应中 AMPs 生成失调会导致对微生物感染的易感性增加[18]。体重指数作为衡量营养状况的一个重要指标，与机体免疫状况密切相关，低体重指数患者往往免疫机能较差，更易感染 Mtb。Rajamanickam 等[19]研究证实，低体重指数患者体内人中性粒细胞防御素、颗粒溶素、人 β 防御素 2 和抗菌肽 LL-37 的水平较正常体重指数患者降低，从而潜在地增加了发展为活动性 TB 的风险。另外，营养不良还与潜伏性 Mtb 感染患者 T 细胞、B 细胞、单核细胞和树突状细胞亚群的紊乱有关[20]。结核病一旦发作，将导致新陈代谢的增加和食欲的下降，进而导致原有营养不良的加剧[21]。

2.4. 长期使用糖皮质激素

有研究报道，接受糖皮质激素治疗的患者患结核病的风险大大增加[22]。在结核病动物模型中，在遏制 Mtb 后进行糖皮质激素治疗会导致疾病重新激活。糖皮质激素可抑制 Mtb 感染后巨噬细胞的先天免疫反应，抑制抗菌物质 NO 的产生，抑制巨噬细胞中 Mtb 吞噬小体的自噬和成熟，从而促进 Mtb 的生存[23]。自噬在抗机体防御 Mtb 方面起关键作用。自噬可促进 Mtb 吞噬小体与自噬小体的融合，并促进随后自噬溶酶体中细菌的清除。缺乏关键的自噬相关基因(Autophagy-related genes, ATGs)，可使小鼠对 Mtb 感染高度敏感，肺部细菌负荷显著增加[24]。Wang 等[23]研究表明，经糖皮质激素处理的巨噬细胞中 ATGs 的表达下调，从而阻碍了自噬。

2.5. 人类免疫缺陷病毒(Human Immunodeficiency Virus, HIV)感染

HIV 感染会损害宿主 CD4 + T 细胞的反应，从而导致 Mtb 继发感染，并影响结核病病情严重程度。

HIV 感染者 Mtb 易感性增加，主要有以下机制：改变效应性 T 细胞和调节性 T 细胞之间的平衡[25]；扰乱巨噬细胞内含有 Mtb 的空泡的 pH 调节，促进细胞内 Mtb 的存活[26]；由 HIV 感染的巨噬细胞 IL-10 产生减少，促进 Mtb 的发病和 HIV 病毒的传播[27]；HIV 蛋白 Nef 可以通过抑制 TNF-α 启动子区域来抑制巨噬细胞的凋亡[28]；HIV 蛋白干扰自噬，抑制吞噬小体的成熟[29]。

2.6. 其它

因恶性肿瘤患者免疫抑制，营养状况差，靶向药物的使用等，其发生 Mtb 感染风险亦高于普通人群[30]，易感机制也多于上述因素有关，故在此不再赘述。此外，有学者指出，慢性肾脏病与结核病亦存在一定关联。Cho 等[31]研究表明，CKD 分期与结核病发病呈正相关。肾小球滤过率每降低 10 ml/min/1.73m^2，结核病风险增加 5.1%。Moran 等[32]证实接受血液透析的患者发生活动性结核病的风险更大。但有关分子机制研究较少，仍有待进一步阐明。

3. 不良生活方式与 Mtb 易感相关机制研究

3.1. 吸烟

吸烟在 Mtb 感染的过程中起着关键作用，并且也是影响结核病治疗成功的主要障碍[33]。烟草烟雾通过改变粘膜纤毛清除率，降低肺泡巨噬细胞活性；肺淋巴细胞的免疫抑制，自然杀伤细胞的细胞毒性活性降低，肺树突状细胞活性的改变增加 Mtb 感染的风险[34]。尼古丁调节 Mtb 感染过程中巨噬细胞中髓样分化因子(Myeloid differentiation fact, MyD88)依赖的信号通路，并加剧炎症反应[35]。Cholo 等[36]研究表明，吸烟与 Mtb 生物膜形成的增加有关，有助于病原体的持续存在，易于疾病再激活，并降低抗菌药物的疗效。香烟燃烧产生的烟雾可削弱巨噬细胞对胞内 Mtb 遏制作用[37]。此外，电子烟亦会损害吞噬功能和细胞因子对 Mtb 的反应[38]。Nizamani [39]证实，与对照组相比，肺结核患者生物样品(头发、全血、血清、唾液、痰液、鼻液)中锌、铁的平均含量较低，而铜的含量较高($P < 0.001$)。此外，不吸烟结核病患者的生物样本中锌和铁的浓度均较吸烟患者高。锌、铁缺乏与吸烟引起的铜高接触可与肺结核相关危险因素产生协同作用。锌稳态可能在调节炎症免疫反应中起重要作用，高浓度锌可诱导外周血单核细胞凋亡并促进细胞因子的产生。相反，低浓度的锌可能会抑制单核细胞功能，降低中性粒细胞吞噬功能[40]。锌还可能与气道上皮相互作用[41]，维持气道内稳态。Mtb 在宿主巨噬细胞内的增殖能力依赖于可获得的铁[42]。铁超负荷患者的巨噬细胞铁负荷会增加结核病的风险，并可能使患者预后恶化。

3.2. 饮酒

研究表明，每天饮酒超过 40 克酒精或被诊断为酒精使用障碍会使患肺结核的风险增加近三倍(RR = 2.94, 95% CI: 1.89~4.59)，并且随着酒精摄入量的增加，患肺结核的风险亦呈上升趋势[43]。Krutko 等[44]研究结果表明，与低度饮酒和适度饮酒的人群相比，过量饮酒患者活动性肺结核发现较晚，肺组织病变范围广，且形成空洞可能性大，排菌量更大。饮酒影响结核病的治疗效果，饮酒者在抗结核 2 月末的痰菌阳性率和死亡率分别比不饮酒者高 1.431 倍和 1.668 倍。当前饮酒者在 2 个月末的痰菌阳性率是从不饮酒者的 1.256 倍[45]。此外，饮酒还可影响结核病治疗依从性，导致随后的获得性耐药性[46]。酒精会严重损害肺部的抗氧化剂防御能力和先天免疫功能，从而增加对 Mtb 易感性，以及重新激活潜伏性 Mtb 感染。正常情况下，肺泡巨噬细胞能够清除大部分 Mtb [47]。长期摄入酒精可降低肺泡巨噬细胞中的粒细胞－巨噬细胞集落刺激因子受体表达和下游信号传导，减弱肺泡巨噬细胞的免疫功能[48]。巨噬细胞的动员和粘附受到抑制，Mtb 吞噬作用和超氧化物的产生均受到影响。此外，酒精可影响单核细胞产生抗炎细胞因子水平[49]。巨噬细胞对这些细胞因子的反应能力和将 Mtb 抗原呈递给淋巴细胞的能力降低，抗

原特异性 T 细胞的激活也受到了损害。基于此，免疫系统对新的和休眠的 Mtb 的反应能力严重减弱[50]。Yeligar 等[51]认为，酒精不仅可致肺泡巨噬细胞氧化应激和吞噬功能障碍，损害肺泡巨噬细胞免疫能力和病原体清除能力，还可通过翻译后修饰介导气道纤毛功能障碍。除了对免疫系统的直接影响外，饮酒还与营养不良有关。酒精可显著抑制肠上皮细胞钠依赖性谷氨酰胺吸收和 Na-K-ATP 酶活性，进而导致营养不良，影响先天免疫系统和后天免疫系统的维持[52]。动物实验表明，酒精可增强受 Mtb 感染的幼鼠肺中 CD11b + Ly6G+细胞产生 IFN-α，进而导致巨噬细胞坏死并增加幼鼠死亡率[53]。

3.3. 睡眠障碍

睡眠障碍作为新型不良生活方式之一，睡眠方式的破坏已成为现代生活中越来越普遍的一部分。睡眠障碍(即失眠、睡眠质量差和(或)睡眠不足)与免疫调节紊乱有关，并且会导致炎症性疾病风险增加[54]，包括增加 Mtb 易感性。睡眠障碍者合并肺结核风险是非睡眠障碍者的 1.172 倍[55]。Kou 等[56]研究证实，睡眠质量差与肺结核发病相关，进一步行亚组多因素分析表明，在糖尿病病程 > 5 年的患者中，睡眠质量差会使结核病的风险增加 3 倍以上(OR = 3.31, 95% CI: 1.08~10.13; P = 0.036)，且睡眠不足还会增加肺结核患者疾病严重程度。戴磊等[57]研究表明，睡眠不足的肺结核患者合并肺部空洞的风险明显高于睡眠充足者(OR = 15.558)。作为免疫反应的重要调节器，睡眠和免疫是相互关联的[58]。在没有病原体感染的情况下，睡眠可通过调节炎症介质(如细胞因子)促进炎症稳态。长期睡眠障碍会削弱机体免疫机能，增加对感染性疾病的易感性。睡眠减少后感染的易感性增加有以下几点原因[59]：在部分睡眠剥夺期间观察到的淋巴细胞有丝分裂增殖受损，HLA-DR 表达降低，CD14+上调，以及 CD4+和 CD8 + T 淋巴细胞的变化。Lungato 等[60]通过研究部分睡眠剥夺(partial sleep deprivation, PSD)和睡眠反弹(sleep rebound, RB)对小鼠疟原虫感染的影响，发现 PSD 可损害免疫系统并导致疟原虫感染的严重性增加，仅 48 小时的恢复睡眠足以使小鼠的对感染反应恢复到基线值。机体本身合并睡眠障碍，或罹患结核病后继发的睡眠问题，均为影响结核病病情演变的重要因素。

3.4. 手机依赖

智能手机的普及及功能的多样化，增加了人们使用手机时间。截至 2020 年 6 月，我国网民规模达 9.40 亿，9.32 亿人(99.2%)使用手机上网[61]。过多使用手机(手机依赖)可使肺结核的风险增加 2.9 倍[55]。El-Gohary 等[62]人通过研究结果表明，暴露于手机辐射会损害大鼠的免疫系统，并且与暴露时长有关。电磁场暴露 1 h/d，连续 30 天，大鼠免疫球蛋白水平(IgA、IgE、IgM 和 IgG)、白细胞总数、淋巴细胞、嗜酸性粒细胞和嗜碱性粒细胞计数显著降低($P < 0.05$)，中性粒细胞和单核细胞计数显著升高($P < 0.05$)。电磁场暴露 2 h/d 的大鼠以上变化更为显著，而补充维生素 D 可逆转这些损害。Singh 等[63]通过动物实验证实，长期暴露于手机发出的射频电磁场辐射会引起大鼠氧化应激，炎症反应和下丘脑－垂体－肾上腺轴失调。同对照组相比，实验组大鼠海马氧化应激显著增加($P < 0.05$)，循环促炎性细胞因子 IL-1β、IL-6、TNF-α 水平均升高，促肾上腺皮质激素和皮质酮明显增加($P < 0.05$)。Yinhui 等[64]研究表明，手机辐射可引起小鼠中性粒细胞数量增加，导致其吞噬作用降低并诱导中性粒细胞凋亡。手机电磁场对生物系统的影响有以下两点：一是由于吸收高频电动势导致体温升高以及细胞和组织损伤而发生的热效应[65]。二则指非热效应，主要表现为细胞膜完整性的破坏、细胞信号转导、神经系统兴奋性改变、内皮功能障碍[66]，和免疫系统生化的变化，这可能直接影响机体的免疫反应[67]。有研究报道，在暴露于 1800 MHz 射频电磁场后，人类单核细胞和淋巴细胞中活性氧的产生显著增加[68]。电磁场干扰淋巴细胞的 Ca^{2+}调节过程，或增加自由基的寿命和细胞内活性氧的浓度，导致主要细胞大分子，如脂质和核酸的氧化损伤，使得细胞生长抑制、蛋白质错误折叠和 DNA 断裂[69] [70]。关于手机依赖与 Mtb 易感是否与以上所述机

制相关，仍有待进一步研究。

4. 结语与展望

以上就结核病易感因素及作用机制作一简要概述，关于以上因素是否会对结核病患者疾病严重程度产生影响，仍有待相关临床研究证实及阐明具体分子机制。目前全球结核病防控重点为尽早发现并确诊结核病患者，全面深刻了解结核病发病危险因素有助于指导结核病早期诊断，辅助相关部门确定将哪些人群作为目标人群以及合理分配医疗资源，实施个体化精准治疗模式，降低我国乃至全球结核病负担。在2020年新型冠状病毒肆虐期间，多个国家采取封城措施控制疫情，结核病主动发现率降低，原有结核病患者治疗不到位等，均可能导致结核病疫情反弹，对实现“2030年终止结核病”这一战略目标提出更为严峻的挑战。

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