DOI: 10.13241/j.cnki.pmb.2014.05.047

·专论与综述·

巨噬细胞凋亡对结核分枝杆菌感染的机制研究进展 *

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摘要:结核病是一种严重危害人类健康的慢性传染性疾病,主要由结核分枝杆菌感染导致,结核分枝杆菌进入人体后,与免疫防御的第一道屏障—巨噬细胞发生反应,部分菌株在细胞内长期生存、繁殖,是导致结核病转归的决定性因素。感染早期,结核分枝杆菌的繁殖受到巨噬细胞凋亡的抑制,随着高效价、高毒力菌株繁殖速度的增加,抗巨噬细胞凋亡作用不断增强,使自身繁殖得到有效保护,为菌株的生长提供了充足、适宜的胞内环境。因此,调控结核分枝杆菌对巨噬细胞凋亡进程的抑制作用,是预防和治疗结核病的关键。

关键词:巨噬细胞;凋亡;结核分歧杆菌;感染;机制;进展

中图分类号:R378.911,R52 **文献标识码**:A **文章编号**:1673-6273(2014)05-972-03

Progress of Research on the Mechanism of Apoptosis of Macrophages Infected with Mycobacterium Tuberculosis*

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ABSTRACT: Tuberculosis is a chronic infectious disease serious harm to human health, is mainly composed of Mycobacterium tuberculosis infection. When Mycobacterium tuberculosis entered into the human body and led immune macrophage reaction, some strains were long-term survival and made reproduction, which is the decisive factor leading to tuberculosis. In the early stage of infection, Mycobacterium tuberculosis growth was inhibited by apoptosis of macrophages. With the increase of high titer, high virulent strains breeding rate, the effect of macrophage on apoptosis increases ceaselessly, and make their own reproduction can be effectively protected, providing sufficient, appropriate intracellular environment for the growth of strains. Therefore, the inhibition of Mycobacterium tuberculosis to the regulation of macrophage apoptosis process is the key to the prevention and treatment of tuberculosis.

Key words: Macrophage; apoptosis; Mycobacterium tuberculosis; infection; mechanism; progress

Chinese Library Classification(CLC): R378.911, R52 Document code: A

Article ID: 1673-6273(2014)05-972-03

前言

结核分枝杆菌(Mycobacterium tuberculosis,MTB)是引起结核病的主要病原菌,可造成全身各器官感染,其中以肺结核最为常见[1]。巨噬细胞是一种免疫细胞,可参与机体非特异性免疫和特异性免疫,是人体免疫防御系统第一道防线的重要组成部分,在抗结核分枝杆菌感染中可起到重要作用。研究表明,MTB 可对巨噬细胞的凋亡产生诱导作用,从而逃避免疫监视和免疫防御,使疾病进展速度增加[2]。目前,全球每年新发结核病患者高达 1000 万,死亡约 300 万,结核病感染现状不容乐观[3]。因此,探讨巨噬细胞凋亡对结核分枝杆菌感染的机制,对进一步明确结核病发病机理、制定治疗措施具有重要意义。

1 结核分枝杆菌的致病机制

1.1 胞内寄生

MTB 形态细长,略带弯曲,其细胞壁脂质肽聚糖外层包裹有大量分枝菌酸,属非运动性细菌[4]。与大多数胞外病原菌感染机制相比,MTB 不会分泌毒素来创造合适的生存环境,而是通过感染巨噬细胞,使其自身被巨噬细胞吞噬后,阻止 ATP/ 质子泵的进入,同时,吞噬小泡的酸化作用使非致病菌被降解,胞内 pH 降低,为 MTP 的繁殖创造了合适的环境[5]。Sakala IG 等[6]研究发现,巨噬细胞缺陷型小鼠在经 MTB 感染时结核病发病率

* 基金项目:国家自然科学基金项目(J1103520)
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(收稿日期:2013-07-11 接受日期:2013-08-10)

较低,提示肺泡巨噬细胞内质体与 MTB 融合后,可对 MTB 的生长、繁殖起到一定的保护作用,促进了 MTB 感染。

1.2 细胞凋亡

细胞凋亡是一种程序性细胞死亡,是一个主动过程,主要目的为维持内环境的稳定。巨噬细胞可识别出现标记信号的凋亡细胞,产生和释放转化生长因子 -β(TNF-β)、白介素 -10(IL-10)等抗炎介质,起到防御胞内寄生菌的作用[7]。感染早期的巨噬细胞凋亡是机体自我防御的表现,可有效清除部分寄生的 MTB,降低 MTB 体内播散速度,而随着巨噬细胞凋亡数量的增加,MTB 分泌的自身毒力因子、蛋白质及毒素成分可起到强抗凋亡作用,加快了病情进展速度[8]。

2 巨噬细胞凋亡对结核分枝杆菌感染的机制

2.1 正向调控机制

2.1.1 酶活性的影响 机体受 MTB 感染后,巨噬细胞会产生大量 TNF-α 和 IL-1β,使蛋白激酶 Caspase 酶系活性上升,其中以 Caspase-1 活性上升最为显著[9]。研究证实,Caspase-1 是启动巨噬细胞凋亡过程中最重要的酶,使用 ICE 抑制剂 YVAD 抑制 Caspase-1 后,患者巨噬细胞凋亡速度明显降低,说明 MTB 感染引发的蛋白激酶活性提高是加剧细胞凋亡的基础因素。

2.1.2 前炎症因子的影响 IL-1、IL-6、IL-8、TNF-α 等前炎症因子可导致炎症反应的出现,对 MTB 感染引发的免疫反应起到了重要影响。Divangahi M 等[10]指出,TNF-α 可激活巨噬细胞与凋亡有关的基因表达,是细胞凋亡的主要环节,其机制主要为:在第二信号胞质磷脂酶 A2(Ctosolicphospholipase A2,cPLA2)的刺激下,巨噬细胞表面的 TNFR1 可与 TNF-α 结合,而结合后的物质可被半胱氨酸蛋白水解酶所裂解,从而激活 Caspase-2 及 Caspase-3,启动凋亡过程。同时,Patil AG 等[11]认为,MTB 诱导巨噬细胞产生的 IL-10,使 TNF-α 活性受到抑制,降低了被 MTB 感染的宿主细胞巨噬细胞凋亡的速度。上述两种机制互相作用,使未被感染的巨噬细胞数量减少,而受到 MTB 感染的巨噬细胞凋亡速度降低,加剧了病程的进展[12]。

2.1.3 转导途径的激活 MTB 对 JAK2/STAT1-α 信号转到途径的激活已得到广泛共识[13],其主要是通过对酪氨酸蛋白激酶(Protein Tyrosine Kinase,PTK)的激活,使 JAK2/STAT1-α 磷酸化,而作为蛋白酪氨酸磷酸激酶的 JAK2 和作为信号传递与转录激活因子的 STAT1-α 受到活化后,会引发细胞产生大量 TNF-α 及 NO[14],使蛋白激酶 Caspase 酶系活性上升,促进了凋亡的进展。而姚楠等[15,29-30]研究发现,MTB 中蛋白质成分葡萄糖脂蛋白 19000(P19)可使 Caspase-8 激活,诱导细胞凋亡的发生。

2.1.4 凋亡蛋白的表达 Bcl-2 蛋白家族可改变细胞凋亡阈值,从而启动凋亡信号。Morris D 等[16]指出,机体受到 MTB 感染后,Bcl-2 和 Bax 会呈现高表达,使抗凋亡信号和促凋亡信号比例失衡,诱导正常细胞凋亡,同时保证 MTB 在宿主细胞中的存活。

2.1.5 线粒体的损伤 细胞受 MTB 感染后,会出现线粒体外膜改变、膜电位消失、通透性转运孔开放等变化,使线粒体破裂数量上升,而 Kleynhans L 等[17,31-32]证实,线粒体在细胞凋亡中可起到重要枢纽作用。因此,当破裂的线粒体数量显著上升时,胞质中可溶性蛋白亦随之上升,启动了核凋亡的发生[18,33-35]。

2.2 反向调控机制

2.2.1 MTB 成分对凋亡的调控 MTB 含结核菌酸、索状因子等菌体成分,具有一定的抑制细胞凋亡作用[19],其细胞壁中的甘露糖末端脂阿拉伯甘露聚糖(ManLAM)可抑制巨噬细胞蛋白激酶 C(PCK)活性,使 PCK 去活化,从而降低 IFN-γ 及 HLA-DR-A 基因表达,抑制 ATP/Ndk 诱导的细胞凋亡过程[20],有助于保护 MTB 在宿主细胞中的生长、繁殖。

2.2.2 毒力对凋亡的影响 MTB 对 IL-10 的生成具有促进作用,而不同毒力的 MTB 株会在巨噬细胞凋亡机制下表现出不同的结局[21],如 H37Rv 毒力最强,其刺激生成 IL-10 数量最多,从而诱导更多的 sTNFR2 生成,使 TNF 生物学活性受到抑制,细胞凋亡速度降低、数量减少,使该毒株在宿主细胞内生长、繁殖速度最快[22]。因此,Luo X 等[23]认为,不同毒力的 MTB 株对巨噬细胞凋亡机制的逃避能力不同,毒力较强的毒株,在胞内代谢率越高,则细胞凋亡速度越低。

3 结语

近年来,随着社会经济的发展和人口流动速度的增加,感染性疾病已成为导致人类死亡的重要疾病[24]。20 世纪 80 年代以来,MTB 耐药菌株的增加使全球结核病疫情再度爆发,目前,全球每年新发结核病 1000 万人次,死亡 300 万人,而我国现有 MTB 感染者 4 亿人,每年因结核病死亡的人数超过 25 万[25]。不论是世界范围内还是就我国而言,结核病疫情已十分严峻,也为结核病的防治工作提出了较高要求。MTB 感染首要步骤为侵袭巨噬细胞,并在巨噬细胞内寄生,但巨噬细胞的凋亡可使 MTB 生存环境受到抑制,使其在体内的传播速度降低[26],而 MTB 又可抑制巨噬细胞的凋亡,使受感染细胞得到保护。因此,探究巨噬细胞凋亡对 MTB 感染的机制,是指导临床治疗、预防和控制结核病疫情蔓延的重中之重。

在综合文献资料及研究成果后,我们发现,MTB 可通过多种机制达到对巨噬细胞凋亡的调控效果,首先,MTB 的入侵会使宿主巨噬细胞内在活性激活,使 TNF-α 介导的凋亡机制启动,使巨噬细胞早期抵御 MTB 效果良好,菌株生长受到抑制;而随着凋亡的进展,MTB 利用细胞凋亡引发的坏死达到了脱离巨噬细胞的作用[27,28],使未感染的巨噬细胞受到感染;最终,高效价、强毒力的 MTB 使巨噬细胞凋亡受到抑制,为其进一步生长繁殖提供了充足空间,导致重症结核病的发生。

综上所述,在免疫防御的早期,MTB 的生长繁殖可因感染细胞的凋亡而受到抑制,而细胞凋亡导致吞噬体数目的降低使宿主细胞免疫反应受到干扰,MTB 抗凋亡逐渐占主导趋势,是引发炎症反应和病情进展的主要原因。因此,在结核病的治疗及防控中,应注重对 MTB 在胞内代谢的控制,从而抑制其抗凋亡进程,促进菌株扩散,防止感染进展。

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