

肺泡巨噬细胞胞葬功能对 COPD 作用的研究进展

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【摘要】 慢性阻塞性肺疾病(COPD)作为全球三大死因之一,严重危害人类健康。巨噬细胞在 COPD 中扮演重要角色,其胞葬功能对结束 COPD 慢性炎症至关重要。COPD 患者肺泡巨噬细胞(AM)胞葬功能受损使肺内细菌感和气道细菌定植风险增加,是诱发 COPD 急性加重,促使 COPD 发病率、病死率上升的主要原因。近年来,调节 COPD 中巨噬细胞的胞葬功能成为研究热点,本文就 AM 胞葬功能对 COPD 作用的研究进展进行综述,并提出中医药改善 AM 胞葬功能障碍的切入点,为防治 COPD 提供新的思路。

【关键词】 慢性阻塞性肺疾病; 肺泡巨噬细胞; 胞葬

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Advances in research on the role of alveolar macrophage burial function in chronic obstructive pulmonary disease

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【Abstract】 As one of the top three causes of death in the world, chronic obstructive pulmonary disease (COPD) is a serious hazard to human health. Macrophages play an important role in COPD, and their efferocytosis function is essential for ending chronic inflammation of COPD. Efferocytosis damage of alveolar macrophages (AM) in patients with COPD causes the rising of bacterial infection and airway bacterial colonization risk in lungs, which is the main reason for the acute exacerbation and the rising of incidence rate and mortality rate in COPD. In recent years, the regulation of macrophage efferocytosis function in COPD has becoming a research hotspot. Progress on the role of macrophage efferocytosis function on COPD, and the breakthrough points of improving AM efferocytosis dysfunction by traditional Chinese medicine is reviewed, so as to provide new ideas for the prevention and treatment of COPD.

【Key words】 Chronic obstructive pulmonary disease; Alveolar macrophages; Efferocytosis

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作为全球范围内亟需解决的健康问题,近年来,慢性阻塞性肺疾病(COPD)的发病率和病死率均呈上升趋势,预计到2060年,全球COPD致死人数将高达700万,病死率上升至6.9%^[1]。据COPD 2018全球倡议报告,COPD是一种可预防和治疗、以持续的呼吸症状和气流受限为主要临床表现的呼吸系统常见病^[2]。COPD的主要发病原因在发达国家为香烟烟雾,而在发展中国家则是环境污染物^[3-4]。目前,有关COPD的发病机制仍未彻底阐明,已被认可的机制包括炎症反应、氧化应激、蛋白酶/抗蛋白酶失衡等,其中炎症反应是造成COPD病程发展与肺功能损伤的首要因素^[5]。

近年研究表明,巨噬细胞作为肺部慢性炎症发生发展的始动细胞,在COPD中扮演重要角色,其胞葬功能对结束肺部慢性炎症有重要意义。胞葬功能,即吞噬细胞清除凋亡细胞的能力。我们认为,COPD中巨噬细胞的胞葬功能障碍并非孤立存在,而是与肺部慢性炎症反应、氧化应激、抗蛋白酶失衡等过程紧密相连,协同影响COPD临床进程。现就近年来有关肺泡巨噬细胞(AM)胞葬功能对COPD作用的研究

进行综述。

1 AM与COPD炎症反应

在COPD受试者气道内可明显发现中性粒细胞、巨噬细胞等炎性细胞的比例增加^[6]。先前COPD炎症机制的探讨多围绕中性粒细胞进行。但近年来,伴随对COPD的深入挖掘,巨噬细胞在慢性炎症中发挥的重要作用逐渐凸显。巨噬细胞作为关键的炎性细胞,主要在先天免疫反应期作为吞噬细胞发挥作用,其吞噬、免疫调节、分泌功能伴随COPD发生发展的全过程。它可识别病原体相关分子模式(PAMP),激活适当的免疫反应,同时启动抗原呈递、发挥吞噬活性,清除体内病原体、凋亡细胞及碎片,最大程度地减少损伤^[7-8]。

AM是呼吸道-肺泡表面的巨噬细胞。AM作为肺内极为重要的免疫细胞,在清除肺部吸入刺激物方面作用显著。此外,AM的另一个重要功能即当肺部出现炎症性损伤后,可及时胞吞和清除受损或凋亡的细胞^[9]。

巨噬细胞的数目在COPD患者的痰液、气道和支气管肺泡灌洗液中异常增多^[10]。COPD患者的AM存在基础免

疫性损伤,其对炎症因子的响应能力受损,细胞内信号转导存在明显障碍^[6]。研究显示,COPD患者AM的吞噬功能、凋亡细胞清除(胞葬)功能有所减退,这使得肺内细菌感染以及气道细菌定植的风险增加,也是造成COPD急性加重,并呈现高发病率和病死率的主要原因^[11]。Hodge等^[12]发现,巨噬细胞的胞葬功能障碍可明显诱发或加重COPD患者持续性的肺部炎症。因此,阐明巨噬细胞胞葬的发生机制、探索有效改善胞葬功能异常的途径,或许对解决COPD慢性炎症反应具有非凡意义。

2 胞葬功能的作用机制

细胞凋亡是具有自主性和程序性的细胞死亡过程,对维持细胞生物体内稳态、调控机体正常发育具有重要意义^[13]。有效的胞葬不仅能清除和降解凋亡、受损细胞,而且可保护组织免受死亡细胞释放的有毒物质与免疫原性物质的损害,这在解决炎症问题方面意义重大^[14]。目前,可发挥胞葬作用的细胞有多种,除树突细胞、巨噬细胞等专职性吞噬细胞外,还包括内皮细胞、成纤维细胞等,而在人肺内,以AM为主^[15]。

研究表明,胞葬过程从细胞凋亡开始就受到了高度调节。濒死细胞在凋亡早期不断释放趋化因子,即“Find me”信号,将巨噬细胞募集到细胞凋亡部位。现已记录4种主要的“Find me”信号,包括核苷酸、趋化因子CX3CL1、溶血磷脂酰胆碱(LPC)和鞘氨醇-1-磷酸(S1P)^[16]。此外,核糖体蛋白S19、内皮单核细胞激活肽II(EMAP II)等具有趋化性的介质也可调节吞噬细胞迁移^[17]。随后,凋亡细胞释放“Eat me”信号,如存在于细胞内部的磷脂酰丝氨酸(PS)以天冬氨酸特异性半胱氨酸蛋白酶(caspase)依赖性方式在外部表达^[18],特异性结合吞噬细胞表面受体。PS作为最关键的“Eat me”信号,可被多种膜受体或桥接分子识别,包括清道夫受体Stab-2、T淋巴细胞膜蛋白4抗体(TIM4)和脑特异性血管生成抑制因子I(BAI)等直接识别的膜受体^[19-20]以及人生长停滞特异性蛋白(Gas)、乳脂肪球表皮生长因子8(MFG-E8)等介导间接识别的桥接分子^[21]。待“Eat me”信号被受体识别后,通过激活小三磷酸鸟苷(GTP)酶调节肌动蛋白纤维网重组、吞噬凋亡细胞,形成吞噬小体。最终,吞噬小体与溶酶体结合,发挥降解作用,消化和清除凋亡细胞,完成胞葬过程^[22]。

3 COPD中AM胞葬功能异常的可能机制

COPD患者AM胞葬功能存在异常。在多种慢性肺疾病患者的气道内,可发现凋亡细胞的数目增加。该现象可由细胞凋亡速度提升或肺部胞葬功能减退引发^[23]。研究表明,造成患者AM胞葬功能低下的主要原因可能是多种AM信号通路异常及识别受体的表达下调^[24-25]。通过观察COPD患者发现,其肺内出现大量集聚的凋亡炎症细胞、内皮细胞等,且反向抑制AM的胞葬功能,猜想这种现象可能由S1P信号通路异常造成^[26]。Vandivier等^[27]发现,AM上的PS受体可被中性粒细胞弹性蛋白酶快速分解,这也会导致肺内凋亡细胞清除受损和慢性炎症的持续存在。Noda等^[28]发现,香烟烟雾可明显抑制组蛋白去乙酰化酶(HDAC)的活

性,以及Rac、CD9信号途径的转导,由此阻碍AM对凋亡中性粒细胞的清除。通过研究一组经香烟烟雾刺激的COPD小鼠发现,RhoA-Rho途径以氧化剂依赖的方式被激活,从而干扰凋亡细胞的清除^[29]。香烟烟雾暴露可明显减弱AM的胞葬能力,COPD患者及健康吸烟者的AM识别受体分子CD71、CD44、CD91等表达均有不同程度的下降^[30-31]。此外,COPD患者体内的氧化应激也可直接影响AM的胞葬功能,这主要表现为氧化剂诱发的肌动蛋白重组受损、胞外蛋白羧基化和细胞骨架的蛋白降解。目前,核因子E2相关因子2(Nrf2)活化剂萝卜硫素、半胱氨酸前体等抗氧化物的应用,可有效改善被削弱的AM胞葬功能^[11,32-33]。

4 中医药改善AM胞葬功能障碍的切入点

近年来,中医药在预防和治疗COPD中积累了大量的临床、实验经验,主要体现在改善COPD临床症状、促进肺部炎症消退、增强肺通气功能、降低急性加重频次以及保障患者生活质量等多方面。根据COPD临床多见的“咳、痰、喘”等症状及病变过程,当归属中医学“咳嗽”“肺胀”等范畴^[34];其病机一般为“本虚标实”,本虚以肺脏为主,兼脾、肾二脏之气血阴阳,标实则多为痰瘀互结^[35];治疗上常采用清热化痰、温肺化饮、补肺益肾、补脾益肺等多种治则对证应用。

对中医药治疗COPD的研究表明,中药的应用可有效改善巨噬细胞吞噬功能损伤,降低气道、肺内炎症性损伤,促进组织和免疫功能修复,优化COPD的治疗效果。邱敬满等^[8]发现,黄芪提取物黄芪多糖能够增强COPD小鼠巨噬细胞的免疫调节及吞噬能力,其机制与黄芪多糖的抗氧化性有关。褚旭等^[36]研究表明,党参的主要成分提取物党参多糖(CPP)能够增强COPD小鼠AM的吞噬效应,显著提升PM_{2.5}刺激后COPD小鼠体内总抗氧化能力(TAC)和谷胱甘肽过氧化物酶(GSH-Px)水平。可见,中医药在修复COPD肺内损伤及缓解气道炎症反应的机制中均涉及到AM吞噬功能的改善。

早期中医药改善AM吞噬功能的检测对象主要为病原体和有害吸入物,但作为系统非特异性免疫功能,AM吞噬研究对象应纳入损伤及凋亡细胞。以此为切入点,从调控巨噬细胞胞葬功能的机制入手进行梳理和研究,将开拓中医药防治COPD的新思路。

5 不足与展望

在COPD、肺气肿等多种呼吸系统疾病中均存在AM吞噬和胞葬功能异常的问题,但目前国内外均缺少对中医药改善AM胞葬功能的系统研究。因此,结合中医药防治COPD的前期成果,细化AM胞葬机制的研究,对深入揭示COPD发病机制、推动其临床治疗的发展及新药物的研发应用都具有重要意义。

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