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HMGB1在心肺系统疾病中的作用机制及运动防治应用进展

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摘 要:高迁移率族蛋白B1(high mobility group protein B1,HMGB1)作为一种重要的损伤相关分子模式(damage-associated molecular patterns,DAMP),在心肺系统疾病中扮演重要的角色。运动是防治心肺系统疾病的非药物手段,其效果及调控 HMGB1的机制仍需系统梳理。通过检索CNKI、PubMed等数据库近几年相关文献,本文系统解析了心肺系统疾病中HMGB1的表达特征和病理机制,并探讨了运动干预如何通过调节HMGB1的表达和活性来防治心肺疾病。结果发现HMGB1作为关键炎症介质,参与多种心肺系统疾病。运动训练能够降低HMGB1的表达水平,进而抑制氧化应激、炎症和纤维化等,有效减缓心肺系统疾病进展,为心肺系统疾病提供新型干预策略。本综述为临床医生在心肺疾病治疗及预后评估方面提供了重要的科学依据和新的治疗思路。

关键词:高迁移率族蛋白B1;运动;心肺系统疾病;炎症
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The mechanism of HMGB1 in cardio-pulmonary system diseases and the progress of their prevention and treatment by exercise

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Abstract: Cardiopulmonary diseases are a leading cause of mortality worldwide, posing a severe threat to human health. As a key damage-associated molecular pattern (DAMP), high-mobility group box 1 (HMGB1) regulates inflammation, oxidative stress, and fibrosis and is considered a core mediator in the pathogenesis of these conditions. Although exercise is widely recognized as an effective non-pharmacological intervention to improve cardiopulmonary health, the specific mechanisms underlying how exercise modulates HMGB1 to exert protective effects remain fragmented and lack systematic integration. The primary objective of this review is to comprehensively summarize the expression characteristics and pathological roles of HMGB1 in major cardiopulmonary diseases by retrieving recent, relevant literature from databases including CNKI, PubMed, and others, and systematically clarifying how exercise interventions target HMGB1 for the prevention and treatment of these disorders. Through systematic integration, this article aims to provide a solid scientific basis for the clinical management of cardiopulmonary diseases and open up novel therapeutic strategies. Firstly, this paper describes the structure and dual functions of HMGB1. Structurally, HMGB1 consists of two DNA-binding domains (A-box and B-box) and an acidic C-terminal tail. Functionally, it exhibits duality depending on the cellular microenvironment: under physiological conditions, HMGB1 is localized in the nucleus and participates in DNA replication, transcription, and repair; when cells are subjected to damage or infection, it is released extracellularly to act as a pro-inflammatory mediator. Secondly, the pathogenic mechanisms of HMGB1 in specific cardiopulmonary diseases are summarized. In cardiovascular diseases, HMGB1 can activate T cells to exacerbate hypertension; accelerate the progression of myocardial infarction through apoptosis mediated by the TLR4/NF-κB pathway; and drive the development of atherosclerosis via the ox-LDL-HMGB1-endothelial injury vicious cycle. In

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pulmonary diseases, HMGB1 participates in airway inflammation in asthma through pathways such as HMGB1/TLR4/NF-κB and HMGB1/RAGE; promotes pro-inflammatory responses to aggravate ventilator-induced or sepsis-induced lung injury; and regulates macrophage polarization and vascular remodeling, which is associated with poor prognosis in chronic obstructive pulmonary disease (COPD) and pulmonary arterial hypertension (PAH). The core section of this article focuses on exercise interventions. Moderate-intensity aerobic exercise can downregulate HMGB1 expression, inhibit downstream inflammatory and fibrotic pathways, and improve the prognosis of diseases, such as hypertension, myocardial infarction, and asthma. For COPD patients, low-intensity exercise combined with pursed-lip and diaphragmatic breathing can suppress HMGB1 while avoiding airway injury. High-intensity exercise may transiently increase HMGB1 levels, whereas long-term moderate-intensity training achieves sustained inhibition of HMGB1. In addition, this review emphasizes that the regulation of HMGB1 by exercise is significantly influenced by duration, intensity, and type, underscoring the need for personalized exercise prescriptions. Based on this review, HMGB1 can serve as a core therapeutic target for cardiopulmonary diseases. In clinical practice, combining exercise interventions to downregulate HMGB1 expression and inhibit its downstream inflammatory pathways may delay disease progression, whereas inappropriate exercise should be avoided depending on the disease type. Future research should focus on investigating the mechanisms by which exercise modulates HMGB1 to ameliorate pulmonary arterial hypertension, conducting large-scale prospective trials to verify the clinical value of HMGB1 as a diagnostic and prognostic biomarker for diseases, and optimizing personalized exercise prescriptions by considering individual differences such as age and gender, thereby promoting the translation of theoretical findings into clinical applications.

Key words: HMGB1; exercise; cardio-pulmonary system diseases; inflammation

在全球范围内,心肺系统疾病,如动脉粥样硬化、慢性阻塞性肺疾病、心力衰竭等严重威胁人类健康,给社会和家庭带来沉重负担,不仅致使患者生活质量大幅下降,还伴有较高的致残率和死亡率[1-3]。

高迁移率族蛋白B1(high mobility group protein B1,HMGB1)作为一种广泛存在于真核细胞内的非组蛋白染色体结合蛋白,在细胞内参与众多生物学过程,如DNA复制、转录与修复等。当身体遭受损伤或感染时,它会被释放到细胞外,充当重要的炎症介质,引发炎症反应[4,5]。此外,HMGB1还能调控细胞死亡等,进而影响疾病的发生发展[6]。HMGB1的表达与心肺系统疾病的发生、发展紧密相关。在心肌缺血期间,HMGB1会被释放至细胞外间隙,作为损伤相关分子模式(damage-associated molecular patterns,DAMP),借助模式识别受体触发免疫反应,加剧心肌组织炎症[7];早产儿支气管肺发育不良的发生与HMGB1表达的持续升高密切关联[8]。

在心肺系统疾病的预防、治疗及康复阶段,运动是有效的非药物干预手段。适量运动能够改善心肺功能,增强机体代谢能力,提升心血管适应性,从而缓解心肺系统疾病症状,降低疾病复发风险[9,10]。适量运动还可通过抗炎、细胞自噬、抑制氧化以及神经调节等多种机制,改善心肺系统疾病的发展与预后[11,12]。

然而,HMGB1在心肺系统疾病中的作用机制以及运动干预效果至今尚不明确。深入探究 HMGB1在改善心肺系统疾病中的作用机制,以及运动防治的应用,有助于揭示运动对心肺系统的保护作用,为心肺系统疾病的治疗开辟新的靶点与思路。

1 HMGB1的结构和功能

HMGB1是高迁移率组盒蛋白家族的成员[13]。HMGB1存在于所有脊椎动物细胞核中,广泛分布于肺、脑、肝、心脏、肾等器官,同时也存在于无脊椎动物、酵母和植物中,并且可能存在于所有真核细胞中[14,15]。HMGB1由两个DNA结合域(A-box、B-box)和酸性C端尾构成,HMGB1的A-box可竞争性结合Toll样受体4(Toll-like receptor 4,TLR4)和晚期糖基化终末产物受体(receptor for advanced glycation end-products,RAGE),发挥抗炎作用;B-box是促炎的核心结构,通过激活核因子κB(nuclear factor kappa-B,NF-κB)通路诱导促炎因子释放;酸性C端尾通过磷酸化修饰调控HMGB1的核输出效率,可促进HMGB1从核内转运至胞质[16,17]。

HMGB在不同的位置具有不同功能,兼具核内稳态调控与胞外炎症信号转导双重功能。在静息状态下HMGB1主要位于细胞核内,与核活动有关,参与 DNA 修复、染色质重塑及基因转录调控[13,18]。在病理状态下,如细胞受到炎症刺激时,HMGB1从细胞核被释放到细胞质和细胞外,通过结合TLR4、RAGE等受体激活NF-κB通路,诱导促炎因子的释放,如肿瘤坏死因子-α(tumor necrosis

factor-alpha，TNF-α）、白介素-6（interleukin-6，IL-6），驱动慢性炎症[13,19-21]。

HMGB1对细胞外微环境高度敏感，其通过激活血管内皮细胞参与血管新生过程，同时可增强造血干细胞的迁移能力，在生理修复与病理炎症反应中均发挥关键作用[22]。HMGB1的氧化还原状态（主要体现为二硫键构型差异）是决定其炎症活性的核心因素：处于还原状态时，HMGB1可通过与TLR4结合，启动下游信号通路并诱导促炎因子释放；而完全氧化型HMGB1则因构象改变丧失促炎功能[23]。

2 HMGB1在心血管疾病中的机制及运动防治应用

心血管疾病作为全球范围内致死率最高的疾病，其引发的突发性死亡严重威胁人类健康。HMGB1在心血管疾病的发生发展及预后评估中占据关键地位：它通过与细胞膜表面受体结合，触发多级信号级联反应，最终诱发炎症级联放大效应，参与高血压、心肌梗死、心力衰竭及动脉粥样硬化等多种疾病的病理进程[24]。当心肌缺血、缺氧时，心肌细胞会释放大量HMGB1至血液循环，这一特性使其成为反映心肌损伤程度的高特异性指标，为心血管疾病的治疗靶点开发提供了重要方向[25]。

2.1 高血压

高血压作为全球高发的慢性疾病，其并发症导致的高死亡率始终是临床关注的重点。长期处于高血压状态下，机体可释放DAMP分子，这类物质通过激活炎症反应参与高血压的病理进展，不仅直接破坏心肌组织，还会进一步提高心脏疾病的发生风险[26]。HMGB1作为一种典型的DAMP分子，在高血压相关炎症反应中扮演重要角色，它是T细胞活化的重要驱动因子，过量释放的HMGB1可显著增强T细胞活性，形成“炎症放大循环”并加剧血压升高[27]。青年高血压患者收缩压、舒张压与血清HMGB1水平均呈正相关[28]。HMGB1在血管紧张素II诱导的平滑肌细胞表型转化过程中显著升高，血浆HMGB1的水平可以作为高血压患者血管重塑的新生物标志物[29]。

有规律的运动训练作为健康生活习惯之一，可以有效降低高血压患者继发性心血管疾病的发生风险以及死亡率[30]。因此，将有氧运动纳入高血压患者的综合治疗方案中，有望进一步降低心血管事件的风险，提高患者的生活质量。2周的中等强度运动干预降低了高血压大鼠下丘脑中小胶质细胞活化和促炎细胞因子的含量，并改善了自主神经控制，即运动诱导的下丘脑中 HMGB1/趋化因子受体4/小胶质细胞/促炎细胞因子轴的下调是一种快速的神经适应，可抵消炎症对自主神经控制的有害影响[31]。12周的有氧运动也可以通过抑制高血压大鼠模型心肌中 HMGB1/TLR4 通路的表达，抑制心肌炎症反应的发生，最终改善心肌纤维化重构[32]。

2.2 心肌梗死

心肌梗死（myocardial infarction，MI）的核心病理机制是冠状动脉血流中断引发的心肌缺血，进而导致心肌细胞坏死与损伤[33]。作为典型的DAMP，HMGB1可通过与RAGE等分子结合，激活TLR4/NF-κB信号通路，诱发炎症反应并加速心肌细胞凋亡，影响疾病进程，这一机制使其成为心梗潜在的治疗靶点[34]。血清HMGB1水平可作为评估急性心肌梗死患者病情的生物标志物[33]。此外，心梗后会伴随HMGB1及其受体TLR4的高表达，后者可能通过巨噬细胞进一步放大炎症反应，加重心功能损伤[35]。在糖尿病合并心梗模型中，HMGB1-RAGE轴通过调控细胞自噬与凋亡过程，加剧心肌缺血再灌注损伤，而抑制HMGB1或RAGE的活性可显著减轻这类损伤，这为糖尿病患者心梗的精准治疗提供了新方向[36]。

运动干预在心梗康复中的价值已得到证实：心梗后患者的HMGB1水平与运动训练强度及心脏重构的改善程度呈负相关[37,38]。具体而言，接受规律运动训练的患者血清HMGB1水平显著低于未训练者，且这种降低与左心室的有利重塑（如心室壁厚度改善、收缩功能增强）相关。因此，将运动训练与HMGB1靶向抑制剂联合应用，可为心衰患者提供更全面的治疗。不过，目前关于运动调控HMGB1治疗心梗的分子机制及下游信号通路的研究仍较匮乏，亟须基础实验进一步探索。

2.3 动脉粥样硬化

动脉粥样硬化是一种以动脉壁纤维脂肪沉积为特征的慢性免疫炎症性疾病，其发生发展由脂质代谢异常驱动，呈多灶性分布，主要累及中大型动脉[39,40]。巨噬细胞、血管内皮细胞、血管平滑肌

细胞及血小板是参与病变进展的核心细胞群体,该疾病的动态进程可大致分为早期(脂质条纹形成)与晚期(斑块破裂)阶段,而炎症作为贯穿始终的基础性病理过程,既触发疾病起始,又持续推动终末期病变恶化[39,40]。HMGB1在动脉粥样硬化中具有重要作用:在细胞内,它参与基因表达调控;在细胞外,坏死细胞与活化巨噬细胞释放的HMGB1可与RAGE结合,诱导炎性细胞因子生成并促进其与内皮细胞血栓调节蛋白相互作用,从而加速动脉粥样硬化进展[41,42]。具体而言,HMGB1通过激活血管内皮细胞,增强单核细胞的黏附能力,促使炎症细胞向血管壁浸润,这一过程是动脉粥样硬化斑块形成的重要驱动力[24,43]。氧化低密度脂蛋白(oxidized low-density lipoprotein,ox-LDL)作为该疾病的关键危险因素,可刺激HMGB1过量释放;而HMGB1水平升高又与内皮功能障碍、炎症反应强度正相关,进一步诱导内皮细胞损伤与凋亡,形成"ox-LDL-HMGB1-内皮损伤"恶性循环,加剧病变进程[44]。

运动作为有效的抗炎干预手段,其对动脉粥样硬化的防治作用与调控HMGB1密切相关。近年来的临床与实验数据表明,规律的有氧运动能促进抗炎介质IL-10的释放,同时抑制促炎介质,如IL-6、TNF-α的释放,还可直接调节HMGB1活性,这种"运动诱导的抗炎效应"可直接抵消HMGB1的促炎作用,延缓动脉粥样硬化斑块的形成与发展[45,46]。

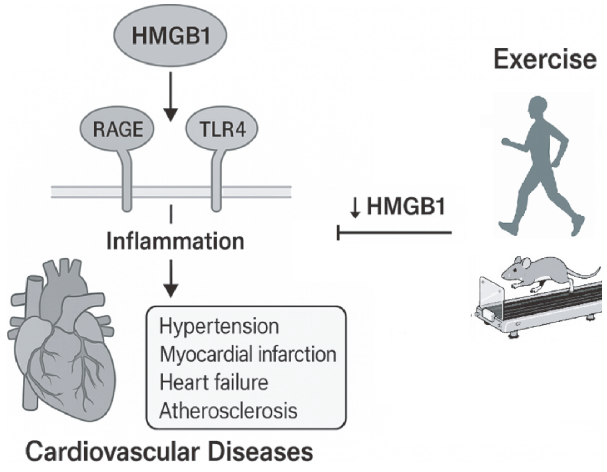

图1 运动通过调节HMGB1改善多种心血管疾病的机制
Figure 1 Mechanisms underlying the amelioration of various cardiovascular diseases by exercise via HMGB1 modulation

3 HMGB1在肺部疾病中的机制及运动防治应用

在肺部疾病的病理过程中,HMGB1通过激活多条信号通路参与炎症反应与细胞凋亡。如在动物实验中,向小鼠气管内注射HMGB1可直接损伤肺功能;而在人和小鼠肺损伤模型中,血清与肺泡液中的HMGB1水平均显著升高[47]。

3.1 哮喘

哮喘是一种慢性呼吸道炎症,常以气促、胸闷、呼吸困难、咳嗽等为主要症状[48]。HMGB1作为一种炎症因子,触发炎症反应和各种免疫反应,在哮喘发展过程中起重要作用。HMGB1还与相应受体结合,进而激活下游底物参与多种生物学效应;同时HMGB1参与多种信号通路,如HMGB1/TLR4/NF-κB、HMGB1/RAGE、HMGB1/转化生长因子-β(transforming growth factor-β,TGF-β)等,最终促进炎症[49,50]。因此,HMGB1是反映哮喘严重程度的潜在生物标志物,早期检测 HMGB1 并阻断其特异性受体是治疗哮喘的有价值的策略[51]。

运动干预不仅能改善哮喘患者的炎症,还可增强其肺功能[52]。在哮喘小鼠模型中,有氧运动通过促进肺部let-7e-5p的表达,可阻断HMGB1与其受体RAGE的结合及下游信号转导,从而减轻气道炎症和重塑进程[53]。在哮喘大鼠模型中,有氧运动可减轻气道炎症与重塑程度,同时使支气管肺泡灌洗液中HMGB1的含量显著下降,其机制是运动上调miR-129-5p等miRNA的表达,进而靶向抑制HMGB1的表达,缓解肺部炎症[54]。

3.2 呼吸机诱导的肺损伤

机械通气是治疗急性呼吸窘迫患者的重要方法,然而机械通气可引起肺损伤,使病情恶化,并增加接受呼吸机治疗的患者死亡的可能性[55]。目前认为促炎介质的变化、肺上皮细胞的凋亡及氧化应激在机械通气诱导的肺损伤中起重要作用[56,57]。成纤维细胞生长因子21(fibroblast growth factor 21,FGF21)的干预减轻了呼吸机诱导的小鼠肺损伤,机制是FGF21降低了含半胱氨酸的天冬氨酸特异性蛋白酶-1的活性,抑制了NOD样受体热蛋白结构域相关蛋白3(NLR-like receptor family pyrin domain containing 3,NLRP3)、凋亡相关颗粒样蛋白(apoptosis-associated speck-like protein containing a CARD,ASC)、IL-1β、IL-18、HMGB1和NF-κB的mRNA水平[58]。

在细胞机制研究中，常采用生理性循环拉伸细胞的方式模拟运动干预。有文献报道，5%强度的生理性循环拉伸可降低肺损伤小鼠模型中HMGB1/IL-6/信号转导与转录激活因子3(signal transducer and activator of transcription 3，STAT3)信号通路的表达水平[59]。HMGB1在呼吸机诱导的肺损伤的发生发展中具有重要作用，适宜的运动训练可通过调节HMGB1水平及其下游信号通路，减轻肺损伤和改善肺功能。

3.3 脓毒症诱导的肺损伤

脓毒症是宿主对感染的反应功能失调而引起的疾病[60]。脓毒症所致急性肺损伤在临床实践中较为常见，其特征是急性炎症、炎症细胞浸润、水肿和肺泡上皮损伤[61,62]。脓毒症患者的血清HMGB1水平升高，且与疾病严重程度密切相关，使其成为监测脓毒症严重程度的重要生物标志物[63]。通过抗体靶向抑制HMGB1分泌或阻断其活性的策略可以防止脓毒症诱导的急性肺损伤，并提高动物脓毒症模型的存活率[64]。

在小鼠脓毒症肺部损伤期间，有氧运动显著减少肺部趋化因子CXC基序配体1(chemokine C-X-C motif ligand 1，CXCL-1)、CXCL-8、IL-6、TNF-α和HMGB1 mRNA的表达，并激活IL-1RN、IL-10、SIRT1和核因子E2相关因子2(nuclear factor erythroid 2-related factor 2，Nrf2) mRNA的表达，从而减轻脓毒症诱导的肺部损伤[65]。

3.4 脊髓损伤诱导的肺损伤

脊髓损伤(spinal cord injury，SCI)是由脊髓结构与功能突发异常改变引发的病症，常伴随多种并发症，如呼吸道感染、泌尿系统感染、神经源性肠道功能障碍及压疮等[66,67]，其中呼吸系统并发症是导致 SCI 患者死亡的主要原因之一[68,69]。颈段及上胸段脊髓损伤所致的呼吸系统并发症，主要与呼吸肌麻痹及限制性呼吸功能障碍相关[70]。

大鼠SCI模型发生继发性肺损伤，其机制是激活HMGB1/TLR4/NF-κB信号通路以及上调促炎因子(IL-1β、IL-6和TNF-α)的表达[71-73]。多项研究发现，跑步机训练能够通过调控HMGB1/TLR4/NF-κB信号通路，抑制炎症反应，进而改善 SCI 大鼠的肺功能[71-73]。

3.5 慢性阻塞性肺病

慢性阻塞性肺病(chronic obstructive pulmonary disease，COPD)是一种常见的致残性呼吸系统疾病，多见于中老年人群，其特征为慢性气流受限引发的呼吸困难，同时伴随气道炎症及下呼吸道重塑[74]。HMGB1作为驱动慢性肺部炎症的核心介质，已成为COPD的炎症干预靶点及潜在生物标志物[75]。一项纳入949名COPD患者的临床队列研究显示，血清HMGB1水平升高与患者死亡风险增加相关，提示循环HMGB1水平可作为评估COPD患者预后的生物标志物[76]。在COPD患者肺组织及经烟雾刺激的体外巨噬细胞中，HMGB1蛋白水平均显著上调；HMGB1可促进巨噬细胞向M1型极化，加剧局部炎症反应，从而加速COPD的病情进展[77]。下调小鼠肺组织中HMGB1的表达，可抑制NF-κB通路，降低肺部炎症反应及上皮间质转化，从而改善烟雾诱发的COPD进程[78]。此外，在COPD小鼠模型中，miR-181a-5p可靶向结合HMGB1并抑制其表达，同时抑制NF-κB等炎症通路，减轻肺部炎症反应[79]。

缩唇腹式呼吸联合有氧/抗阻运动训练能改善COPD患者的肺功能和血气分析指标，提高运动耐力，减轻肺部炎症反应和血管重塑，值得临床推广[80]。但高强度有氧训练引起运动员气道上皮细胞损伤，并增强HMGB1的表达，加重肺部炎症和气道重塑，引发或加重COPD[81]。因此，COPD患者采用缩唇腹式呼吸+低强度有氧/抗阻运动(如弹力带训练)，可在抑制HMGB1的同时避免气道损伤。

3.6 肺动脉高压

肺动脉高压(pulmonary arterial hypertension，PAH)是一种以肺动脉压力异常升高为显著特征的病理状态[82]。HMGB1作为一种由受损细胞释放的核蛋白，参与PAH的发病。临床上COPD伴肺动脉高压患者血清HMGB1、TNF-α含量升高，能有效反映其病情进展及机体肺功能情况[83]。在PAH大鼠模型中也观察到HMGB1表达和内质网应激上调，用甘草酸抑制HMGB1或4-苯基丁酸抑制内质网应激可以减轻PAH症状[84]。雄性PAH大鼠出现肺部坏死和坏死性凋亡，缓解坏死或坏死性凋亡可以防止TLR4激活并减轻PAH的严重程度[85]。HMGB1通过调节细胞外调解蛋白激酶1/2(extracellular signal-regulated kinases 1/2，ERK1/2)/骨成型蛋白受体2(bone morphogenetic protein receptor 2，BMPR2)轴促进肺动脉平滑肌细胞增殖/迁移和肺血管重塑[86]。因此，靶向HMGB1信号通路在PAH的治疗干预中具有

潜在价值。

多项研究证实HMGB1靶向抗体或者中药复方可以通过调节HMGB1的表达改善PAH[87-91]。如靶向HMGB1的中和抗体能够抑制低氧诱导的肺动脉平滑肌细胞异常增殖、迁移,改善肺血管重构,该作用与其抑制细胞焦亡有关[87,88]。一种细胞穿透肽(αHMGB1-Cys106)可以改变HMGB1的细胞内动态,使其从细胞核中释放并随后降解,使用该穿透肽可以减轻缺氧诱导的动物PAH发生和进展[89]。复方葶苈子汤可以改善COPD-PAH大鼠肺功能、肺动脉压力、炎症反应以及气管/肺泡/肺动脉的病变情况,其作用机制与HMGB1介导的肺动脉平滑肌细胞焦亡及辅助性T细胞/调节性T细胞失衡有关[90]。槲皮素可能通过HMGB1/RAGE/NF-κB通路促进凋亡改善肺动脉高压[91]。

目前尚无探索运动通过调控HMGB1水平改善PAH的研究,这一空白亟待填补。明确运动与HMGB1以及肺动脉高压之间的潜在联系,可以为肺动脉高压的治疗开辟全新的途径。

4　运动持续时间、强度和类型对HMGB1的影响

运动作为一种可调控的生理性刺激,可以调节细胞代谢、氧化应激程度及炎症信号通路,还能调节机体内HMGB1的表达与释放。这种调节效果并非固定不变,而是取决于运动的持续时间、强度以及具体类型。

4.1　运动持续时间

有研究追踪了马拉松运动员赛前及赛后12周内细胞损伤标志物的动态变化,结果显示,51名运动员在赛后即刻,其体内 HMGB1、RAGE、核小体及高敏肌钙蛋白 T 水平均显著上升,但24~72 h内可恢复至基线水平,即马拉松运动后HMGB1从炎症细胞中释放,对心肺系统起到保护作用,能预防心肺组织的病理性重塑[92]。急性运动时,机体会释放包括HMGB1在内的多种炎症因子,这可视为机体对运动应激的一种适应性反应,是应对运动所致损伤、参与组织修复与功能适应的重要信号。

长期规律的运动训练能对HMGB1的表达产生持续性调节。经过一段时间的系统运动后,大鼠血清HMGB1水平会显著降低[71]。这一发现将为运动作为非药物干预手段应用于心肺疾病的预防与治疗提供了新的思路。

4.2　运动强度和运动类型

运动强度与类型也是影响HMGB1表达的关键因素。中低强度运动(如快走、慢跑,心率维持在

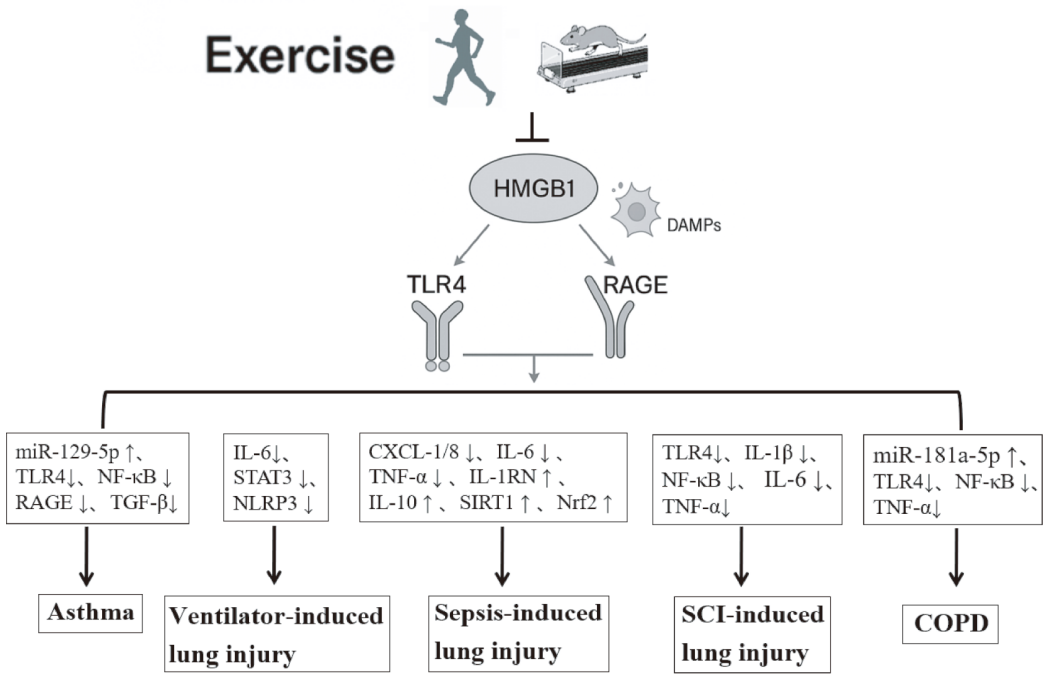

图2　运动通过调节HMGB1改善多种肺部疾病的机制

Figure 2　Mechanisms underlying the amelioration of various pulmonary diseases by exercise via HMGB1 modulation

最大心率的 40%~79%)可抑制HMGB1的异常激活。如阿尔茨海默病患者进行6个月的踏车运动(强度为最大心率的70%)后,血清中TNF-α、单核细胞趋化蛋白-1、HMGB1水平均显著低于干预前,说明有氧运动能有效抑制炎症反应的激活,减少炎症介质的合成与分泌[93]。肿瘤小鼠3周自主轮跑可下调其血清和移植肿瘤组织中HMGB1的表达,抑制肿瘤细胞增殖和促进细胞凋亡,增强免疫细胞浸润和全身炎症反应,调节肿瘤微环境中的局部抗肿瘤作用[94]。6 周中低强度跑台干预能抑制脊髓损伤大鼠肺部HMGB1/TLR4/NF-κB 信号通路的表达,减轻肺组织炎症,促进运动功能与呼吸功能的恢复[71]。此外,注射内毒素显著上调小鼠血清中乳酸和HMGB1水平,8周低强度跑台干预可有效下调脓毒症小鼠血清中乳酸和HMGB1的水平[65]。

高强度间歇训练(心率维持在最大心率的≥80%)作为一种高强度运动方式,因其高效的健康改善效果而受到关注。高强度间歇训练不仅能提升心血管健康指标,还能改善血糖、血脂等代谢参数,这些改善与HMGB1及相关炎症因子的调节密切相关[95,96]。在一项运动实验中,6周自重-高强度间歇运动可改善人类及小鼠的心脏代谢健康,调节抗炎标志物、激素水平及胰岛素敏感性,且运动后循环HMGB1水平的变化使其有望成为心脏代谢疾病的标志物[97]。不过,高强度有氧运动也会增加HMGB1的释放,这可能与细胞应激及组织缺氧有关,即运动引发的细胞应激和氧气供应不足可能触发HMGB1的释放[5]。高强度离心运动还会导致肌肉细胞发生程序性死亡,进而释放HMGB1,这可能与高强度运动引发的二次损伤性炎症所致免疫应激相关[98]。

综上,合理调整运动时间和强度不仅有助于提升运动效果,还能通过调节HMGB1表达在炎症相关疾病的预防中发挥积极作用,对制定个性化运动处方、优化运动干预策略具有重要的临床意义。

5 当前研究的局限性

尽管HMGB1在心肺疾病中的作用及运动干预的价值已得到初步证实,但该领域研究仍面临诸多核心挑战,制约了理论向临床的转化。

5.1 机制研究的深度不足

HMGB1在不同细胞中的释放效应存在差异。如上皮细胞被动释放的HMGB1主要介导屏障损伤,而巨噬细胞主动分泌的HMGB1则主要放大炎症反应。HMGB1与其他DAMP模式存在协同作用,例如HMGB1 与内毒素可通过TLR4共激活以放大炎症反应,但运动如何调控这种协同效应尚不清楚;此外,HMGB1与肠道菌群代谢产物的交互作用也未被探索。

5.2 临床转化的瓶颈

HMGB1水平与疾病严重程度相关,但缺乏大规模前瞻性研究验证其作为诊断或预后标志物的价值。如尚未确定急性期COPD的最佳诊断标准(HMGB1),也未评估与其他标志物的联合诊断效能。年龄、性别及基础疾病状态等因素会影响运动效果。年龄较大的个体在相同运动干预下,HMGB1水平的变化可能弱于年轻人,可能与年龄相关的代谢变化及运动适应能力下降有关;女性在相同运动强度下,可能因激素水平不同而呈现不同的HMGB1调节变化。建立标准化运动处方是实现个性化心肺疾病管理的关键,但目前研究多聚焦于运动持续时间和强度对HMGB1的影响。理想的运动处方应结合患者个体差异以最大化运动对心血管健康的益处。

6 结论与展望

HMGB1在心肺系统功能调节中扮演关键角色,通过调控 HMGB1有望有效控制病情进展、延缓病程、减少并发症,并为预后评估提供参考。适当强度的有氧运动可通过调控HMGB1的释放、受体结合及下游信号通路,改善高血压、心肌梗死、哮喘、肺损伤等多种心肺系统疾病。本文为运动在心肺疾病临床应用中的价值提供了更坚实的科学依据,也为制定精准运动处方奠定了基础。

未来研究可聚焦以下方向:①揭示HMGB1在不同病理状态下的动态变化及调控网络,为心血管疾病治疗提供新策略;②探索运动通过HMGB1实现跨器官调控(如心/肺-肠道菌群)的机制,绘制运动干预下跨器官调控HMGB1的动态图谱;③开发新型生物标志物,如囊泡中的HMGB1可能作为心肺疾病的早期诊断指标,血清HMGB1动态变化或可用于预测运动干预效果;④研究不同运动类型、运动强度对不同组织的特异性效应,同时关注年龄、性别及基础疾病对运动效果的调节作用,以实现个性化运动治疗;⑤推动临床转化,开展大型

临床试验及精准医学应用研究。

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