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运动对天然免疫系统的调控作用及其相关分子机制*

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摘要 天然免疫系统是机体抵御病原体入侵的第一道防线，在炎症调控、免疫稳态维持和肿瘤免疫监视中发挥重要作用。近年来，“运动即良药”理念深入人心，运动对免疫系统的影响受到广泛关注。中等强度规律运动被证实可从多个层面增强天然免疫功能。本文系统梳理了运动对皮肤黏膜屏障、分泌型免疫球蛋白（sIgA）、自然杀伤细胞、中性粒细胞、巨噬细胞、树突状细胞、补体系统和炎症因子的作用，并重点分析了AMPK、NF-κB、SIRT1、mTOR、STAT3等典型信号通路的调节机制。文中进一步探讨了运动诱导的线粒体功能增强、自噬激活、表观遗传修饰、肠道菌群重塑及代谢通路介导的免疫表型转化等新兴机制。考虑到年龄、性别、基础疾病等个体差异的影响，文章总结了不同人群的运动干预策略及其免疫效应，提出以频率、强度、时间、类型（frequency，intensity，time，type，FITT）原则为基础制定个体化运动处方的临床路径，强调了双相调节效应在感染、自身免疫病和组织修复等不同病理情境下的指导意义。综上所述，规律运动可通过多通路增强天然免疫功能，为慢性炎症、感染性疾病和免疫衰老等问题提供安全有效的干预手段。

关键词 运动，免疫系统，天然免疫，分子机制
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免疫系统是指参与机体免疫反应的细胞、组织和器官，它是人体的防御系统[1]。人体免疫系统分为特异性免疫系统和天然免疫系统[2]。天然免疫系统是机体抵御病原体入侵的第一道防线，其功能状态与感染性疾病[3]、慢性炎症[4]及癌症等密切相关[5]。运动作为一种非药物干预手段，在调节免疫功能中的作用也日益受到关注。然而，目前关于运动与天然免疫系统之间的关系的综述十分匮乏，近10年的专题论述尚未见报道。随着COVID-19的大流行，人们对免疫调节的研究越来越多。近年研究表明，运动可通过多种途径调控天然免疫系统的活性，但其具体分子机制尚未完全阐明。本文旨在系统总结运动对天然免疫系统的调控作用，并探讨其潜在的分子通路，以期为运动免疫学的科研与临床应用提供理论依据。

1 天然免疫系统概述

天然免疫系统是机体应对外来病原体入侵的初级防御机制，具有快速响应的特点，且其反应不依赖于特定抗原的识别。该系统包括物理屏障、免疫细胞和可溶性分子，这些组分通过协同作用进行免疫监视和病原清除。天然免疫系统的主要特点在于通过识别病原体相关分子模式（pathogen-associated molecular patterns，PAMPs）或损伤相关分子模式（damage-associated molecular patterns，DAMPs），进而启动一系列的炎症反应与免疫清除机制[6]。

天然免疫系统的核心组成部分包括吞噬细胞[7]、自然杀伤（natural killer，NK）细胞[8]、补体系统[9]和细胞因子[10]等。吞噬细胞，如中性粒细胞和巨噬细胞，能够通过吞噬作用清除病原体，并通过产生活性氧类（reactive oxygen species，ROS）进一步消灭入侵微生物[11-12]。NK细胞在细胞毒性反应中发挥重要作用，能够直接识别并杀伤

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被病毒感染或转化为肿瘤细胞的宿主细胞，其细胞毒性机制主要依赖于穿孔素和颗粒酶的释放[13]。补体系统通过经典途径、旁路途径和凝集素途径三条激活途径调节免疫反应，其主要功能包括标记病原体、促进免疫细胞的趋化，以及通过膜攻击复合物（membrane attack complex，MAC）直接裂解病原体[14]。此外，细胞因子如白介素（interleukin，IL）-6、肿瘤坏死因子α（tumor necrosis factor-alpha，TNF-α）和γ干扰素（interferon gamma，IFN-γ）在天然免疫应答中发挥关键作用，IL-6和TNF-α通过促进炎症反应及免疫细胞的激活，干扰素则具有抑制病毒扩散和增强抗病毒免疫的作用[15]。

在天然免疫系统的激活过程中，PRRs识别PAMPs和DAMPs后，通常通过核因子κB（nuclear factor kappa B，NF-κB）信号通路或干扰素调节因子（interferon regulatory factors，IRFs）等途径激活一系列下游免疫反应。这些信号通路的激活不仅增强免疫细胞的效应功能，还可能促进免疫记忆的建立[16]。补体系统和吞噬细胞之间的协同作用显著提高了病原体的清除效率，补体通过标记病原体，增强了吞噬细胞的识别与吞噬功能[17]。除了上述免疫成分外，树突状细胞在天然免疫中也扮演着重要角色。它们通过特有的受体识别病原并激活适应性免疫反应[17-18]。此外，以防御素等为例的抗菌肽，在天然免疫中也具有抗微生物作用，参与了机体对病原的防御[19]（图1）。

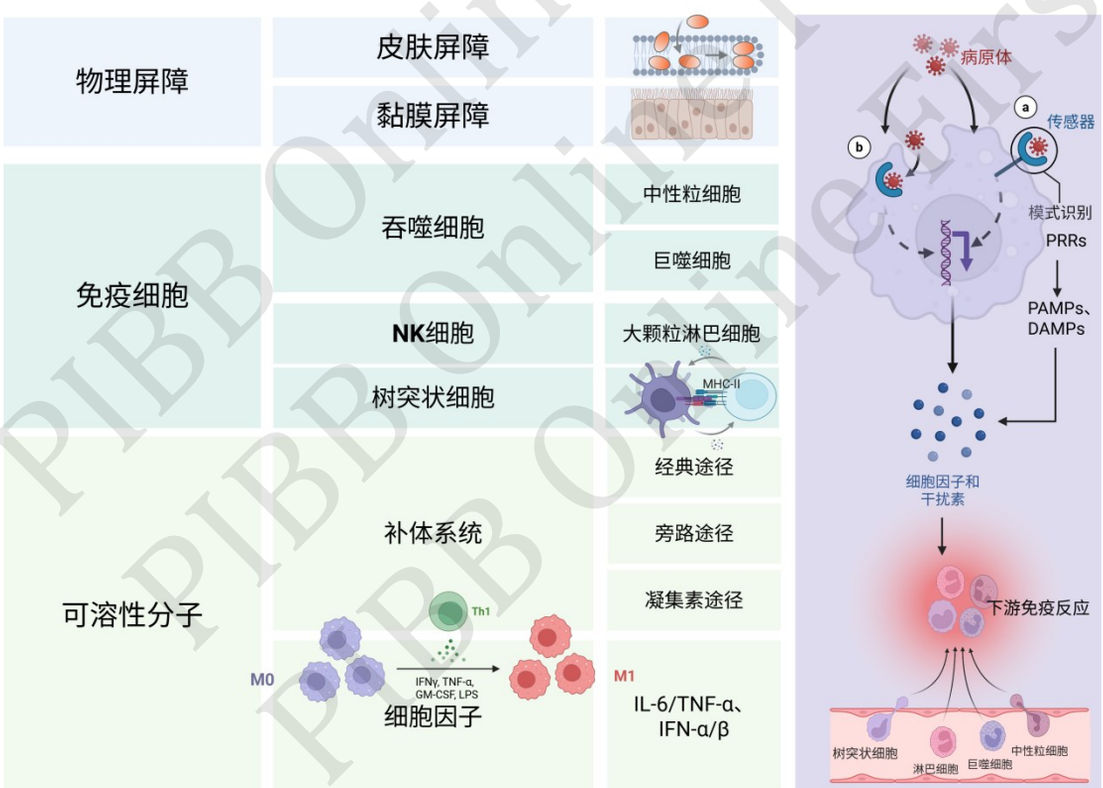

Fig.1　Core components and characteristics of the natural immune system

图1　天然免疫系统的核心组成部分及特点

NK细胞：自然杀伤细胞（natural killer cell），MHC-II：主要组织相容性复合体II类分子（major histocompatibility complex class II），PRRs：模式识别受体（pattern recognition receptors），PAMPs：病原体相关分子模式（pathogen-associated molecular patterns），DAMPs：损伤相关分子模式（damage-associated molecular patterns），IFN-γ：γ干扰素（interferon gamma），TNF-α：肿瘤坏死因子α（tumor necrosis factor alpha），LPS：脂多糖（lipopolysaccharide），IL-6：白介素-6（interleukin-6），Th1：辅助性T细胞1型（helper T cell type 1），M0：初始型巨噬细胞（macrophage 0），M1：M1型巨噬细胞（type 1 macrophage）。

2　运动对天然免疫系统的作用

天然免疫系统是机体抵御病原体入侵的第一道防线，主要包括物理屏障（如皮肤、黏膜）、补体系统及多类天然免疫细胞。越来越多的研究表明，规律的中等强度运动能在多个层面增强天然免疫系统的防御效能[20]，主要包括：强化物理屏障与分泌性免疫，增强免疫效应细胞功能，以及动态调节炎症反应状态，从而提高机体对感染和肿瘤的免疫监视与清除能力。

2.1　增强物理屏障与分泌性免疫

皮肤和黏膜屏障构成免疫防御的第一层物理屏障。运动可通过改善皮肤和肠道的血流灌注、促进上皮细胞再生以及增强紧密连接蛋白的表达，从而提升皮肤和肠道屏障的完整性与通透性调控能力[21]。此外，规律运动已被证实能显著提高唾液及肠道中分泌型免疫球蛋白A（secretory immunoglobulin A，sIgA）的水平[22]。sIgA作为黏膜免疫的关键因子，能有效阻断病原体在上皮表面的黏附与侵入，并中和多种病毒颗粒，从而在呼吸道和消化道形成第一时间的免疫保护[23-24]。

2.2　增强免疫细胞效应功能

运动可促进多种天然免疫细胞的数量和功能活性，尤其是在NK细胞、中性粒细胞和单核-巨噬细胞系统中表现尤为突出。

NK细胞是重要的细胞毒性效应细胞，能快速识别并清除病毒感染细胞和肿瘤细胞。中等至高强度的短期有氧运动显著提升外周血中NK细胞数量，并增强其穿孔素与颗粒酶B等细胞毒性因子的表达[25]。此外，运动诱导的去甲肾上腺素升高可促进NK细胞迁移至感染或肿瘤灶，进一步增强清除效应[26-27]。中性粒细胞是天然免疫系统中最早募集的细胞类型之一，具有较强的趋化、吞噬和氧爆发（ROS生成）能力[28]。运动能显著提升其对趋化因子的响应能力，增强其吞噬细菌颗粒和生成ROS的能力，从而提高早期病原清除效率[29]。单核-巨噬细胞系统同样受运动显著影响。规律运动促进$CD14^+$等单核细胞的募集与活化，并诱导其分化为M2型巨噬细胞（M2 macrophages）[30]，这类细胞具有免疫耐受和组织修复功能，并通过分泌IL-10与精氨酸酶-1等因子展现出抗炎特性[31]。此外，运动还可促进树突状细胞（dendritic cells，DCs）增强抗原摄取与主要组织相容性复合体II类分子（major histocompatibility complex class II，MHC II）表达，提升其抗原呈递功能，从而在天然免疫激活后高效引导适应性免疫反应[32]。

2.3　调节炎症反应状态

运动对机体炎症状态的影响具有典型的“双相调节效应”：在急性阶段激活炎症以启动防御反应，而在长期干预中缓解慢性低度炎症，维持免疫稳态。

在急性运动应激过程中，尤其是高强度或力竭性运动，可观察到促炎细胞因子（如IL-6、TNF-α、IL-1β）的短暂升高[33]。这一反应有助于动员免疫细胞、提高病原清除效率。IL-6作为肌源性细胞因子，在运动中同时发挥促炎与抗炎功能，可诱导IL-10释放、抑制TNF-α持续升高，从而构建有限时空范围内的炎症应答[34-35]。

在长期规律运动条件下（如3~5次/周中等强度有氧运动），则表现出对系统性慢性炎症的显著抑制作用[20]。研究发现，规律运动能显著降低血清中C反应蛋白（C-reactive protein，CRP）、TNF-α、IL-6等促炎因子水平[36-38]，同时上调IL-10、可溶性IL-1受体拮抗剂（interleukin-1 receptor antagonist，IL-1Ra）及转化生长因子β（transforming growth factor beta，TGF-β）等抗炎因子的表达[39-40]。此外，运动减少脂肪组织含量[41]、提升抗氧化系统活性[42]、改善免疫细胞代谢状态[43]，均有助于建立持久稳定的抗炎免疫微环境，有效延缓因慢性炎症所驱动的代谢性疾病与免疫老化过程[44]。

值得注意的是，高强度或持续力竭运动可能诱发“免疫开窗期”[45]，表现为NK细胞活性降低、中性粒细胞功能抑制及促炎因子暂时升高，这与急性氧化应激和糖皮质激素分泌过度有关[46]。因此，控制运动负荷与强度是实现免疫获益的关键因素。

2.4　激活补体系统通路

运动通过多维度调控补体系统增强天然免疫的机制，已成为运动免疫学研究的重要方向。现有证据表明，规律运动能够协同激活补体系统的经典、旁路及凝集素三大途径，形成动态联动的免疫防御网络[47]。在经典途径中，运动通过促进B淋巴细胞介导的抗体生成，增强抗原-抗体复合物对裂解酶识别蛋白C1q（complement component 1q，C1q）的激活效率，进而提升C4/C2转化酶活性，显著强化病原体的特异性识别能力。旁路途径的激活则体现为运动诱导的C3持续水解，其产生的C3b调理素不仅优化中性粒细胞及巨噬细胞的吞噬功能，还

通过稳定MAC的形成增强溶菌效应。凝集素途径的活化机制与运动上调甘露糖结合凝集素（mannose-binding lectin，MBL）等模式识别分子密切相关，这些分子通过靶向病原体表面保守的糖基结构，在感染早期启动补体级联反应，为后续免疫应答奠定分子基础。

补体系统的运动适应性改变对免疫稳态具有系统性调节作用。C3裂解产生的活性片段通过双重机制增强免疫效能：其趋化作用可显著提高单核细胞及中性粒细胞的定向迁移能力，同时通过共受体系统调控B细胞的活化阈值。C4的动态平衡则成为连接经典途径与凝集素途径的关键枢纽，其持续表达不仅维持补体级联反应的放大效应，更在时空维度上优化免疫应答的协同性。临床观察发现，这种调控特性可有效缩短机体应对病原体入侵的“免疫开窗期”，其机制涉及补体介导的吞噬效率提升及溶菌效应增强。值得注意的是，补体活化产物还能通过调控树突状细胞成熟状态，在先天免疫与获得性免疫间建立功能性桥梁（图2）。

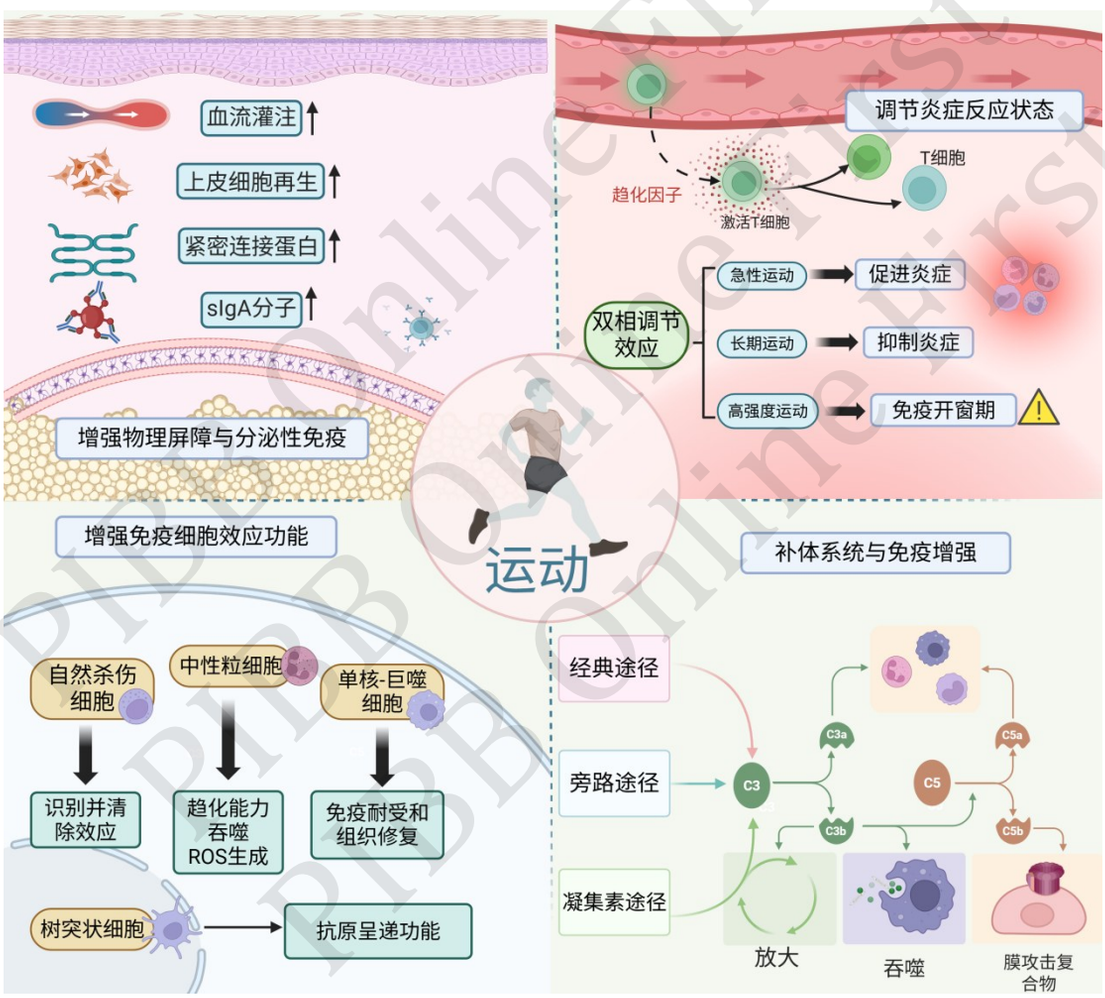

Fig.2　Exercise enhances the defense effectiveness of the natural immune system on multiple levels

图2　运动能在多个层面增强天然免疫系统的防御效能

sIgA：分泌型免疫球蛋白A（secretory immunoglobulin A）。

2.5　个体差异对运动天然免疫效应的影响

个体差异显著影响运动对先天免疫的调节效应。年龄层面：青少年期免疫细胞功能活跃，中高强度间歇训练可提升NK细胞毒性并扩增$CD16^+$亚群[48]；老年群体则面临免疫衰老（immunosenescence），其特征为慢性炎症及NK细胞功能减退，中等强度有氧运动可降低CRP水平并增强中性粒细胞氧爆发能力[49]，但高强度运动

易诱发炎症失衡[50]。性别差异表现为：雌激素通过抑制NF-κB通路使女性运动后炎症因子释放幅度降低[51]，而男性高强度运动后易出现NK细胞数量下降等免疫抑制现象[52]。基础疾病状态需针对性干预：肥胖者经8~12周联合训练可促进巨噬细胞向M2型转化；糖尿病患者通过AMP活化的蛋白质激酶（AMP-activated protein kinase，AMPK）通路激活提升NK细胞IFN-γ产量；慢性阻塞性肺疾病（chronic obstructive pulmonary disease，COPD）患者经耐力训练降低肺泡炎症；癌症患者运动中NK细胞向肿瘤微环境浸润并上调IL-15。未来需整合年龄、性激素及代谢参数构建精准干预模型优化个体化处方。（表1）

表1　不同人群运动干预对天然免疫指标的影响及潜在机制

Table 1　Effects and potential mechanisms of exercise interventions on natural immunity indicators in different populations

研究类型	对象分类	运动方式	运动时长及频率	主要先天免疫指标	免疫变化趋势	关键机制	参考文献
动物模型	C57小鼠	有氧训练	12周、60 min/d、5 d/周	肌源性IL-15、IFN-γ、NK浸润	IL-15↑、IFN-γ↑、NK细胞浸润↑、肿瘤体积↓	**调节炎症通路、延缓免疫老化**	[53]
动物模型	C57小鼠	抗阻训练	10周、4次/周	胸腺指数	胸腺指数↑	**影响免疫衰老**	[54]
动物模型	C57小鼠	高强度间歇运动	4周，5次/周	大脑胶质激活程度、IL-4、BDNF	HIIT↓胶质炎性激活、IL-4、BDNF↑	**激活胶质细胞**	[55]
动物模型	Wistar大鼠	有氧训练	10周、5次/周	淋巴细胞亚群	淋巴细胞亚群↓	**调节细胞免疫**	[56]
人群研究	青少年	高强度间歇运动	4×4 min@90% HR_max、约20 min	CD56^dim NK细胞、ILC1、总NK数量	NK细胞及ILC类群即刻↑、1小时后回落	**促进NK细胞激活**	[57]
人群研究	青少年	有氧训练	12周、3次/周	CRP、IL-6、NK活性	炎症↓、NK↑	**调节炎症通路**	[48]
人群研究	青少年	抗阻训练	6~8周、3次/周	炎症因子、全身免疫炎症指数（SII）	炎症↓、SII↓	**调节炎症通路**	[58]
人群研究	中老年	高强度间歇运动	8周、4次/周	NK密度、炎症因子	NK↑、炎症↓	**调节炎症通路**	[57]
人群研究	中老年	有氧训练	12周、3次/周、60 min/次	TLR4、IL-6、IL-1β、NLRP3	TLR4↓63%、IL-6↓、IL-1β↓	**调节炎症通路、延缓免疫老化**	[59]
人群研究	中老年	抗阻训练	45 min/次	NK、IL-6、IL-1β	NK↑、IL-6↓、IL-1β↓	**调节炎症通路**	[60]
人群研究	中老年	联合运动	≥150 min/周、12~24周	CRP、IL-10、NK	CRP↓、IL-10↑、NK↑	**调节炎症通路**	[61]
人群研究	男性	高强度有氧间歇运动（HIIT）	4~8周、4次/周	NK	NK↑	**促进NK细胞激活**	[57]
人群研究	男性	有氧训练	未提及	IL-6、NK	IL-6↑、NK↑	**自主神经激活免疫**	[62]
人群研究	女性	有氧训练	12周、3次/周	NK、TNF-α、IL-6、SOD、MDA	NK细胞活性↑、TNF-α↓、IL-6↓、SOD↑、MDA↓	**调节炎症通路、增强NK细胞功能、抗氧化防御增强**	[63]
人群研究	女性	抗阻训练	12周、3次/周	NK、TNF-α、IL-6、SOD、MDA	NK细胞活性↑、TNF-α↓、IL-6↓、SOD↑、MDA↓	**调节炎症通路、增强NK细胞功能、抗氧化防御增强**	[63]

续表

研究对象类型	研究对象分类	运动方式	运动时长及频率	主要先天免疫指标	免疫变化趋势	关键机制	参考文献
人群研究	健康人群	抗阻训练	12周、3次/周	CD4、CD8、IFN-γ、IL-2、IL-6 、IL-10	CD4↑ 、CD8↑、IL-2↑ 、IL-6↓、IL-10↑、IFN-γ↑	**改善免疫功能**	[64]
人群研究	慢病患者	有氧训练	4次/周	CD206、IL-6	CD206↓、IL-6↓	**免疫代谢重塑**	[65]
人群研究	慢病患者	抗阻训练	9个月、3次/周	血清游离轻链（Serum Free Light Chain，sFLC）、IL-6，CRP	sFLC↓、IL-6↓、CRP↓	**调节炎症通路、免疫协同**	[66]
人群研究	慢病患者	组合运动	16周、3次/周、60 min/次	CD28、TNF-α、IL-10	CD28↑、TNF-α↓、IL-10↑	**AMPK上调、调控表观遗传**	[67]

HIIT：高强度间歇训练（high-intensity interval training）、NK细胞：自然杀伤（natural killer）细胞、ILC：先天淋巴细胞（innate lymphoid cell）、CRP：C反应蛋白（C-reactive protein）、SII：全身免疫炎症指数（systemic immune-inflammation index）、TLR4：Toll样受体4（Toll-like receptor 4）、NLRP3：核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3（nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3）、BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）、IFN-γ：γ干扰素（interferon gamma）、TNF-α：肿瘤坏死因子α（tumor necrosis factor alpha）、SOD：超氧化物歧化酶（superoxide dismutase）、MDA：丙二醛（malondialdehyde）、sFLC：血清游离轻链（serum free light chain）、AMPK：AMP活化的蛋白质激酶（AMP-activated protein kinase）。

3　运动对天然免疫系统作用的分子机制

3.1　细胞信号通路调控

近年来大量研究表明，运动能够激活AMPK信号通路，并通过多途径抑制NF-κB介导的促炎反应，从而调节天然免疫系统的功能。AMPK作为细胞能量代谢的关键感应器，能够响应运动过程中三磷酸腺苷（adenosine triphosphate，ATP）耗竭与细胞内Ca^{2+}浓度升高所导致的能量失衡状态。上游激酶肝激酶B1（liver kinase B1，LKB1）[68]和Ca^{2+}/钙调蛋白依赖性蛋白质激酶（Ca^{2+}/calmodulin-dependent protein kinase kinase，CaMKKβ）[69]磷酸化激活AMPK，尤其是其α亚基Thr172的磷酸化对于形成活化复合物至关重要[70]。活化的AMPK可通过多种机制负向调控NF-κB信号通路。其一，AMPK可通过增强κB抑制蛋白α（inhibitor of kappa B alpha，IκBα）的稳定性，抑制IκB激酶（IκB kinase，IKK）复合物的活性，进而阻止NF-κB p65亚基转位入核，减少IL-1β、TNF-α等促炎因子的转录[71]。其二，AMPK的活化可增强沉默信息调节因子1（sirtuin 1，SIRT1）的表达与活性[72]，SIRT1通过去乙酰化NF-κB p65亚基的赖氨酸残基，抑制其转录活性，进一步下调促炎细胞因子的合成[73]。动物实验亦发现，长期有氧运动能够显著上调老年小鼠骨骼肌与免疫相关组织中的AMPK与SIRT1蛋白水平，同时抑制Toll样受体（Toll-like receptor，TLR）/NF-κB信号轴的激活，促使巨噬细胞向抗炎表型转化，改善年龄相关的慢性低度炎症状态[74]。

此外，运动对促分裂原活化的蛋白质激酶（mitogen-activated protein kinase，MAPK）通路的调控同样关键。p38 MAPK通过激活下游的MK，进而稳定炎症相关mRNA，促进M1表型的基因表达。而运动通过上调MAPK磷酸酶1（MAPK phosphatase-1，MKP-1）的表达，促进p38 MAPK的失活，进而诱导Arg-1、IL-10等M2表型标志物的表达，实现免疫耐受与组织修复[75]。

运动过程中，骨骼肌作为内分泌器官可释放肌源性IL-6（myokine IL-6），其通过结合IL-6信号受体复合物（gp130-IL-6 receptor complex，gp130-IL-6R），激活JAK1/2并磷酸化信号转导及转录激活蛋白3（signal transducer and activator of transcription 3，STAT3）（Tyr705位点），促进STAT3二聚体转位入核，诱导IL-10、细胞因子信号抑制蛋白3（suppressor of cytokine signaling，SOCS3）等抗炎因子表达[76]。SOCS3可负反馈抑制IL-1/IL-6类促炎因子的信号转导，进一步维持炎症反应的动态平衡[77]。

3.2　线粒体功能与自噬

运动对免疫细胞能量代谢的重塑是其免疫调节功能的重要基础。运动通过促进线粒体生物合成（过氧化物酶体增殖物激活受体γ辅激活因子1α（peroxisome proliferator-activated receptor gamma coactivator 1-alpha，PGC-1α）介导）[78]和自噬

（如轻链蛋白3（microtubule-associated protein 1A/1B-light chain 3，MAP1LC3，LC3）表达增加）[79]，清除受损细胞器，维持免疫细胞稳态。运动通过CaMKKβ和AMPK信号通路上调PGC-1α的表达[80]。作为转录共激活因子，PGC-1α与核呼吸因子1/2（nuclear respiratory factor 1/，NRF1/2）结合，促进线粒体转录因子A（mitochondrial transcription factor A，TFAM）的表达，驱动线粒体DNA的转录，从而提升氧化磷酸化（oxidative phosphorylation，OXPHOS）能力[81]。在巨噬细胞和树突状细胞中，增强的线粒体代谢支持M2表型，并抑制ROS的产生[82]。进一步地，运动可通过AMPK磷酸化自噬激活激酶1（Unc-51 Like Autophagy Activating Kinase 1，ULK1）（Ser555位点）并抑制哺乳动物雷帕霉素靶蛋白复合体1（mammalian target of rapamycin complex 1，mTORC1）活性，激活自噬起始复合物，增强自噬流[83]。随后，Beclin-1与液泡蛋白分选34（vacuolar protein sorting 34，VPS34）复合物介导隔离膜的形成，LC3-I在自噬相关蛋白（autophagy-related protein，ATG）7/3的介导下脂化成LC3-II，参与自噬体膜的延伸。该机制对于清除受损线粒体、调控NLRP3的活性尤为重要。

3.3　表观遗传调控

运动作为外源性生理刺激，能够通过表观遗传机制塑造免疫细胞的功能性转录图谱。运动通过DNA甲基化、组蛋白修饰及非编码RNA（如miR-155、miR-21）调节免疫相关基因表达[84-85]。在DNA甲基化方面，运动可通过下调DNA甲基转移酶（DNA methyltransferase，DNMT）的活性或调控TET酶的表达，改变免疫相关基因启动子（如TLR4、IL-1β）的甲基化状态[86]。研究显示，在单核细胞中，耐力运动可显著减少TLR4启动子区域的CpG二核苷酸序列（cytosine-phosphate-Guanine，CpG）甲基化，增强其对脂多糖（lipopolysaccharide，LPS）的敏感性，从而优化免疫响应[87]。运动同样影响组蛋白去乙酰化酶（histone deacetylase，HDAC）和组蛋白乙酰转移酶（histone acetyltransferase，HAT）的活性，改变炎症相关基因的染色质可及性[88]。在组蛋白修饰层面，运动诱导SIRT1上调，导致第9位赖氨酸修饰的组蛋白H3（histone H3 lysine 9，H3K9）与第16位赖氨酸修饰的组蛋白H4（histone H4 lysine 16，H4K16）位点去乙酰化，抑制炎症相关增强子区域的开放性[89]。此外，运动还可能通过调节多梳基因*EZH2*活性，增强H3K27me3沉默标记，抑制促炎基因的表达[90]。在非编码RNA方面，运动影响多种免疫调节性微RNA（microRNA，miRNA）的表达。运动下调miR-155（一种M1表型促进因子），上调miR-21，从而调节炎症微环境[91]。miR-21还可通过靶向磷酸酶及张力蛋白同源物（phosphatase and tensin homolog，PTEN），增强磷脂酰肌醇3-激酶/蛋白激酶B通路（phosphoinositide 3-kinase/protein kinase B，PI3K/AKT）信号，促进巨噬细胞M2极化及调节性T细胞（regulatory T cells，Tregs）的扩增，进一步塑造抗炎微环境[92-93]。

3.4　肠道菌群相互作用

运动通过调节肠道菌群结构，特别是增加短链脂肪酸（short chain fatty acids，SCFAs）菌群的丰度，促进免疫稳态[94]。SCFAs，如乙酸盐、丙酸盐、丁酸盐通过激活免疫细胞及肠上皮细胞表面的G蛋白偶联受体（G蛋白偶联受体（G-protein-coupled receptor，GPCR）41/游离脂肪酸受体（free fatty acid receptor，FFAR）3、GPCR43/FFAR2、GPCR109A/羟基羧酸受体2（hydroxycarboxylic acid receptor 2，HCAR2）），发挥免疫调节作用[95-97]。这些受体的激活在免疫调节中发挥关键作用：SCFAs通过GPR43促进Tregs的扩增和功能增强，进而抑制过度的免疫反应，维持免疫耐受性[98]。丁酸盐等SCFAs可抑制HDAC活性，增加转录因子叉头盒蛋白P3（forkhead box protein P3，Foxp3）启动子区组蛋白乙酰化水平，从而上调Foxp3的表达，促进Tregs的分化和功能[99]。SCFAs通过GPCRs信号通路促进肠道上皮细胞紧密连接蛋白的表达，增强肠道屏障的完整性，防止病原体和毒素的侵入[96]。

运动对肠道菌群的调节还涉及肠-脑-免疫轴的复杂相互作用：运动可增加黏蛋白阿克曼菌（*Akkermansia muciniphila*）的丰度[100]，这种菌株通过其表面膜蛋白与肠上皮细胞相互作用，激活Wnt信号通路，增强肠道屏障功能，减少炎症反应[101]。同时，肠道菌群代谢产物，如SCFAs，能够通过激活肠道内分泌细胞，促进神经递质的释放，进而通过迷走神经影响中枢神经系统，调节免疫反应和炎症状态[102]（图3）。

3.5　代谢通路与免疫调控

运动对先天免疫的代谢调控核心在于重塑免疫

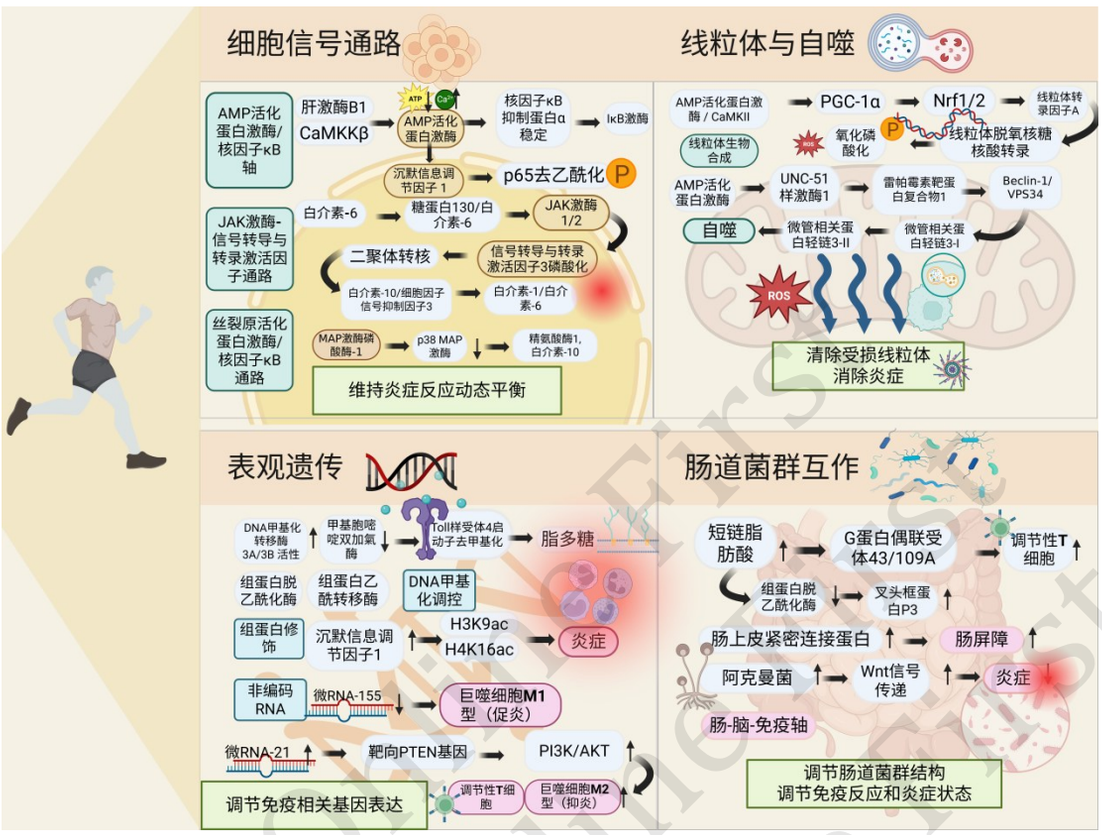

Fig.3　Molecular mechanisms of the action of exercise on the natural immune system

图3　运动对天然免疫系统作用的分子机制

CaMKKβ：钙离子/钙调素依赖性蛋白激酶激酶β（calcium/calmodulin-dependent kinase kinase beta）、CaMKII：钙/钙调素依赖性蛋白激酶II（calcium/calmodulin-dependent kinase II）、PGC-1α：过氧化物酶体增殖物激活受体γ辅激活因子1α（peroxisome proliferator-activated receptor gamma coactivator 1-alpha）、Nrf2：核转录因子红系2相关因子/2（nuclear factor-erythroid 2-related factor）、Beclin-1：盘卷肌球蛋白样Bc1-2-相互作用蛋白（Beclin1）、VPS34：液泡分选蛋白（vacuolar protein sorting 34）、H3K9ac：组蛋白 H3第9位赖氨酸残基乙酰化（histone H3 lysine 9 acetylation）、H4K16ac ：组蛋白H4第16位赖氨酸残基乙酰化（histone H4 lysine 16 acetylation）、PTEN：磷酸酯酶与张力蛋白同源物（PTEN）、PI3K：磷脂酰肌醇3激酶（phosphoinositide 3-kinase）、AKT ：蛋白激酶B（protein kinase B）

细胞能量代谢程序，其机制涵盖线粒体功能重编程、代谢通路切换及代谢物信号介导的免疫表型转化。有研究指出，运动诱导的代谢重塑不仅影响能量供应，还通过调控免疫细胞的功能状态与极化方向，在慢性炎症与免疫稳态维持中发挥关键作用[103]。线粒体作为代谢中枢，在运动诱导下通过PGC-1α/TFAM轴增强生物合成与自噬能力，清除损伤线粒体并抑制线粒体DNA（mitochondrial DNA，mtDNA）泄漏，从而降低NLRP3炎症小体异常激活风险[104]。关键代谢枢纽AMPK–mTOR通路动态调控免疫细胞功能表型：运动激活AMPK-SIRT1-PGC1α级联反应，抑制mTORC1信号，促使巨噬细胞从糖酵解依赖的M1促炎型向氧化磷酸化主导的M2抗炎型转化[105]，同时优化中性粒细胞趋化与NK细胞杀伤效能。运动衍生的代谢物更直接参与免疫调节：乳酸通过平衡炎症因子释放与抗原呈递能力维持免疫动态平衡；β-羟基丁酸（beta-hydroxybutyrate，BHB）抑制NLRP3炎症小体发挥系统性抗炎作用[106]；SCFAs则经GPR43受体激活促进Treg分化与巨噬细胞耐受表型形成[107]。此外，运动通过减少DAMPs（ATP/mtDNA）释放，下调TLR/NOD样受体（NOD-like receptor，NLR）通路敏感性，重设炎症阈值并诱导"训练免疫"效应——表观遗传修饰（如乙酰辅酶A合成酶调控）使天然免疫细胞获得持续高应答能力[108]。这种代谢-免疫重塑网络，为运动增强抗感染防御及抑制慢性炎症提供了分子基础。

4　运动干预的临床转化与实践路径

运动作为非药物的免疫调节手段，在基础研究中已显示出显著效益，但其临床转化仍面临实际操作标准缺失、适用人群界定模糊及干预效果评估不足等障碍。为了实现从实验室到临床的有效过渡，亟需建立科学、标准化且可个体化调整的“运动处方”体系，使运动干预成为疾病管理和免疫调节的系统工具。

临床运动处方应依据频率、强度、时间、类型（frequency，intensity，time，type，FITT）原则制定，结合个体健康状况与免疫目标动态调整。研究显示，中等强度的有氧运动（50%~70%最大心率，3~5次/周，30~60 min/次）能显著提升NK细胞活性和抗原呈递，增强天然免疫功能[109-110]。抗阻训练则可通过分泌IL-15和irisin等肌肉因子，调节免疫细胞代谢，联合训练可实现更广泛的系统性免疫效应[111]。

由于天然免疫系统与炎症反应之间存有高度动态的双向调节，运动对其影响在感染、损伤与自身免疫病等不同状态下具有复杂的双相效应。运动对天然免疫-炎症平衡的双相调节效应在不同病理情境下呈现差异化机制：感染期适度运动通过肌肉因子（IL-6等）增强免疫细胞活性降低感染风险[112]，但高强度训练可诱发CRP/TNF-α升高及氧化应激[113]，故急性感染期需规避剧烈负荷以抑制免疫抑制风险。组织修复期低-中强度运动通过血流优化及代谢重编程，驱动巨噬细胞向修复型M2极化，促进成骨/肌再生[114]；而急性期高负荷训练则因MMP-9/金属蛋白酶组织抑制因子1（tissue inhibitor of metalloproteinase-1，TIMP-1）失衡加剧炎症损伤[115]。自身免疫性疾病患者经规律中高强度训练可降低CRP、IL-6等炎症标志物[116-117]，但疾病活动期需暂停高强度运动，以防人类白细胞抗原DR+（human leukocyte antigen-DR positive，HLA-DR+）/CD38+双阳性T细胞扩增激发病理应答[118]。

针对不同生理或病理背景下的运动实践应科学设计。对感染易感人群或亚健康个体，建议采用中等强度有氧运动以激活免疫细胞动员和维持抗炎平衡；感染急性期或高炎症状态下，则应避免剧烈运动，选择散步、拉伸等低强度活动以维持代谢稳态。对于损伤康复阶段个体，运动强度应随损伤类型与修复阶段分期调整，早期主张“低强度+高频率”原则，逐步过渡至中等强度的功能性训练。自身免疫患者则推荐开展周期性、个体化的多模态运动处方（如结合太极、低冲击瑜伽与抗阻训练），以提升Treg功能，减缓慢性炎症。

未来应加强对运动剂量-反应曲线（dose–response curve）的研究，明确不同运动形式、时长与强度对免疫路径的特异性影响，为疾病防控和精准康复提供更有力的实证基础与个体化运动干预策略。

5　结论与展望

天然免疫系统作为机体抵御病原体侵袭的第一道防线，依赖多种免疫细胞、可溶性因子及物理屏障的协同作用，实现对病原体的快速识别与清除。近年来，关于运动干预对天然免疫系统调控作用的研究逐渐深入，揭示了其在免疫防御增强、炎症调节及免疫稳态维持中的多维度积极效应。本综述系统梳理了运动对天然免疫系统的功能影响及其潜在分子机制，强调了规律性中等强度运动在增强皮肤与黏膜屏障、提升sIgA水平、激活NK细胞与中性粒细胞功能、诱导M2型巨噬细胞分化、激活补体通路以及缓解慢性炎症等方面的广泛作用。这些免疫学效应不仅显著提升了机体对感染与肿瘤的免疫监视能力，也为防控与缓解慢性炎症性疾病提供了重要的生活方式干预策略。在分子机制层面，运动通过激活AMPK/SIRT1轴、调控NF-κB与STAT3信号、优化线粒体功能、自噬过程以及表观遗传状态，实现了对免疫细胞功能和表型的动态调控，构建了从能量代谢到基因表达的多层次免疫调节网络。此外，运动诱导的肌源因子（如IL-6）亦在抗炎反应中发挥桥梁作用，进一步彰显了骨骼肌作为免疫调节器官的内分泌特性。补体系统的激活和重塑，为快速而高效的免疫清除反应提供了分子基础，并通过树突状细胞的功能调节促进天然免疫与适应性免疫之间的联动。

尽管当前研究已初步揭示运动调控天然免疫系统的多重效应及分子机制，但仍存在诸多待解的问题。首先，运动干预对不同亚型免疫细胞（如M1/M2型巨噬细胞、不同表型的NK细胞）功能分化与重塑的精细调控机制尚不明晰；其次，不同类型、频率、强度与持续时间的运动干预对免疫效应的剂量反应关系尚缺乏系统研究。此外，个体差异（如年龄、性别、基础健康状态）对运动免疫效应的调节作用仍需进一步探索。未来研究应加强多组

学联合分析，结合代谢组、单细胞转录组和空间转录组等前沿技术，揭示运动干预下天然免疫网络的重塑过程。同时，应推动临床转化研究，探索运动对感染性疾病、慢性炎症性疾病及肿瘤患者免疫功能改善的应用价值。随着研究的深入，运动有望成为精准免疫调控的重要策略之一。

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RegulatoryEffects of Exercise on The Aatural Immune System and Related Molecular Mechanisms*

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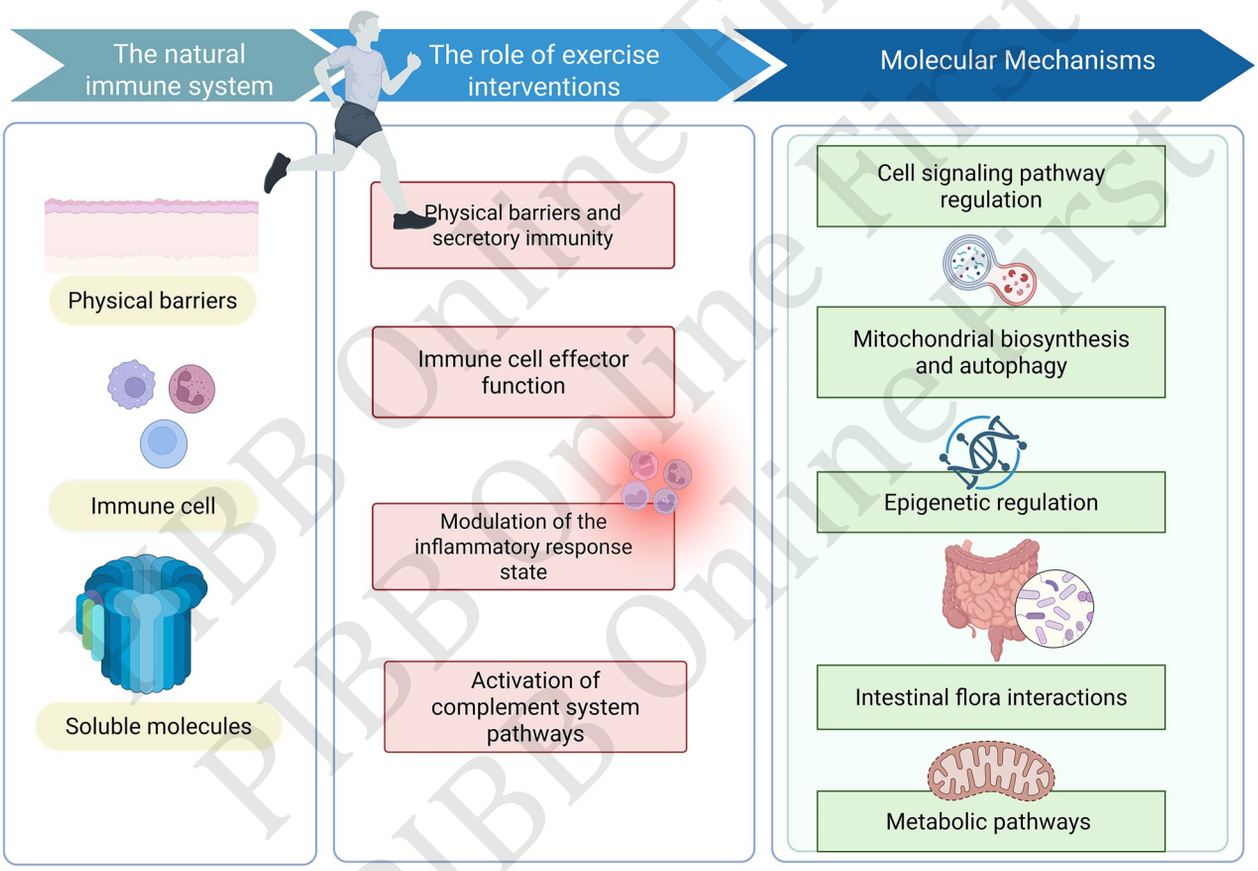
Graphical abstract



Abstract　The innate immune system serves as the body's first line of defense against pathogens and plays a central role in inflammation regulation, immune homeostasis, and tumor immunosurveillance. In recent years, with the growing recognition of the concept "exercise is medicine," increasing attention has been paid to the immunoregulatory effects of physical activity. Accumulating evidence suggests that regular, moderate-intensity exercise significantly enhances innate immunity by strengthening the skin–mucosal barrier, increasing levels of secretory immunoglobulin A (sIgA), and improving the functional capacity of key immune cells such as natural killer (NK) cells, neutrophils, macrophages, and dendritic cells. It also modulates the complement system and various inflammatory mediators. This review comprehensively summarizes the effects of exercise on each component of the innate immune system and highlights the underlying molecular mechanisms, including activation of AMP-activated protein kinase (AMPK), inhibition of nuclear factor-kappa B (NF-κB), enhancement

of mitochondrial function *via* the PGC-1α/TFAM axis, and initiation of autophagy through the ULK1/mTOR pathway. Emerging mechanisms are also discussed, such as exercise-induced epigenetic modifications (*e. g.*, histone acetylation and miRNA regulation), modulation of the gut microbiota, and metabolite-mediated immune programming (*e. g.*, short-chain fatty acids [SCFAs], β -hydroxybutyrate). The effects of exercise on innate immunity vary considerably among individuals, depending on factors such as age, sex, and comorbidities. For example, adolescents exhibit enhanced NK cell mobilization, whereas older adults benefit from reduced chronic inflammation and immune aging. Sex hormones and metabolic conditions (*e. g.*, obesity, diabetes, chronic obstructive pulmonary disease, cancer) further modulate the immune response to exercise. Based on these insights, we propose a personalized approach to exercise prescription guided by the FITT principle (Frequency, Intensity, Time, and Type), aiming to optimize immune outcomes across diverse populations. Importantly, given the dual role of exercise in immune activation and regulation, caution is warranted: while moderate exercise enhances immune defense, excessive or high-intensity activity may induce transient immunosuppression. In pathological contexts such as infection, autoimmune diseases, or tissue injury, exercise intensity and timing must be carefully adjusted. This review provides practical guidelines for exercise-based immune modulation and underscores the need for dose–response studies and advancements in precision exercise medicine. In conclusion, exercise represents a safe and effective strategy for enhancing innate immune function and mitigating chronic inflammatory diseases.

Key words exercise, immune system, innate immunity, molecular mechanisms
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