PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2025,52(3):669~680
www.pibb.ac.cn

运动改善胰岛素抵抗的新视角：代谢重编程诱导训练免疫耐受*

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摘要 近年发现先天免疫同样具备免疫记忆特征，即训练免疫（trained immunity，TI）。已有研究表明，高脂膳食诱导先天性免疫细胞TI，致使其对继发性代谢紊乱的免疫应答显著增强，是诱发胰岛素抵抗（insulin resistance，IR）及相关代谢性疾病的重要机制。通过诱导先天性免疫细胞TI耐受来打破IR与TI间的恶性循环，抑制多种IR继发性代谢紊乱引起的过度炎症反应，是早期防治相关代谢性疾病的新策略。众所周知，运动干预发挥抗炎效应促进机体代谢稳态，但目前运动抗炎效应的潜在机制尚未阐明。最近发现，TI耐受过程主要由代谢重编程驱动，而运动已被证明能调节多种细胞的代谢重编程。三羧酸循环中间产物衣康酸（itaconate）是最新发现的平衡先天性免疫细胞TI及其耐受的中心调控点，且运动可调节免疫反应基因1（IRG1）/itaconate信号。因此，深入探讨运动干预IR中TI及TI耐受、代谢重编程和IRG1/itaconate信号间的相互关系，总结运动改善IR的TI耐受机制，可为运动在IR及相关代谢性疾病中的防治效应提供理论支持，为针对运动不耐受者的模拟药物开发提供新思路。

关键词 训练免疫，胰岛素抵抗，运动，代谢重编程，衣康酸
中图分类号 R392.1，Q493 **DOI**：10.16476/j.pibb.2024.0365 **CSTR**：32369.14.pibb.20240365

随着人口老龄化及人们生活方式改变，全球范围内2型糖尿病（diabetes mellitus type 2，T2DM）、非酒精性脂肪性肝病（non-alcoholic fatty liver diseases，NAFLD）、动脉粥样硬化等代谢性疾病发病率骤增，成为严重威胁人类健康的世界性公共卫生问题[1]。胰岛素抵抗（insulin resistance，IR）是当前公认的多种代谢性疾病的共同发病基础[2]。现有多项证据表明，训练免疫（trained immunity，TI）是诱发IR及相关代谢性疾病的重要机制[3-5]，而通过诱导先天性免疫细胞TI耐受来打破IR与TI间的恶性循环，抑制多种IR继发性代谢紊乱引起的过度炎症反应，是早期防治相关代谢性疾病的新策略[6-8]。

作为改善IR及相关代谢性疾病的有效手段，运动发挥全身性抗炎效应来促进机体代谢稳态的积极作用已得到诸多验证[9-10]，但其抗炎机制尚未阐明。最近研究发现，TI耐受过程主要由代谢重编程驱动[11]，而运动已被证明能调节多种细胞的代谢重编程[12-13]，提示运动可能通过调节先天性免疫细胞代谢重编程诱导TI耐受。作为三羧酸循环的重要中间代谢物，衣康酸（itaconate）是最新发现的平衡先天性免疫细胞TI及其耐受的中心调控点，介导TI耐受[14]，且免疫反应基因1（immune-responsive gene 1，IRG1）/itaconate可靶向抑制糖酵解关键酶3-磷酸甘油醛脱氢酶（glyceraldehyde 3-phosphate dehydrogenase，GAPDH）的酶活性，调节先天性免疫细胞代谢重编程[15-16]，而运动可调节IRG1/itaconate信号[17-19]，提示运动可能通过诱导IRG1/itaconate信号调节巨噬细胞代谢重编程，发挥抗炎效应。基于以上证据，推测运动可能通过调节衣康酸水平来对先天性免疫细胞进行代谢重编程，诱导TI耐受，减轻IR继发性代谢紊乱导致的过度炎症，进而发挥改善IR和防治相关代谢性疾病的抗炎效应。因此，本文深入探讨运动干预IR

* 国家自然科学基金（32200944），江苏省高校“青蓝工程”和江苏省体育科学研究所基金（BM-2023-03）资助项目。
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收稿日期：2024-08-12，接受日期：2024-10-08

中的TI与TI耐受、代谢重编程和IRG1/itaconate信号间的相互关系，总结运动改善IR的TI耐受机制，一方面为运动在IR及相关代谢性疾病中的防治效应提供理论支撑，另一方面为针对运动不耐受者的模拟药物开发提供新思路。

1 训练免疫与胰岛素抵抗相关代谢性疾病

1.1 训练免疫（TI）概念及特性

在经典理论中，免疫反应分为先天性免疫反应和适应性免疫反应[20]。先天性免疫反应主要由单核/巨噬细胞、中性粒细胞、自然杀伤细胞等介导，通过模式识别受体识别具有病原体相关分子模式或损伤相关分子模式的生物大分子来募集免疫细胞，反应速度快，不具特异性[21-22]。适应性免疫反应主要由T淋巴细胞和B淋巴细胞介导，免疫应答产生较慢，依赖于基因重组，具抗原特异性，淋巴细胞受到刺激后部分分化为记忆细胞，可建立免疫记忆[23]。然而，近年来这一观点受到了挑战。最近研究发现，先天免疫系统也具备免疫记忆，即先天免疫系统的细胞在病原体攻击后也可以获得类似记忆的能力，从而在受到相同或不同刺激物的二次刺激时表现出增强的反应性，即TI[24-25]。

了解TI的特性将有助于更好地理解宿主防御机制和免疫介导疾病的发病机制。TI可分为中枢性TI和外周性TI[26]。中枢性TI主要由骨髓祖细胞及其他先天性免疫细胞前体介导，是长期免疫记忆的内在基础[27]。外周性TI则主要由血液循环和外周组织中的单核/巨噬细胞、自然杀伤细胞等介导，主要负责执行免疫反应[28]。研究表明，与适应性免疫相比，TI的显著特点主要表现为对二次刺激的反应性增强不针对特定病原体，即不具有抗原特异性[29]。例如，最新流行病学研究显示卡介苗、麻疹疫苗和口服脊髓灰质炎疫苗等灭活疫苗均可通过诱导TI来非特异地预防目标疾病以外的其他感染，且除外源感染外，一些内源刺激如尿酸、氧化型低密度脂蛋白、儿茶酚胺和醛固酮等也可诱导先天性免疫细胞产生免疫记忆，诱发TI[30-31]。同时，TI主要由先天性免疫细胞代谢重编程和表观遗传修饰所驱动，不依赖于适应性免疫，且初次刺激消失后炎症反应可降至基础水平，但免疫记忆可持续数周至数月，其间若出现二次感染则表现出更强的免疫反应[32-33]。

尽管通过诱导TI可有效提高机体免疫防御能力以预防多种病原体的再次感染[30-31]，同时TI在多种肿瘤治疗中发挥特殊作用[34]。但随着对TI认识的不断深入，最新研究发现，TI与炎症性肠病、痛风、过敏、动脉粥样硬化及其临床后果心肌梗死与中风等一系列疾病发生发展密切相关[35-36]。在这些疾病中，炎症反应的加剧会加快疾病发展进程，调节炎症是预防相关疾病及并发症的常用策略，TI则是其中的重要治疗靶点。因此，防止或抑制TI成为许多慢性炎症相关疾病的有效治疗方式。此外，最近研究还发现器官移植同样诱发TI[37]，而通过在小鼠心脏移植模型中使用髓系分化初级反应蛋白质88（myeloid differentiation primary response protein 88，MyD88）抑制剂来抑制TI，可有效地使髓系细胞从促炎性重新平衡到抗炎性，显著延长异体移植存活时间[38]。因此，在不同的疾病背景下，对TI的调节可能成为有效的治疗范式[39]。根据病情不同，通过诱导TI来辅助治疗特定的癌症或治疗与败血症有关的免疫麻痹可能是有益的，而另一个令人兴奋的治疗前景是在慢性炎症性疾病中抑制过度的TI和在器官移植中防止出现有害的TI[40]。

1.2 训练免疫是诱发胰岛素抵抗相关代谢性疾病的重要因素

IR是当前公认的T2DM、NAFLD、动脉粥样硬化等多种代谢性疾病的共同发病基础，其致病过程一般为：IR→继发性高胰岛素血症→糖脂代谢紊乱及血管内皮细胞损伤→T2DM、NAFLD、心脑血管疾病等[2]。细胞、动物、人体等不同水平研究表明，代谢性疾病发病过程与免疫过程紧密相关：能量过剩诱发的慢性炎症与IR联系密切，二者同时存在、相互促进，共同诱发代谢性疾病[41-42]。

如前所述，TI是一把双刃剑，一方面其增强宿主免疫防御能力以预防相同或不同病原体的再次感染[30-31]，但过度的TI则导致IR及慢性炎症，对机体造成损害，诱发T2DM、NAFLD、动脉粥样硬化等多种代谢性疾病[43-44]。最新研究表明，高糖高脂膳食可激活先天免疫，诱发IR并产生免疫记忆，之后多种继发性代谢紊乱均可触发先天免疫过度激活，诱导相关代谢性疾病，这也是目前靶向高糖高脂等单一因素治疗和管理IR及相关代谢性疾病效果不佳的重要原因[3-5]。如Christ等[3]证实，巨噬细胞等先天性免疫细胞可识别高糖高脂膳食诱发的“无菌”炎症信号并形成免疫记忆，诱发TI，即使在转为正常膳食后这一先天免疫记忆仍然存在，继发性脂多糖刺激诱发增强的先天免疫反应，

导致慢性炎症和IR相关代谢性疾病。Charles-Messance等[4]发现，早在代谢性疾病发病前，高脂膳食即可诱导IR和先天性免疫细胞TI，进而诱发相关疾病，提出未来关键的研究方向是探索如何将TI作为治疗靶点来防治IR及相关代谢性疾病。Chou等[5]也提出，IR及相关代谢性疾病防治研究重点应聚焦于打破先天免疫炎症和IR间的恶性循环，进而改善机体代谢功能紊乱。因此，高脂膳食诱导的TI是诱发IR及相关代谢性疾病的重要因素，而终止这一恶性循环的关键环节是提供外源性干预来逆转TI，进而改善IR及相关代谢性疾病。

2　运动诱导训练免疫耐受

2.1　训练免疫耐受概念及特征

不同于TI引起的继发性刺激后免疫反应的增强，TI耐受则指接受继发性刺激时免疫反应被抑制，促炎因子分泌减少，发挥抗炎效应[45-46]。与TI相比，TI耐受的特点（图1）主要表现为：初次刺激消失后TI与TI耐受免疫反应能力均降低至基础水平，但二次感染时，二者则分别上调和下调免疫反应性[47]。其共同调节机制是微生物的特殊成分和细胞因子诱导表观遗传和代谢重编程来调控基因表达和细胞生理的持续变化，从而导致先天性免疫细胞呈现训练或耐受表型，使机体对相同或不同刺激物的再次刺激产生更强或更弱的反应，具有可逆转的特点[48]。因此，作为抑制先天免疫炎症的治疗方法，提高TI耐受的策略可促进TI的逆转，抑制过度炎症引起的组织损伤，为慢性炎症和相关代谢性疾病提供新的治疗可能性[49]。

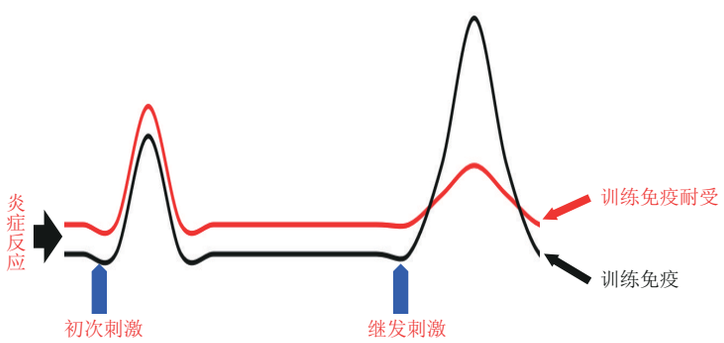

Fig. 1　The difference between trained immunity and trained immunity tolerance

图1　TI与TI耐受区别

尽管TI耐受可能导致机体无法对二次入侵的病原体产生有效的免疫应答而增加脓毒症等感染性疾病致死率，但其对慢性炎症性疾病具有潜在治疗价值[50]。如Wendeln等[50]研究发现，阿尔茨海默病（Alzheimer's disease，AD）小鼠模型中，小胶质细胞TI加剧大脑β淀粉样蛋白（amyloid β-protein，Aβ）变性，导致症状加重，而诱导TI耐受则显著降低大脑Aβ沉积，改善AD症状。对于治疗IR及相关代谢性疾病，大量研究证实通过诱导TI耐受来降低IR继发性代谢紊乱引起的过度炎症同样具有潜在治疗价值[49，51-53]。例如，作为先天免疫的重要组成部分，巨噬细胞是机体应对危险信号的第一道防线，广泛存在于脂肪、肝脏、骨骼肌等外周组织中，是诱发慢性炎症的中心介质[51]。研究表明，巨噬细胞可通过训练获得适应性免疫功能，其促炎或抗炎表型主要取决于不同刺激诱导的TI或TI耐受，而通过诱导巨噬细胞TI耐受来降低机体炎症水平可能对于改善IR及相关代谢性疾病具有重要治疗价值[49，52-53]。如，Edgar等[53]研究发现，高糖诱导巨噬细胞TI导致其对多种继发刺激的应答显著增强，呈促炎表型，诱发IR及动脉粥样硬化，这也解释了以高血糖为靶点治疗糖尿病大血管病变效果不佳的原因，同时提出诱导巨噬细胞TI耐受对于改善IR及动脉粥样硬化具有潜在治疗价值。Novakovic等[49]研究发现，外源性药物干预通过诱导巨噬细胞TI耐受，使其呈抗炎表型，进而避免因机体处于过度炎症状态而诱发IR及相关代谢性疾病。因此，诱导先天免疫细胞TI耐受是早期防治IR相关代谢性疾病的有效策略，为基于免疫代谢学的疾病干预策略研究提供新的方向。

2.2 训练免疫耐受在运动改善胰岛素抵抗及相关代谢性疾病中的重要作用

目前IR临床干预效果不佳，改善IR的生活方式干预研究及机制探讨对于相关代谢性疾病早期防治具有重要意义[54]。运动是改善IR及相关代谢性疾病的有效手段，大量研究证实运动发挥全身性抗炎效应促进机体代谢稳态[55-56]。尽管目前运动抗炎效应机制尚未阐明，但Nieman等[57]提出免疫系统对运动干预高度敏感，运动诱导的先天性免疫细胞功能改善可能在其对抗慢性病发生发展中发挥关键作用，运动免疫学研究将成为未来研究的活跃领域。如，Javaid等[58]研究发现，8周运动干预通过抑制脂肪组织先天性免疫细胞巨噬细胞中NLRP3炎性小体激活来诱导先天性免疫细胞巨噬细胞抗炎表型，改善高脂膳食诱导的IR。Padilha等[59]提出，运动训练显著诱导骨骼肌中巨噬细胞抗炎性极化，维持骨骼肌代谢稳态并促进肌再生。Zhang等[17]研究发现，术前进行4周运动干预可训练肝脏枯否细胞呈抗炎表型，保护肝脏免受缺血再灌注引起的炎症损伤。本课题组前期研究也发现，高脂膳食干预诱导小鼠IR并伴随巨噬细胞促炎性极化显著增加，之后进行有氧运动干预可有效调节巨噬细胞功能表型[60-61]，降低机体炎症水平[62]，改善骨骼肌、脂肪IR[63-65]和NAFLD[66-67]。以上研究结果提示，高脂膳食产生先天免疫记忆后，运动干预可能通过诱导先天性免疫细胞TI耐受来减轻IR继发性代谢紊乱导致的过度炎症反应，促进相关代谢性疾病早期防治。因此，靶向先天性免疫细胞TI耐受来研究运动干预IR的抗炎机制具有令人兴奋的广阔前景。同时，由以上可知，目前相关领域研究主要聚焦于运动对外周性TI的调控作用，而关于运动在中枢性TI中的调节作用仍有待进一步探索研究。

此外，尽管胰岛素主要靶器官脂肪、骨骼肌和肝脏间存在异质性，但现有研究表明，高脂膳食诱导的肥胖小鼠中以上组织均出现先天性免疫细胞巨噬细胞浸润和M1型极化增加，介导组织IR[68]。运动有效改善以上组织中巨噬细胞功能表型，维持代谢稳态[58-67]。Chen等[69]研究也发现，高脂膳食诱导的肥胖小鼠髓系细胞中特异性敲除甲酰肽受体2（formyl peptide receptor 2，*Fpr2*）后，脂肪、骨骼肌和肝脏中巨噬细胞浸润和M1型极化均一致性降低，有效提高组织胰岛素敏感性，减轻肝脏损伤。因此，未来研究应于脂肪、骨骼肌和肝脏这三大胰岛素靶器官中探索运动诱导的先天性免疫细胞TI耐受对IR的改善效应并分析可能出现的差异性，以全面分析TI耐受在运动干预IR及相关代谢性疾病中的重要作用。

3 代谢重编程在运动调节训练免疫中的作用

3.1 代谢重编程概念

代谢重编程指细胞在特定生理病理条件下，为适应外界环境变化和满足自身增殖分化的需要，其能量需求和代谢模式发生系统性调整与转变的过程[70]。这种能量需求的改变需要细胞调整其代谢机制，通过增加或减弱合成反应来抵御外界环境胁迫并赋予细胞新功能，涉及细胞对能量和生物合成原料的获取与使用方法的根本改变，包括氧化磷酸化、糖酵解、脂肪酸代谢和氨基酸代谢等多个代谢途径的调控[71]。

大量研究表明，代谢重编程在肿瘤生物学、免疫学、干细胞研究以及多种疾病的发生发展中都扮演重要角色[72-79]。其中，肿瘤发生过程中的Warburg效应是代谢重编程的典型表现。这一效应由德国生物化学家Warburg于20世纪20年代首次提出，他发现即使在氧气充足的情况下，癌细胞也偏好于通过糖酵解来获取能量，且伴随着葡萄糖消耗增加、氧化磷酸化减少和乳酸生成增加，即其能量产生逐渐从线粒体氧化磷酸化向有氧糖酵解转变以维持其快速生长和增殖的能量需求[72]。近年来，随着对Warburg效应研究的进一步深入，人们发现，该效应不仅发生在癌细胞中，也存在于其他快速分裂的细胞[73-75]。如，动脉粥样硬化、肺动脉高压等病理条件下的血管平滑肌细胞，其通过有氧糖酵解消耗的葡萄糖占其葡萄糖总摄取量的90%以上，使得细胞持续增殖和迁移，进而导致血管重构和疾病进展[73]。免疫学研究则发现，免疫细胞的代谢重编程在感染和炎症应对中至关重要，静息状态下免疫细胞通常表现出较低的生物合成需求，主要依靠氧化磷酸化和脂肪酸氧化供能，而激活后的免疫细胞能量代谢方式从氧化磷酸化向有氧糖酵解转变，以满足其增殖和功能需求[74-75]。干细胞研究同样发现干细胞的代谢重编程对其自我更新和分化具有重要影响[76]。此外，越来越多的的证据提示代谢重编程在IR及相关代谢性疾病、自身免疫性疾病、神经性疾病等多种疾病的发生发展中发挥着重要作用[77-79]，这对于揭示相关疾病发生机制及防

治新思路和新靶点的寻找具有重要意义。

3.2　代谢重编程与训练免疫调节

如上所述，代谢途径对先天性免疫细胞功能表型的调节作用已被广泛认识。越来越多的证据表明，代谢重编程是先天性免疫细胞应对外界刺激以执行免疫功能的关键机制[80-81]。先天性免疫细胞TI主要由免疫细胞代谢重编程和表观遗传修饰所驱动：当细胞暴露于外源或内源性刺激时发生代谢改变和表观遗传学改变，使得被训练的免疫细胞再次受到初始刺激相关或无关的刺激时发生更快、更强烈的免疫反应[80-81]，其中细胞代谢又是先天性免疫细胞及其祖细胞表观遗传重编程的关键介质[82]。如，研究表明接种卡介苗可诱导单核细胞等先天性免疫细胞代谢重编程，使得其代谢方式相较于未活化的单核细胞出现明显改变，发生从氧化磷酸化向有氧糖酵解的代谢重编程，最终使得机体再次受到刺激时先天性免疫细胞形成免疫增强和持续的免疫表型，避免结核分枝杆菌等微生物的再次感染[80]。

具体而言，多种免疫细胞均具备TI功能，包括单核/巨噬细胞、中性粒细胞、自然杀伤细胞等[83]。作为先天免疫的重要组成部分，单核/巨噬细胞具有高度可塑性，在不同微环境下可极化为功能迥异的促炎性M1型或抗炎性M2型，调节IR等多种重要病理生理过程[84]。正常情况下，炎症早期巨噬细胞以M1型极化为主，促进炎症反应；随后M2型极化增加且M1型向M2型转变，抑制炎症并促进组织修复和伤口愈合。IR发生发展中，脂肪、骨骼肌和肝脏等胰岛素靶器官中巨噬细胞浸润增加且持续向M1型极化，导致M1/M2稳态失衡，诱发慢性炎症[84]。其中，促炎性M1型巨噬细胞主要利用糖酵解产生能量，以满足其在短时间内分泌更多促炎因子来杀灭微生物的需求，抗炎性M2型巨噬细胞主要利用氧化磷酸化产生能量，以持续提供促进组织重塑和修复所需的大量能量[85-86]。最新研究发现，巨噬细胞TI或TI耐受过程主要由代谢重编程驱动[82，87]。巨噬细胞TI发生时，β葡聚糖等TI诱导剂引起多种糖酵解酶活性增加，同时巨噬细胞线粒体功能受损，导致细胞质中还原型烟酰胺腺嘌呤二核苷酸（nicotinamide adenine dinucleotide，NADH）水平升高、NAD^+/NADH比值下降，致使细胞代谢从氧化磷酸化向糖酵解转变，代谢特征为葡萄糖消耗、乳酸生成、糖酵解途径和丙酮酸转化率的升高以及氧化磷酸化的降低，这是巨噬细胞发生TI的先决条件，也是受训的巨噬细胞能维持长期功能的关键因素[82，87]（图2）。TI耐受发生时，巨噬细胞中糖酵解酶活性降低，NAD^+/NADH比值提高，细胞从高糖酵解代谢的促炎状态转化为以氧化磷酸化代谢为主的抗炎状态[88]。另外，尽管巨噬细胞TI有赖于代谢重编程和表观遗传重编程间的相互作用，但诸多研究表明，多种代谢产物可诱导巨噬细胞表观遗传变化，共同诱发巨噬细胞TI[89]。关于代谢重编程在自然杀伤细胞TI中的调节作用，研究同样发现自然杀伤细胞在激活后大量增加糖酵解速率，类似于肿瘤细胞中的Warburg效应，不仅为细胞提供快速的能量来源，还产生必要的生物合成前体来支持细胞增殖和功能分子生成，使得自然杀伤细胞能够迅速响应外界刺激并有效执行其免疫机能[90]。中性粒细胞在应对感染时则产生大量活性氧类（ROS）分子，同时伴随谷氨酰胺异生增强，为细胞提供能量和生物合成前体[91]。因此，从代谢重编程角度研究先天性免疫细胞TI及TI耐受的机制，有望为慢性炎症和相关代谢性疾病防治研究提供新的方向。

3.3　运动调节代谢重编程

目前，关于运动对新陈代谢和免疫功能的影响已被大量研究，现有研究表明运动能启动多种细胞的代谢重编程。如Koelwyn等[92]提出运动通过促进骨骼肌细胞氧化磷酸化代谢来调节骨骼肌代谢重编程，促进骨骼肌再生与重塑，提高其适应性。Bianchi等[93]研究发现，中等强度有氧运动通过刺激肝脏NAD^+从头合成来对肝细胞紊乱的代谢和炎症过程进行重编程，使得衰老和脂肪变性的肝细胞恢复正常的代谢和免疫稳态，最终逆转肝脏脂肪变性并缓解炎症。Mela等[94]研究发现，运动训练通过抑制小胶质细胞的糖酵解来改善老年小鼠的认知能力，说明运动通过调节小胶质细胞代谢重编程来发挥其抗炎作用。尽管目前关于运动调节免疫细胞代谢相关研究较为有限[95]，但已有结果提示运动可能通过抑制先天性免疫细胞糖酵解并提高其氧化磷酸化水平，诱导初次激活的先天性免疫细胞出现TI耐受，进而减轻机体过度炎症反应，达到早期防治IR相关代谢性疾病的目的。未来研究应聚焦于相关领域以进一步探索和验证先天性免疫细胞代谢重编程在运动调节TI进而改善IR及相关代谢性疾病中的关键作用。

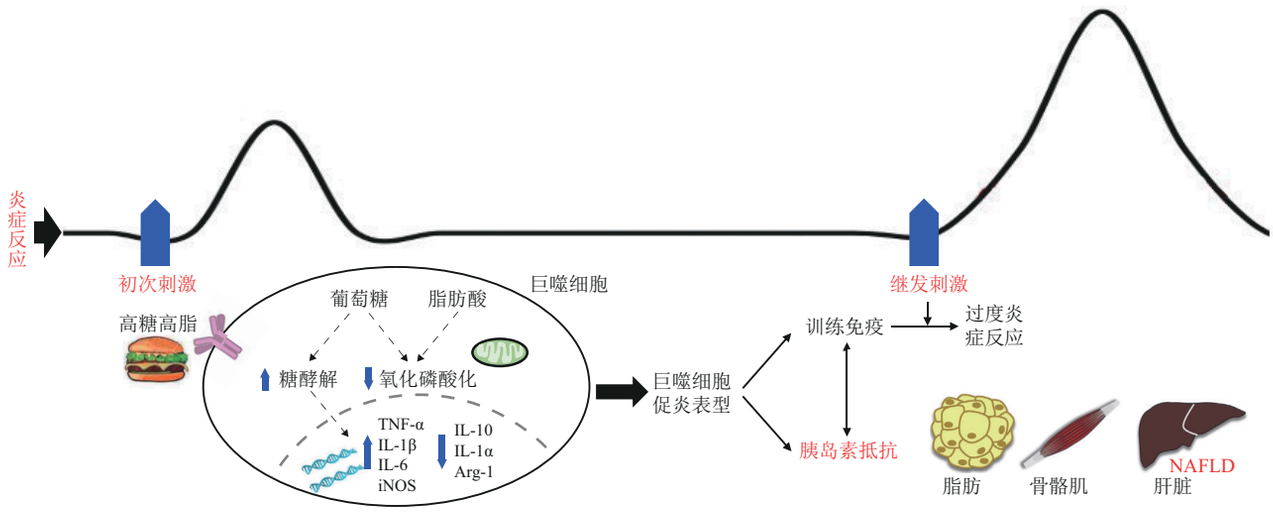

Fig. 2　The TI mechanism in macrophage during the development of IR

图2　IR发生发展中的巨噬细胞TI机制

4　运动诱导训练免疫耐受的代谢重编程机制

多种代谢中间产物可对免疫细胞进行代谢重编程，以满足免疫细胞发挥不同功能的能量需求，因此通过代谢中间产物重塑免疫功能可作为疾病干预策略研究的新思路[96]。衣康酸是源于三羧酸循环（tricarboxylic acid cycle，TAC）的抗炎性代谢产物，是TAC中顺乌头酸在IRG1的调节下由乌头酸脱氢酶1催化产生[97-98]。最近，衣康酸与TI耐受相关的免疫调节特性在科学界引起关注。如Domínguez-Andrés等[99]研究发现，衣康酸途径是平衡先天性免疫细胞TI及其耐受的中心调节点，其通过抑制TI中上调的糖酵解代谢和炎性因子来诱导TI耐受，并提出，在TI诱发的炎症性疾病中，衣康酸可作为潜在的治疗工具。

研究发现，在先天性免疫细胞巨噬细胞中，衣康酸是诱导TI耐受时最显著上调的代谢产物[100]。β葡聚糖则通过下调IRG1表达，抑制巨噬细胞衣康酸生成，诱发TI，使机体应对继发感染时产生更强的促炎反应[99]。诸多研究表明，IRG1/itaconate信号与巨噬细胞糖酵解之间存在负反馈关系，调节巨噬细胞代谢重编程[101-102]。如Qin等[101]研究发现IRG1/itaconate通过显著抑制巨噬细胞中糖酵解来减轻其炎症水平。糖酵解过程中，GAPDH催化3-磷酸甘油醛转化为1,3-二磷酸甘油酸，是维持糖酵解途径的关键酶。最近研究发现，衣康酸通过诱导GAPDH的Cys22残基烷基化靶向抑制GAPDH活性，导致巨噬细胞糖酵解能力显著下降，促炎因子生成减少，而高浓度的葡萄糖则逆转衣康酸的抗炎作用并增强糖酵解[102]。以上提示，IRG1/itaconate可能通过靶向抑制GAPDH导致糖酵解受阻来调节巨噬细胞代谢重编程，进而成为介导巨噬细胞TI耐受的重要调控点。

深入探索运动诱导TI耐受中先天性免疫细胞代谢重编程的机制将进一步加深人们对于疾病和健康的认识，同时可能为运动不耐受人群提供潜在的药物治疗分子靶点。尽管目前运动干预IR的先天性免疫细胞代谢重编程机制尚未阐明，但研究表明，运动显著上调巨噬细胞IRG1/itaconate信号，诱导其抗炎表型，减轻机体炎症水平[17-19]。如Zhang等[17]研究发现，运动中上调的血清HMGB1可通过枯否细胞膜上的Toll样受体TLR4显著激活细胞内IRG1/itaconate信号，诱导肝脏枯否细胞抗炎表型，减轻机体炎症水平进而有效缓解过度炎症引发的肝脏损伤。提示，运动干预可能通过激活IRG1/itaconate/GAPDH轴来调节先天性免疫细胞代谢重编程，诱导TI耐受。

综上，运动可能通过调节IRG1/itaconate信号来对先天性免疫细胞进行代谢重编程，诱导TI耐受，减轻IR继发性代谢紊乱导致的过度炎症，进而发挥改善IR和防治相关代谢性疾病的抗炎效应

（图3）。未来聚焦于该领域的相关研究将为运动防治IR相关代谢性疾病及其TI耐受效应提供生物学支撑，为IR运动处方制定与实施提供科学依据，为相关代谢性疾病防治研究提供新思路、新方法。

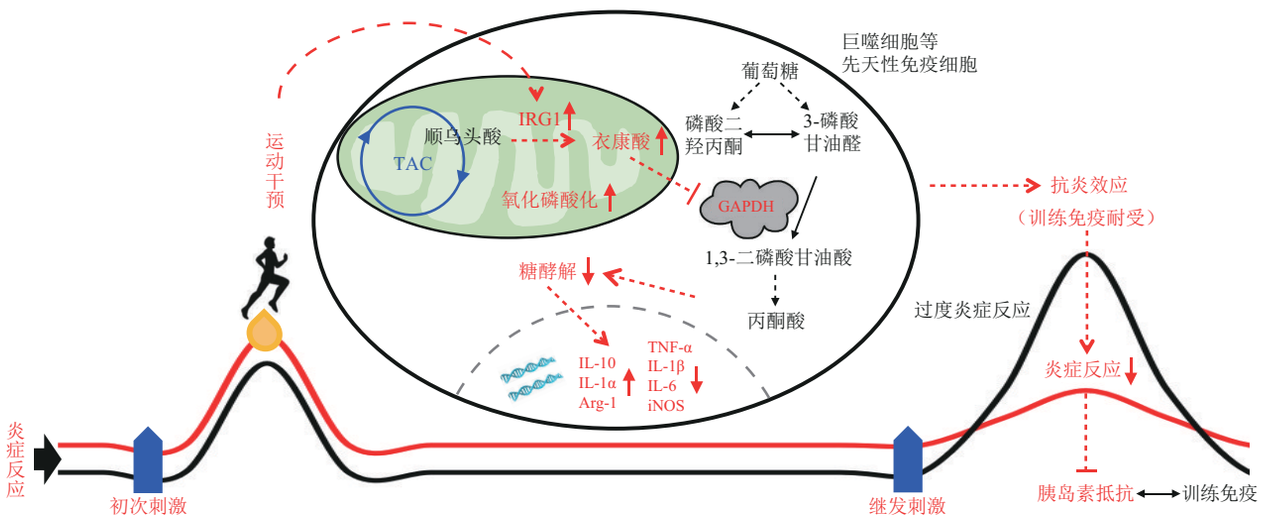

Fig. 3　Possible mechanisms of exercise intervention to IR *via* TI tolerance

图3　运动通过TI耐受改善IR的可能机制

5　总结与展望

TI是一把双刃剑，参与多种慢性炎症性疾病的发生发展。高脂膳食诱发先天性免疫细胞TI，致使其对继发性代谢紊乱的免疫应答显著增强，是诱发IR及相关代谢性疾病的重要机制。通过诱导先天性免疫细胞TI耐受来打破IR与TI间的恶性循环是早期防治相关代谢性疾病的新策略。现有研究表明，运动干预发挥抗炎效应促进机体代谢稳态，但目前运动抗炎效应的潜在机制尚未阐明。最近发现，先天性免疫细胞TI耐受过程主要由代谢重编程驱动，而运动已被证明能调节多种细胞的代谢重编程，提示运动可能通过调节先天性免疫细胞代谢重编程诱导TI耐受。衣康酸是最新发现的平衡先天性免疫细胞TI及其耐受的中心调控点，且IRG1/itaconate可靶向抑制糖酵解关键酶GAPDH的酶活性，调节先天性免疫细胞代谢重编程，而运动可上调IRG1/itaconate信号，提示运动可能通过诱导IRG1/Itaconate信号调节巨噬细胞代谢重编程，发挥抗炎效应。基于以上证据，推测运动可能通过调节IRG1/itaconate信号来对先天性免疫细胞进行代谢重编程，诱导TI耐受，减轻IR继发性代谢紊乱导致的过度炎症，进而发挥改善IR和防治相关代谢性疾病的抗炎效应。

但就目前而言，该领域研究仍处于较初级阶段，尚有大量科学问题亟待解决。如：a. TI耐受在运动发挥抗炎效应进而改善机体糖脂代谢中的关键作用尚需明确；b. 先天性免疫细胞代谢重编程在运动诱导TI耐受进而改善IR相关代谢性疾病中的介导作用仍需深入探讨；c. IRG1/itaconate信号在运动调节先天免疫细胞代谢重编程和诱导TI耐受中的调节作用及其下游机制仍值得进一步研究，以及是否存在其他分子机制参与调节尚不清楚。此外，多种先天性免疫细胞均具备TI功能，不同细胞在运动发挥抗炎效应进而改善机体糖脂代谢中的作用及机制尚待阐明。运动形式多种多样，不同运动方式、强度对TI耐受的调控，以及对IR及相关代谢性疾病的改善机制是否存在差异也值得深入探讨。总之，已有越来越多的证据指向IRG1/itaconate信号介导的代谢重编程和TI耐受在运动改善IR及相关代谢性疾病中发挥重要作用，但仍需进行大量人体和动物试验来对这一问题进行深入研究和验证，并对其中的分子机制问题进行更为明确的解释。

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The Emerged Perspective on Improving Insulin Resistance Through Exercise: Metabolic Reprogramming Induces Trained Immunity Tolerance*

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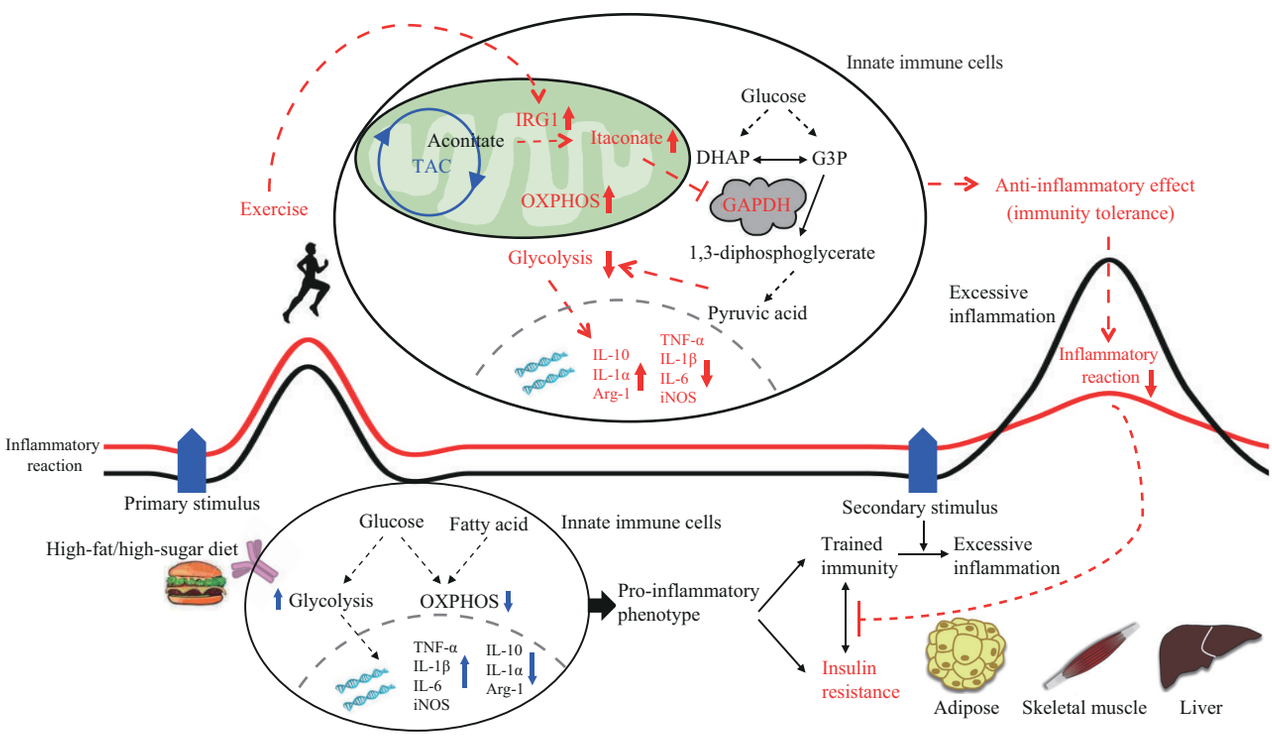
Graphical abstract



Abstract　In recent years, it has been discovered that innate immunity also exhibits immune memory characteristics, referred to as trained immunity. This refers to the ability of innate immune cells to acquire a memory-like capacity after being attacked by pathogens, thereby demonstrating enhanced reactivity upon secondary stimulation from the same or different stimuli. Existing research indicates that high-fat diet stimulates innate immune cells to undergo trained immunity, thereby significantly boosting their immune response to secondary metabolic disorders. This process serves as a crucial mechanism underlying the development of insulin resistance-associated metabolic diseases. Breaking the vicious cycle between insulin resistance and trained

* This work was supported by grants from The National Natural Science Foundation of China (32200944), "Qing Lan" Project of Jiangsu Province, and The Jiangsu Research Institute of Sports Science Foundation (BM-2023-03).

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Received：August 12，2024　Accepted：October 8，2024

immunity by inducing innate immune cells to establish immune tolerance and inhibiting excessive inflammatory reactions caused by various secondary metabolic disorders of insulin resistance represents a novel strategy for early prevention and treatment of related metabolic diseases. As is widely known, exercise intervention serves as an effective means to improve insulin resistance-related metabolic diseases. It promotes metabolic homeostasis by exerting anti-inflammatory effects, yet the underlying mechanism of these anti-inflammatory effects remains unclear. Numerous studies suggest that after a high-fat diet generates innate immune memory, exercise intervention may alleviate excessive inflammatory reactions caused by secondary metabolic disorders due to insulin resistance by inducing immune tolerance in innate immune cells, and promote early prevention and treatment of related metabolic diseases. Therefore, targeting innate immune cell immune tolerance to explore the anti-inflammatory mechanism of exercise intervention in insulin resistance holds exciting and vast prospects. Metabolic reprogramming refers to the process in which cells undergo systematic adjustments and transformations in their energy requirements and metabolic patterns to adapt to changes in the external environment and meet their own needs for proliferation and differentiation under specific physiological and pathological conditions. Numerous studies have shown that metabolic reprogramming plays a crucial role in tumor biology, immunology, stem cell research, and the occurrence and development of various diseases. Increasing evidence suggests that metabolic reprogramming is also a key mechanism for innate immune cells to respond to external stimuli and perform immune functions. The process of immune tolerance is also driven by metabolic reprogramming. Studying the mechanisms of innate immune cell immune tolerance from the perspective of metabolic reprogramming is expected to provide new directions for the prevention and treatment of chronic inflammation and related metabolic diseases. Meanwhile, exercise has been proven to regulate metabolic reprogramming in various cells. It may induce immune tolerance in activated innate immune cells by inhibiting glycolysis and enhancing their oxidative phosphorylation levels, thereby mitigating excessive inflammatory reactions and achieving early prevention and treatment of insulin resistance-related metabolic diseases. Itaconate, an intermediate product of the tricarboxylic acid cycle, represents a newly discovered central regulatory point for balancing the trained immunity and immunity tolerance in innate immune cells. Additionally, exercise modulates IRG1/itaconate signaling. Therefore, conducting an in-depth exploration of the interrelationships between trained immunity, immunity tolerance, metabolic reprogramming, and IRG1/itaconate signaling in exercise intervention for insulin resistance, as well as summarizing the immune tolerance mechanism of exercise in improving insulin resistance, can provide theoretical support for the preventive and therapeutic effects of exercise in insulin resistance and related metabolic diseases. This can also offer new insights for the development of simulated drugs tailored for individuals with exercise intolerance.

Key words trained immunity, insulin resistance, exercise, metabolic reprogramming, itaconate

DOI：10.16476/j.pibb.2024.0365 **CSTR**：32369.14.pibb.20240365