Advances in Clinical Medicine 临床医学进展, 2024, 14(2), 3911-3916
Published Online February 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.142544

Hans汉斯

单核－巨噬细胞调控脂质代谢的研究进展

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收稿日期：2024年1月27日；录用日期：2024年2月21日；发布日期：2024年2月28日

摘　要

脂质代谢是一个复杂的生理过程，涉及营养调节、激素调节和稳态。脂质代谢紊乱和脂质代谢相关疾病给社会和个人带来巨大的负担，然而这些疾病的具体发病机制尚未明确。免疫代谢领域的发展，揭示了慢性代谢性疾病中复杂的免疫学机制，为这些疾病的治疗开创了很多潜在的新型治疗靶点。单核－巨噬细胞是目前免疫代谢领域中涉及研究最广泛的免疫细胞，其在脂质稳态和脂质代谢紊乱相关疾病中都发挥着重要作用。本文总结了单核－巨噬细胞在调控脂质代谢和促进脂质代谢紊乱中的机制，旨在寻找全新的脂质代谢相关疾病的治疗靶点。

关键词

脂质代谢，单核－巨噬细胞，脂质代谢相关疾病，免疫代谢

Research Progress of Monocytes-Macrophages on Regulation of Lipid Metabolism

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Received: Jan. 27th, 2024; accepted: Feb. 21st, 2024; published: Feb. 28th, 2024

Abstract

Lipid metabolism is a complex physiological process that is involved in nutrient adjustment, hormone regulation, and homeostasis. Lipid metabolism disorders and lipid-related diseases bring a

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文章引用: 冯睿智, 邓国民. 单核-巨噬细胞调控脂质代谢的研究进展[J]. 临床医学进展, 2024, 14(2): 3911-3916.
DOI: 10.12677/acm.2024.142544

huge burden to society and individuals, while the underline mechanism of these diseases is still unrevealed. The development in the field of immunometabolism has revealed the complex immunological mechanisms in chronic metabolic diseases and created lots of potential therapeutic targets for the treatment of these diseases. As the most widely studied immune cell in this field, monocytes-macrophages play an important role in both lipid homeostasis and lipid-related diseases. In this review, we summarize the role of monocytes-macrophages in lipid homeostasis and lipid metabolism disorders, aiming to find novel therapeutic targets for lipid-related diseases.

Keywords

Lipid Metabolism, Monocytes-Macrophages, Lipid Metabolism-Related Diseases, Immunometabolism

1. 引言

脂质对维持细胞膜的结构完整性，调节能量代谢和生物信号转导都发挥着至关重要的作用[1]。脂质代谢是一个复杂的生理过程，涉及营养调节、激素调节和稳态。不健康的生活方式和慢性营养超负荷会导致脂质代谢紊乱的发生，进而引起脂质代谢相关疾病，包括肥胖、非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)，动脉粥样硬化(atherosclerosis, AS)和 2 型糖尿病(diabetes mellitus type 2, T2DM)。这些疾病给社会和个人带来了巨大的负担，但是这些疾病的具体发病机制至今仍未被完全阐明[2]。

在过去的几十年中，联系免疫与代谢的分子和细胞机制被逐渐揭示，形成了一个全新的研究领域，现在被称为“免疫代谢(immunometabolism)”。这一领域的兴起，揭示了慢性代谢性疾病中复杂的免疫学机制，为这些疾病的治疗开创了很多潜在的新型治疗靶点[3]。适应性免疫细胞(T 淋巴细胞和 B 淋巴细胞)的活化和代谢重编程在肥胖和 T2DM 的发生发展中起到了重要作用[4]。肝脏巨噬细胞参与肝脏稳态的维持和疾病的发生发展，在酒精性肝病(alcoholic liver disease, ALD)，NAFLD 和肝细胞癌(hepatocellular carcinoma, HCC)等疾病的病理过程都起到了关键作用[5] [6]。

单核－巨噬细胞是目前免疫代谢领域中涉及研究最广泛的免疫细胞，单核－巨噬细胞在脂质稳态和脂质代谢紊乱相关疾病中都发挥着重要作用[7]。命运图谱和单细胞分析等全新的实验技术的出现，使科学家们对单核细胞的发育和功能有了更加深入的了解。现已知单核－巨噬细胞群体中存在着发育和功能各异的多个分化亚群，它们涉及到组织稳态的维持、炎症反应、组织损伤后修复和代谢调控等多个生理过程中[8]。本文就针对单核－巨噬细胞在调控脂质代谢和促进脂质代谢性紊乱的机制进行总结，以期待探索治疗脂质代谢相关疾病的新途径。

2. 单核－巨噬细胞调控脂质代谢

起源于骨髓中的髓系祖细胞的单核细胞，在被释放到外周循环中数天后，进入组织并补充组织内的巨噬细胞[8]。机体的脂质代谢调控主要涉及到脂肪组织和肝脏，这些组织中驻留的巨噬细胞对脂质代谢的调控发挥着重要作用。

脂肪组织被认为处在机体免疫与代谢相互作用的枢纽[9]。脂肪组织中除脂肪细胞外，含有大量的免

疫细胞，包括巨噬细胞、树突状细胞、嗜酸性粒细胞、淋巴细胞、中性粒细胞和自然杀伤细胞，它们对脂肪组织乃至整个机体的代谢都发挥着重要的调控作用[7] [10]。肥胖个体脂肪组织扩增的过程就伴随着免疫细胞分群的扩增和免疫细胞功能的质变[7]。这些免疫反应扰乱了脂肪组织的代谢功能，免疫细胞，特别是脂肪组织内巨噬细胞(adipose tissue macrophages, ATMs)在脂质稳态中也具有重要的调节功能[7]。

脂肪组织内脂质相关巨噬细胞(lipid-associated macrophages, LAMs)亚群以 Term2 依赖性的方式控制代谢稳态，并影响下游信号通路对小鼠体脂含量，血清胆固醇和葡萄糖耐受量的调控[11]。Rao RR 等的研究发现，来自肌肉组织的激素 Metrnl 通过调节米色脂肪组织中巨噬细胞抗炎相关基因的表达来促进脂肪产热和改善糖耐受量[12]。Knights AJ 等揭示了米色脂肪组织中的巨噬细胞是调节适应性产热的乙酰胆碱的重要来源，而这些细胞的活化主要被肾上腺素能信号调节，特别是通过 β2 肾上腺素能受体[13]。脂肪组织巨噬细胞分泌细胞因子 Slit3 (slit guidance ligand 3, Slit3)，Slit3 与交感神经元上的 ROBO1 (roundabout guidance receptor 1, ROBO1)受体结合以刺激 Ca^{2+}/钙调蛋白依赖性蛋白激酶 II (calcium/calmodulin dependent protein kinase II)信号传导和去甲肾上腺素释放，增强脂肪细胞产热[14]。

肝脏是许多生理过程的关键枢纽，包括营养素代谢、血容量调节、免疫系统支持、生长信号通路的内分泌控制、脂质和胆固醇稳态以及外源化合物的分解[15]。肝脏组织中，肝细胞仅占肝脏细胞总数的三分之二；库普弗细胞(kupffer cells, KCs)作为体内最大的巨噬细胞群体，占据了肝脏中非实质细胞的 20% [16]。KCs 作为肝脏的关键细胞成分，对于维持组织稳态和确保对肝损伤的快速反应至关重要[5]。

Remmerie A 等人的研究发现，代谢相关脂肪肝(metabolic associated fatty liver disease, MAFLD)中的 KCs 被源自骨髓的巨噬细胞取代而减少，募集的巨噬细胞存在于两个不同激活状态的亚群中，其中一个亚群与稳态 KCs 非常相似，另一亚群与肥胖脂肪组织的脂质相关巨噬细胞(LAMs)非常相似。类似 LAMs 的巨噬细胞亚群会表达骨桥蛋白(osteopontin, OPN)，而 OPN 是非酒精性脂肪肝炎(nonalcoholic steatohepatitis, NASH)患者的生物标志物，与纤维化的发展有关[17]。Kaffe E 等构建了由人肝细胞和非实质细胞(non-parenchymal cells, NPCs)组成的人肝组织的小鼠，对这种小鼠体内的人源化肝细胞的研究揭示了肝细胞的关键代谢功能受到其微环境中的 NPCs 的调控[18]。Blériot C 等人发现肝脏中 KCs 的一个 CD206 高度表达的亚群通过 CD36 的表达调控肝脏的代谢过程[19]。Loft A 等人揭示了巨噬细胞内糖皮质激素受体(glucocorticoid receptor, GR)的活化抑制肿瘤坏死因子(tumor necrosis factor, TNF)的表达，促进肝细胞 GR 的核转位，被激活的 GR 和肝细胞中过氧化物酶体增殖物激活受体 α (peroxisome proliferator activated receptor α, PPARα)共同诱导的脂肪氧化和生酮相关基因的表达[20]。

3. 单核－巨噬细胞参与脂质代谢紊乱

脂质代谢紊乱是一种复杂的临床综合征，主要以胆固醇和甘油三酯的紊乱为主，通常在肥胖，糖尿病，非酒精性脂肪肝等继发性背景下出现的[1]。这些代谢性疾病的相关研究揭示了单核－巨噬细胞参与疾病发生发展过程并促进脂质代谢紊乱的机制。

脂肪组织的重塑是肥胖引起的基本病理改变，这个过程主要由巨噬细胞的趋化浸润和随后的炎症反应介导[21]。Kratz M 等人揭示了巨噬细胞驱动的炎症在肥胖相关的胰岛素抵抗和 2 型糖尿病中起到了关键作用[22]。Laurencikiene J 等人证实了肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)通过丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)家族促进哺乳动物脂肪细胞的脂肪分解，导致围脂滴蛋白(perilipin, PLIN)的表达降低[23]。此外，炎性细胞因子 TNF-α 促进肥胖和肥胖相关的 2 型糖尿病中胰岛素抵抗的发生[24]，白细胞介素-1β (interleukin-1β, IL-1β)参与了巨噬细胞诱导的人原代脂肪细胞胰岛素信号通路的损伤[25]。表达 Kdm6a 的巨噬细胞能促进白色脂肪细胞的脂肪生成和抑制米色脂肪细胞的产热，通过损害白色脂肪组织(white adipose tissue, WAT)分化和米色脂肪组织(beige adipose tissue, BAT)产热活

性来驱动肥胖和代谢综合征的发生[26]。巨噬细胞的 IRE1α 信号通路引导 ATMs 的极化，通过抑制褐色脂肪组织(brown adipose tissue, BAT)产热和 WAT 棕色化来引起肥胖和脂质代谢紊乱[27]。

脂肪组织通过分泌生物活性物质－脂肪因子(adipokine)，例如瘦素、脂联素等来发挥关键的内分泌器官功能，这些物质参与全身新陈代谢和免疫功能的调控[28]。Sarraf P 等人的研究发现，炎性细胞因子 TNF-α 和 IL-1 能够引起血清瘦素(leptin)水平升高和脂肪组织中瘦素 mRNA 表达的增加[29]。Takahashi K 等人揭示了 TNF-α 对脂肪细胞中抵抗素表达的负调节作用[30]。3T3-L1 脂肪细胞中脂联素(adiponectin)基因的表达和分泌被白细胞介素-6 (interleukin-6, IL-6)抑制[31]。巨噬细胞的趋化浸润和炎性活化构建了脂肪组织中的炎性微环境，脂肪细胞代谢功能和分泌功能受到炎性因素的影响而发生改变，从而促进了机体代谢紊乱的发生。

非酒精性脂肪性肝病(NAFLD)作为一种代谢性疾病，涉及了多种免疫细胞介导的炎症过程[32]。肝脏中的 KCs 和趋化的巨噬细胞在 NAFLD 的疾病进展中起核心作用，肝巨噬细胞的炎性极化，促进了脂肪变性、炎症和纤维化的发展，导致胰岛素抵抗和脂质代谢紊乱的发生[33]。Tosello-Trampont AC 等人的研究证实了肝脏中产生 TNF-α 的 KCs 的增加对 NAFLD 早期发展阶段至关重。此外，KCs 炎性激活促进了肝脏组织中的单核细胞趋化浸润和脂质堆积[34]。Nonogaki K 等人研究发现，IL-6 刺激肝脏甘油三脂的分泌，诱导高甘油三酯血症的发生[35]。Bijnen M 等人将来自肥胖小鼠脂肪组织中的巨噬细胞移植到肝脏中，发现这些巨噬细胞能够促进饮食诱导的小鼠肝脏中性粒细胞募集、巨噬细胞趋化和 NAFLD 的进展[36]。O'Doherty RM 等人的研究表明，肝脏中 KCs 增加肝细胞甘油三酯的积累并促进胰岛素抵抗发生，使用氯化钆清除巨噬细胞可以有效抑制这些代谢紊乱的发生。此外，针对 TNF-α 的中和抗体能够改善肝细胞的甘油三酯积累和胰岛素抵抗[37]。

4. 展望

免疫代谢领域的快速发展，使我们更加深入的认识了免疫与代谢之间的密切联系，脂质代谢相关疾病背后潜在的复杂免疫学相关机制也不断被新的研究结果揭示。脂肪组织和肝脏中的单核－巨噬细胞对组织内实质细胞的代谢过程发挥着重要的调控作用。单核－巨噬细胞参与了代谢性疾病的发生发展过程，促进脂质代谢紊乱等代谢综合征的发生。然而，目前的研究仅仅揭示了单核－巨噬细胞参与脂质代谢调控的部分机制，后续还需要更多的研究来阐明免疫与代谢复杂的相互作用机制，为治疗代谢性疾病开辟新途径。

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