综 述

瘦素对类风湿关节炎主要效应细胞的调控作用研究进展

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[摘要] 瘦素是由脂肪组织合成的一种脂肪因子，最初研究显示其可作为调节体脂平衡的激素类物质发挥作用。深入研究后发现，瘦素具有与细胞因子白细胞介素-6(IL-6)类似的结构，其受体属于Ⅰ型细胞因子受体超家族成员。瘦素与其受体结合后，不仅可调节摄食及能量平衡，还兼具对免疫系统的调控作用。类风湿关节炎(RA)是由多种遗传和环境因素引起的常见的自身免疫性疾病，其基本病理变化是滑膜慢性炎症和血管翳的形成，导致软骨、骨及周围组织的破坏。虽然RA发病的确切机制尚不清楚，但已经证实多种免疫细胞和常驻基质细胞参与了RA的病理过程。RA动物模型已证实瘦素与关节炎症反应有关，可能参与了该疾病的发病和进展。本文综述了瘦素对RA主要效应细胞的免疫调节作用，旨在为相关研究拓展思路。

[关键词] 瘦素；类风湿关节炎；免疫调节

Research progress of the modulation of leptin on the main effector cells of rheumatoid arthritis

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[**Abstract**] Leptin, a fat factor synthesized in adipose tissue, is initially worked as a hormone substance regulating body fat balance. With in depth-study, researchers found that leptin has structural homology with such cytokines as interleukin-6 (IL-6), and its receptor, Ob-R, belongs to class Ⅰ cytokine receptor superfamily. Through binding to corresponding receptor, leptin can not only regulate the food intake and energy balance, but can also regulate the immune system. Rheumatoid arthritis (RA) is one of the common autoimmune diseases caused by many genetic and environmental factors. The fundamental pathological change of RA is chronic synovial inflammation and pannus formation, and leads to the destruction of cartilage, bone and surrounding tissue. Many immune cells and resident stromal cells are involved in RA pathological progress although the exact pathogenesis of RA remained unclear. It has been proved by *in vivo* experiment of RA animal model that leptin is related to the joint inflammation, and may participate in the pathogenesis and process of the disease. The immunomodulatory effects of leptin on the main effector cells of RA has been reviewed in present paper, aiming to expand ideas for related research.

[**Key words**] leptin; rheumatoid arthritis; immunoregulation

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瘦素主要由脂肪组织按照体脂质量比例产生，并与体重指数呈正比[1]。有研究指出，瘦素可作为能量平衡的负反馈信号，通常被认为是肥胖、代谢及自身免疫之间的纽带[2]。它不仅可以维持能量平衡，还参与免疫和炎症反应的调节、骨形成、生殖(人类青春期的开始)、造血(血细胞的形成)、血管生成(新血管的发育)和伤口愈合等其他多种生理功能[3]。类风湿关节炎(rheumatoid arthritis，RA)是一种全身性慢性炎症性疾病，主要表现为滑膜增生伴成纤维样滑膜细胞增生、自身抗体生成、血管生成、淋巴细胞等炎性细胞浸润、受累关节骨质破坏等[4-5]。虽然导致RA病理过程的分子及细胞机制尚未阐明[6-7]，但目前研究已证实T细胞、成纤维样滑膜细胞及巨噬细胞是RA的主要效应细胞。本文综述了瘦素对RA主要效应细胞的免疫调控作用，旨在通过探究瘦素对RA免疫细胞及基质细胞的调控作用及机制，为以瘦素为靶标的RA相关研究提供思路和借鉴。

1 瘦素及其受体

Zhang等[8]于1994年成功克隆了肥胖基因(obese gene，Ob)，该基因的编码产物瘦素是由167个氨基酸组成的细胞因子结构类似物。作为脂肪家族最具代表的脂肪因子，瘦素主要由脂肪组织产生，是激素类物质，其他组织(如胃、肺、肠、大脑等)也可产生，其循环浓度与体内脂肪储存含量相关[9]，同时能量摄入量也会影响瘦素的分泌，短期禁食可减少其分泌[10]。多种细胞因子，如肿瘤坏死因子(tumor necrosis factor，TNF)、白细胞介素-6(interleukin-6，IL-6)和IL-1β均对瘦素分泌具有促进作用[11]。已经证实，瘦素在长期的体重控制中发挥关键作用，可进入血液循环参与糖、脂肪及能量代谢的调节，减少食物的摄入量，增加能量利用[12-13]，从而使体重减轻；而瘦素含量偏低的人体重会有所增加，其原因是大脑缺乏体内脂肪充足的信号，因此机体会继续增加能量的摄入，表明瘦素可通过向大脑提供信号来调控代谢过程，进一步达到控制体重的目的[14]。此外，肥胖也可能与瘦素抵抗相关，与2型糖尿病患者的胰岛素抵抗类似，瘦素抵抗现象可能与瘦素循环水平升高，以及外源性瘦素不能有效减少食物摄入和体重有关[15]。

瘦素除作为能量代谢的调控分子[16]外，对生殖、免疫、造血、骨代谢、伤口愈合及血管再生等过程也具有一定影响。作为促炎脂肪因子，瘦素可能与超重或肥胖人群的“低级别炎症状态”相关。在免疫系统中，瘦素对固有免疫细胞、适应性免疫细胞具有调控作用[17]，可增强自然杀伤(NK)细胞的细胞毒性，激活中性粒细胞、巨噬细胞和树突状细胞等，从而维持或加重炎症状态[18]；瘦素也可参与调节$CD4^+$ T细胞向辅助性T细胞(T helper cell，Th)1和Th2细胞的分化，并能促进$CD4^+CD25^+$调节性T细胞(regulatory T cell，Treg)增殖及刺激B细胞产生促炎因子等[19]。本课题组的研究表明，RA患者血清瘦素水平升高与RA疾病活动性评分DAS28、类风湿因子和抗环瓜氨酸肽抗体呈正相关[20]，表明瘦素在RA中可能发挥潜在促炎作用。此外，如图1所示，在RA患者血清及关节液中升高的瘦素也能影响RA主要效应细胞的功能，且多数研究者认为

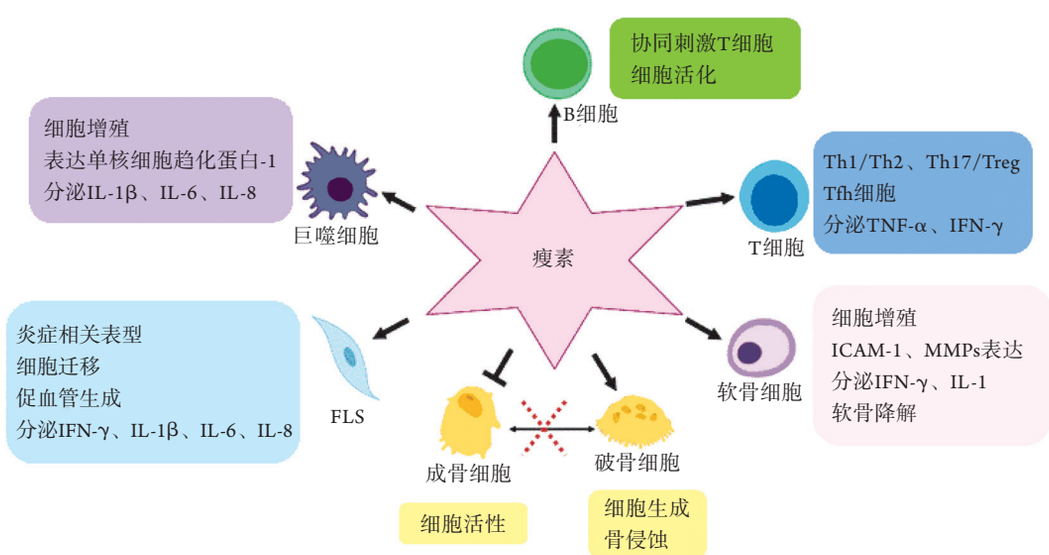

图1 瘦素对RA主要效应细胞的免疫调控作用

Fig.1 Immunomodulatory effect of leptin on RA main effector cells

FLS. 成纤维样滑膜细胞；Th. 辅助T细胞；Treg. 调节性T细胞；Tfh. 滤泡辅助性T细胞；IL-6. 白细胞介素-6；IL-8. 白细胞介素-8；IL-1β. 白介素-1β；IL-1. 白细胞介素-1；TNF-α. 肿瘤坏死因子-α；IFN-γ. γ干扰素；ICAM-1. 细胞间黏附分子-1；MMPs. 基质金属蛋白酶

其在RA中发挥促进疾病发展的作用。

瘦素发挥作用的主要方式是通过与其受体(Ob receptor，ObR)结合启动下游信号转导[21]。ObR属于Ⅰ型细胞因子受体，由位于4号染色体上的糖尿病基因编码，下丘脑、脂肪组织、固有及适应性免疫细胞上均可检测到其表达[18,22]。现已发现并鉴定了6种ObR的异构体：ObRa、ObRb、ObRc、ObRd、ObRe、ObRf。这些异构体细胞外结构域同源，但不同选择性剪接使其细胞内结构域存在一定差异[23]。ObR的长异构体ObRb主要作用于大脑中的瘦素信号传导通路，包含信号转导所需的所有元件，能够充分激活酪氨酸激酶/信号转导和转录激活因子(Janus tyrosine kinase/signal transducer and activator of transcription，JAK/STAT)胞内信号通路；而短异构体ObRa和ObRc被认为参与了瘦素在血脑屏障的运输[24]。ObRe是一种可溶性ObR，完全由胞外结构域组成，是人血浆中主要的瘦素结合蛋白[25]。

2 瘦素对RA主要效应细胞的作用

2.1 对T细胞亚群及功能的影响 在RA微环境下，瘦素可直接调控多种免疫细胞的生物学功能[26]。有研究发现，瘦素缺乏小鼠可表现为细胞免疫缺陷和淋巴结萎缩[27]，$CD4^+$ T细胞在RA基本病理变化中发挥至关重要的作用[28]，且已证实瘦素可影响$CD4^+$ T细胞的活化、增殖和细胞因子分泌等功能[29]，抑制瘦素可导致小鼠和人体内$CD4^+$ T细胞总数减少[30]。Siegmund等[31]比较了瘦素缺乏ob/ob小鼠与野生型抗原诱导的关节炎小鼠T细胞增殖的差异，结果发现前者的抗原特异性T细胞增殖明显降低；此外，瘦素还可通过上调$CD4^+$ T细胞*Bcl-2*基因表达、抑制细胞凋亡的方式参与RA的疾病进展[32]。

根据$CD4^+$ T细胞的功能特征，可将其分为Th1、Th2、Th17、Tfh、Treg等亚群，瘦素可通过上调Th1分泌的炎性细胞因子TNF-α和γ干扰素(interferon-γ，INF-γ)促进细胞免疫应答的效应[31,33]，并可与雌二醇通过协同作用促进Th1细胞增殖、抑制Th2细胞增殖，而雄激素则通过抑制瘦素的产生间接下调Th1细胞介导的免疫应答，从而缓解RA的症状[34]。但也有研究发现，瘦素表达水平降低与Th2分泌细胞因子能力降低及Th1细胞数量升高有关，瘦素刺激后的外周血单核细胞及过敏性鼻炎患者的鼻上皮细胞中均可检测到Th2型细胞因子比例明显上调[35]。瘦素是能量代谢的关键调节因子，在关于胞内代谢对细胞功能调控作用的研究中发现，RA炎症微环境中的Th1细胞增殖依赖高糖酵解效率[36]，瘦素可通过上调葡萄糖转运蛋白来调节葡萄糖代谢，影响活化T细胞功能[37]，但瘦素能否通过改变RA患者T细胞代谢影响其功能及具体机制尚未明确。

$Foxp3^+CD25^+CD4^+$ Treg在维持免疫耐受和抑制效应T细胞损伤方面具有关键作用。已有研究证实，RA患者Treg细胞的免疫抑制功能减弱，与效应T细胞比较，ObR在Treg细胞中高表达，利用单克隆抗体中和瘦素可促进RA Treg细胞增殖，增强其免疫抑制功能[38]。此外，也有研究指出，瘦素可能参与了初始T细胞向Th17细胞的分化，但瘦素在该过程中发挥直接作用还是间接作用仍需深入探讨[39]。

滤泡辅助性T细胞(follicular helper T cell，Tfh)是辅助B细胞产生抗体的关键细胞。更重要的是，本课题组前期研究发现，瘦素可通过激活STAT1和STAT3途径增加IL-6水平来上调RA患者外周血Tfh细胞的占比，支持了瘦素可能通过促进T细胞向Tfh分化参与RA病理过程的观点[20]。

2.2 参与维持成纤维样滑膜细胞“类瘤样”特性 成纤维样滑膜细胞(fibroblast-like synoviocytes，FLS)是关节滑膜处的主要细胞类型[40]，具有成纤维细胞的许多共同特征，如表达多种胶原和波形蛋白等细胞骨架丝的重要部分，也表达许多对细胞黏附有重要调节作用的分子，如钙黏素-11、各种整合素等，最终导致关节破坏[41]。这主要是由于存在于RA微环境的FLS细胞表型发生明显变化，丧失了接触抑制特性，呈现“类肿瘤样”生长[42]；此外，RA中异常激活的FLS细胞可辅助激活关节微环境中的其他细胞，从而加重炎症反应和关节损伤[43]，故有研究者认为，FLS是RA病理变化的主要效应细胞[44]。滑膜增生肥厚并伴有FLS的迁移和侵袭，形成血管翳，可进一步损伤基质和软骨[45]。FLS不仅可以从所在的关节滑膜组织向该关节软骨表面迁移，而且可通过淋巴系统等转移到未受影响的关节软骨表面，另外，FLS释放IL-6、IL-8、前列腺素和基质金属蛋白酶(matrix metalloproteinase，MMPs)等与炎症反应及基质破坏密切相关的因子，可直接或间接破坏关节软骨及骨[46]。

FLS表达ObR，且RA关节滑液中表达升高的瘦素可通过与其受体结合来调控FLS细胞功能[47]。虽然研究者对瘦素在RA中的作用持不同观点，但多认为瘦素对RA FLS的炎症相关表型具有促进作用[48-49]。Sun等[50]的研究结果提示，瘦素可通过上调活性氧簇(reactive oxygen species，ROS)促进RA FLS迁移，并以ROS/缺氧诱导因子-1α依赖的方式增强人脐静脉内皮细胞的血管生成能力。还有研究发现，瘦素可通过激活其受体和核因子κB(NK-κB)诱导RA FLS分泌IL-8[51-52]，且瘦素与IL-1β、IL-6的表达呈剂量

依赖性，证实瘦素可通过激活JAK2/STAT3信号通路上调IL-6水平，干扰ObR表达则可抑制RA FLS分泌IL-6[53]。此外，瘦素与其受体结合后经由信号转导，还可增强IFN-γ在RA FLS中的作用[54]。

综上所述，虽然多数研究表明，瘦素通过影响FLS功能参与RA滑膜病变，但由于RA的发病机制复杂，多种细胞、细胞因子参与其中，因此，瘦素调控RA FLS的具体机制、作用方式及信号通路仍需进一步系统研究。

2.3 调控巨噬细胞功能 巨噬细胞是先天免疫系统的关键组成部分，可参与RA的发生[55]。新近研究发现，巨噬细胞数量异常是包括RA在内的多种自身免疫性疾病的特征[56]。瘦素或ObR遗传异常的啮齿动物体内外研究发现，巨噬细胞吞噬功能和促炎细胞因子的表达与肥胖相关，而外源性瘦素可促进其吞噬作用及细胞因子的产生[57]。此外，还有研究发现，瘦素缺乏的肥胖小鼠巨噬细胞表型存在异常[58]。滑膜巨噬细胞对关节炎症和骨损伤的发展至关重要，活化巨噬细胞的减少可缓解RA小鼠模型的疾病症状[59-60]。已经证实，瘦素可激活巨噬细胞释放促炎细胞因子TNF-α和IL-6[61]。在胶原诱导的关节炎小鼠中，血清瘦素/脂联素比值与巨噬细胞的数量、单核细胞趋化蛋白-1的产生呈正相关[62]。瘦素还可通过JAK/STAT途径诱导RA滑膜巨噬细胞产生IL-8，募集炎症反应细胞、加重关节损伤[46]。

2.4 对RA其他效应细胞功能的影响 RA另一重要特征是软骨和骨组织的退化，可导致关节功能障碍。软骨细胞、破骨细胞和成骨细胞也作为效应细胞，在RA的病理过程中发挥作用。破骨细胞和成骨细胞是骨组织代谢的基本功能细胞，二者通过吸收旧骨及形成新骨保持骨量的动态平衡，而骨丢失与骨稳态的异常密切相关。瘦素是免疫系统和骨代谢之间相互影响、相互联系的重要中介物，破骨细胞主要来源于单核/巨噬细胞谱系细胞的多核细胞[63]。有研究发现，胶原诱导性关节炎模型小鼠局部注射瘦素可明显增强Th17细胞效应，而Th17作为B细胞κ轻链增强子的核因子配体受体的关键诱导剂，对破骨细胞生成和骨侵蚀具有促进作用[39]。而瘦素对成骨细胞功能的影响目前仍在研究中，有报道显示瘦素不仅可通过中枢神经系统下调成骨细胞的活性，还可直接与成骨表面受体结合，发挥成骨作用[64]。

软骨是滑膜关节的重要组成部分，主要由软骨细胞组成。软骨细胞在用趋化因子配体6和成纤维细胞生长因子-2刺激后可分泌MMPs和聚集蛋白聚糖酶，导致软骨功能障碍[65-66]。已经证实，瘦素可促使人和小鼠软骨细胞分泌细胞间黏附分子-1(intercellular adhesion molecule 1，ICAM-1)，趋化中性粒细胞和单核细胞向RA炎症关节浸润，从而加重软骨基质降解[67]。瘦素对软骨细胞增殖、细胞外基质合成具有促进作用，因此，瘦素对骨及软骨形成具有直接的影响[68]。瘦素还可通过促进和激活MMPs，并与其他促炎刺激因子如IFN-γ、IL-1协同作用，使软骨细胞释放Ⅱ型一氧化氮合酶[69-70]，导致软骨降解。

B细胞在RA发病机制中也起着关键作用，已经证实自身反应性B细胞可作为抗体产生细胞参与RA的发生[71]。B细胞作为专职抗原递呈细胞，可协同刺激T细胞及其他炎症细胞[72]，且其数量异常与RA患者的临床症状具有明显的相关性[73]。B细胞表达ObR，提示瘦素对B细胞功能具有潜在影响[74]，相关研究已证实瘦素可促进B细胞活化[27]。与标准体重小鼠比较，肥胖小鼠的B细胞数量减少，给予瘦素处理后B细胞数量明显增加[75]。此外，瘦素也可通过抑制B细胞凋亡促进其增殖，参与抗体介导的免疫损伤[19]。

3 总结与展望

瘦素兼具影响机体代谢及调控免疫细胞功能的双重作用，在多种自身免疫性疾病的发病过程中均起重要作用。RA作为一种较常见的自身免疫病，动物实验及细胞层面的大量研究表明瘦素在其免疫发病机制中可能起关键作用。因此，瘦素有望成为监测RA疾病活动度的指标，抑制瘦素活性或拮抗瘦素功能可能成为RA治疗的潜在靶标。然而，目前的研究多源于体外实验或动物模型，缺乏体内数据支持，也缺乏在RA发病不同阶段作用的探讨，且对RA主要效应细胞的免疫调控作用多局限于现象观察及功能探索，缺乏机制研究。能否通过干预瘦素的作用开发RA治疗的新靶点、改善患者疾病活动度及预后等诸多问题仍需深入研究。

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