

· 综述 ·

Th17/Treg 失衡与肥胖人群中类风湿关节炎患病率升高的相关性

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摘要: 类风湿关节炎(RA)是一种常见的慢性炎症性自身免疫疾病,有高致残率和死亡率,而肥胖增加患RA的风险,但其发病机制和病因尚不明确,给治疗带来很大困难。辅助性T细胞(Th)17和调节性T细胞(Treg)由一个共同的前体细胞(幼稚的CD4⁺T细胞)发育而来,它们是两个功能相反的淋巴细胞亚群,Th17/Treg平衡在RA的发生和发病机制中发挥重要作用。肥胖人群中脂肪组织积累可改变T细胞数量和功能,Th17细胞数量增多、功能亢进,Treg细胞数量减少、功能低下,加重了RA病程的发展。研究Th17/Treg失衡与肥胖人群中RA患病率升高的相关性,对RA的发病机制及诊治的研究具有重要价值。

关键词: 类风湿关节炎; 肥胖; 辅助性T细胞; 调节性T细胞; Th17/Treg平衡

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Relationship between Th17/Treg imbalance and increased prevalence of rheumatoid arthritis in obese patients

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Abstract: Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease with high disability and mortality. It has been widely publicized that obesity increases the risk of RA, but unclear pathogenesis and etiology of RA brings great difficulties to treatment. Helper T (Th) cells and regulatory T cells (Treg) are developed from a common precursor cell (naive CD4⁺T cells). They are two subgroups of lymphocytes with opposite functions. Th17/Treg balance plays an important role in the occurrence and pathogenesis of RA. The accumulation of adipose tissue in obese people can change the number and function of T cells. The increased quantity and hyperfunction of Th17 cells with the reduced number and function of Treg cells aggravates the development of RA. The study of the correlation between Th17/Treg imbalance and the increased prevalence of RA in obese people is of great value in exploring the pathogenesis, diagnosis and treatment of RA.

Keywords: Rheumatoid arthritis; Obesity; Helper T cells; Regulatory T cells; Th17/Treg balance

类风湿关节炎(RA)是一种以持续滑膜和全身炎症为特征的慢性自身免疫性疾病,它造成关节炎和骨质破坏,有较高致残率、死亡率,严重影响人们的生活质量并缩短预期寿命^[1],其病因和发病机制复杂,受到遗传、感染、环境等多种因素影响,其中免疫紊乱是RA的主要发病机制,而CD4⁺T细胞是启动特异性免疫应答的关键细胞^[2],近来研究发现,在RA患者中,辅助性T细胞(helper T cells, Th)17数量增加、功能亢进,而调节性T细胞(regulatory T cells, Treg)在数量和功能上存在明显不足,Th17/Treg细胞失衡在RA发病过程中发挥着重要作用^[3]。Th17和Treg细胞由一个共同的前体细胞(幼稚的CD4⁺T细胞)发育而来,在局部微环境、炎症因子[如转化生长因子(TGF-β)]的刺激下,幼稚的CD4⁺T细胞向Th17

和Treg细胞分化^[4]。Th17细胞主要表达转录因子——维甲酸相关孤核受体(retinoid acid-related orphan receptor, RoRγt),可分泌白细胞介素(IL)-17并诱导IL-22、IL-23等细胞因子的表达,在自身免疫病与炎症方面发挥作用^[3,5],Treg细胞主要表达特征性转录因子——叉头框蛋白(Foxp)3,可以抑制自身免疫、感染以及肿瘤细胞的整体免疫^[6]。Th17和Treg细胞在功能上相互拮抗,分化上相互影响。随着对Th17和Treg的深入研究发现,肥胖和类风湿关节炎患者两细胞亚群的平衡状态被打破,向致病性的Th17亚群靠近^[3,7]。近年有研究报道肥胖可增加患RA的风险,而关于两者之间的发病机制尚不明确,探索RA和肥胖与Th17/Treg平衡的关系及发病机制,对RA的预防和诊治具有重要价值。

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1 RA 与 Th17/Treg 平衡

CD4⁺T 细胞介导的免疫反应在 RA 的发病机制中发挥了重要作用,其中 Th17/Treg 失衡及细胞因子在 RA 发病和疾病进展方面越来越重要^[2-3]。IL-17 是 Th17 细胞产生的特征性细胞因子,具有强大的促炎效应。Th17 和 Treg 细胞及其相关细胞因子在多项动物模型和人类试验中都证明与 RA 发病密切相关。多项研究发现与正常人相比,RA 患者外周血中、滑膜、滑液中 Th17 细胞及其细胞因子 IL-17、IL-23、IL-6、TNF- α 明显升高,Treg 及其细胞因子 TGF- β 明显降低,不过滑膜及滑液中 IL-17、IL-6 等细胞因子水平更高^[8-9]。在动物模型胶原性关节炎(CIA)研究中显示,IL-17 缺乏或 IL-17 中和抗体治疗,可以减轻关节炎。Th17 细胞通过激活关节腔中的各种细胞,如巨噬细胞、树突状细胞、中性粒细胞或成纤维细胞样滑膜细胞产生 IL-17,IL-17 又可以诱导 TNF- α 、IL-6 和 IL-1 β 等细胞因子及趋化因子加重 RA 的关节炎^[10];此外,IL-17 也在 RA 的软骨破坏和骨侵蚀中发挥重要作用。研究表明破骨细胞是 RA 的骨质破坏的决定因素之一,核因子- κ B 受体活化因子配基(RANKL)是破骨细胞生成的启动信号。Th17 细胞在所有 T 细胞中表达 RANKL 的水平最高,一方面 IL-17 通过上调滑膜成纤维细胞及破骨细胞间充质细胞上的 RANKL 表达,诱导破骨细胞破坏导致骨质侵蚀,另一方面又促进 TNF- α 、IL-6 等炎症因子加重关节破坏^[11],此外,IL-17 也可以通过诱导软骨基质金属蛋白酶(MMP)表达而促进骨破坏^[12]。

Treg 功能缺陷或数量减少在 RA 中发挥免疫抑制的核心作用,其通过抑制破骨细胞上 RANKL 的表达而保护关节^[11]。在 CIA 关节中发现 CD4⁺CD25⁺Treg 细胞的耗竭加剧了 CIA,而 CD4⁺CD25⁺Treg 细胞的转移改善了关节炎的发展,说明 Treg 细胞在 RA 中的关键作用^[13]。最近的报告显示,炎症细胞因子(比如大量 TNF- α 、IL-6)通过抑制 Foxp3 磷酸化,导致 Foxp3 失活^[14],在 CIA 小鼠中,Foxp3 Treg 细胞可转化为新的 Th17 细胞亚群(称为 exFoxp3 Th17 细胞),exFoxp3 Th17 细胞与滑膜成纤维细胞协同作用诱导破骨细胞生成的程度远远大于 Th17 细胞,导致软骨破坏及骨侵蚀的作用也更大^[11]。

综上所述,在 RA 的发病过程中,Th17 细胞增加,Treg 细胞数量减少、功能转变,最终导致 Th17/Treg 平衡失调,而加重炎症反应,出现更严重的滑膜炎、关节破坏、骨质侵蚀等,加重 RA 病程的发展。此外 Jin 等^[15]报道 Maresin1 通过调节 Th17/Treg 细胞平衡改善 RA 病程可为治疗 RA 提供新的思路。

2 肥胖与 Th17/Treg 平衡

肥胖不仅表现为脂肪组织的积累,系统性慢性炎症更是其发病的核心环节,研究发现脂肪组织中巨噬细胞的浸润及相关炎症细胞因子表达上升,如:TNF- α 、IL-6、IFN- γ 、IL-1 β 、瘦素,其中巨噬细胞是关键免疫细胞^[16],因此,肥胖相关炎症的研究焦点开始集中在免疫系统中,进一步研究发现肥胖可通过改变脂肪组织中的 CD4⁺T 细胞数量,从而导致脂肪组

织炎症和胰岛素抵抗,这种变化与 Th17 的增加和 Treg 的减少有关^[17]。Winer 等^[18]的研究首次证明饮食诱导的肥胖(DIO)易导致 Th17 细胞增加,随后多项研究证明,肥胖选择性地促进 Th17 细胞亚群的扩张,Vega-Cárdenas 等^[19]发现肥胖个体中 Th17 细胞表达频率较高,而 Foxp3 mRNA 表达水平较低。正常人的脂肪组织是 Tregs 聚集的优先部位,然而在肥胖、2 型糖尿病中 Treg 的数量减少^[7,14],而通过过继性回输 Treg 细胞可逆转炎症状态,进一步证实 Treg 的抑制炎症作用^[20-21]。与上述研究相反,一些实验表明在饮食诱导的肥胖小鼠模型中,Treg 细胞的频率和总数都显著增加^[22],但是在 BMI 30~50 的肥胖患者中,有一半人处于代谢健康状态^[23],可以理解为在代谢不健康的肥胖人群中更易出现 Th17/Treg 失衡。随后多项研究探讨了肥胖影响 Th17/Treg 平衡的机制,脂肪组织分泌大量的脂肪因子与细胞因子为肥胖和自身免疫性疾病的联系搭起桥梁,其中巨噬细胞是脂肪组织中与肥胖相关的炎症的关键免疫细胞,肥胖导致巨噬细胞从抗炎的 M2 向促炎的 M1 转变,M1 分泌促炎细胞因子,如 TNF- α 、IL-6、IL-1 β 、IL-12、IL-23^[24],而这些细胞因子的大量产生又促进肥胖个体中 Th17 细胞的扩张和随后 IL-17 的产生,增加肥胖的炎症状态^[5],此外,CD11c,一种未成熟的脂肪组织巨噬细胞表型(ATDCs),可作单核细胞/巨噬细胞的激活标记物,被发现肥胖小鼠脂肪组织中数量显著增加,其表达较高水平的 IL-6、TGF- β 和 IL-23 并促进促炎性 Th17 细胞的产生,而促炎性 Th17 细胞又在肥胖脂肪组织炎症中起着突出的作用,导致 Th17 细胞反应增强,进而促使饮食诱导的肥胖脂肪组织炎症^[25]。最近的一项研究提出,Rab4b(一种控制细胞内转运的小 GTPase),在肥胖小鼠和患者的脂肪 T 细胞中表达减少,而 Rab4b 的缺乏会导致 Th17 细胞增加和 Treg 细胞降低^[17]。过氧化物酶体增殖物激活受体 γ (PPAR γ),是脂肪细胞分化的“主调节因子”,是 Treg 细胞积累、表型和功能的重要协调因子,瘦素可以通过激活 PPAR γ 的表达,影响 Treg 细胞的表型与功能^[26]。因此,可以认为,肥胖可有效地触发 CD4⁺T 细胞向 Th17 分化,Th17 细胞频率升高,Treg 细胞频率减低,Th17/Treg 平衡在肥胖人群的炎症持续方面发挥了重要作用。

3 肥胖和 RA

脂肪组织可发挥免疫和促炎作用,其可分泌脂肪因子和炎症介质,介导自身免疫病的发生,进而导致自身耐受机制的缺陷。大量研究报道了肥胖增加了患 RA 的风险,Feng 等^[1]的研究报道,肥胖者患 RA 的风险增加了 23%,超重者患 RA 的风险增加了 12%。Qin 等^[27]的一项荟萃分析显示,与正常体重个体相比,肥胖或超重的人患 RA 的风险分别增加了 31% 和 15%。有研究指出 RA 患者的 BMI 与炎症指标 C 反应蛋白、血沉以及 DAS28 等疾病活动度呈正相关^[28],Jhun 等^[29]实验研究发现,肥胖 CIA 和 CIA 都会激活 Th17 细胞,但肥胖 CIA 小鼠循环血中 IL-17 以及脾细胞 IL-17mRNA 水平更高,此外肥胖 CIA 的关节损坏更严重,由此认为肥胖通过 Th17 细胞分化和关节滑膜产生 IL-17 来放大 CIA 小鼠的关节炎,增加

RA 疾病活动度。近年研究发现,脂肪组织分泌的其他脂肪因子(例如脂联素、内脏脂肪素以及抵抗素)会影响 RA 的滑膜细胞、成纤维细胞产生细胞因子以及血管内皮生长因子(VEGF)和 MMP 的产生,不仅导致关节炎和破坏,也会影响 RA 的疾病活动度^[30]。所以说肥胖和 RA 互为影响,肥胖增加患 RA 的风险,反过来 RA 的炎性浸润及关节破坏又影响患者进一步肥胖,进一步研究脂肪因子与 Th17/Treg 平衡的关系,有望成为预防和治疗肥胖人群中 RA 的有效方法之一。

4 展望

Th17 细胞表现为促炎作用,而 Treg 细胞则表现为抗炎和免疫抑制作用,两者功能相反,共同维持自身免疫及慢性疾病处于相对稳定状态。研究发现肥胖人群 RA 的患病率增加,而 RA 和肥胖患者都存在 Th17 细胞升高,Treg 细胞数量减少和功能缺陷,Th17/Treg 平衡状态被打破。RA 通过药物,包括激素、传统改善病情的抗风湿药(DMARDs)、生物制剂治疗后,仍有一部分人未能得到有效缓解,尤其肥胖的 RA 患者,故探讨肥胖影响 Th17/Treg 平衡的机制,可为肥胖人群 RA 的防治提供新思路。

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