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阻塞性睡眠呼吸暂停低通气综合征免疫功能的研究进展

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摘 要

阻塞性睡眠呼吸暂停低通气综合征(OSAHS)是一种呼吸性睡眠障碍，主要表现为睡眠时，上呼吸道有时被部分，有时被完全阻塞，并且反复发生的夜间打鼾，白天困倦，甚至有时出现夜间憋醒等情况，引起低通气或者呼吸暂停等症状。在低通气或呼吸暂停事件中，肺泡通气不良导致动脉血氧饱和度(SaO_2)降低和二氧化碳动脉分压($PaCO_2$)逐渐升高，从而引起一系列并发症，如：高血压、胰岛素抵抗、冠心病等多器官、多系统损伤。此间歇性缺氧必然引起机体免疫功能及多种炎症指标发生改变，本文就OSAHS患者免疫及炎症指标做出综述，以增加对OSAHS免疫的了解，提高对OSAHS重视。

关键词

阻塞性睡眠呼吸暂停低通气，间歇性缺氧，白介素6，肿瘤坏死因子α，细胞免疫，体液免疫，炎症指标

Advances in the Study of Immune Function in Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract

Sleep apnea-hypopnea syndrome (OSAHS) is a respiratory sleep disorder, which is mainly manifested by partially or completely blocked upper respiratory tract during sleep, recurring nocturnal snoring, daytime sleepiness, and sometimes even nocturnal awakening, causing symptoms such as hypopnea or apnea. In hypopnea or apnea events, poor alveolar ventilation leads to decreased arterial oxygen saturation (SaO_2) and a gradual increase in arterial partial pressure ($PaCO_2$) of carbon dioxide, resulting in a series of complications such as hypertension, insulin resistance, coronary heart disease and other multi-organ and multi-system injuries. This intermittent hypoxia will inevitably cause changes in the body's immune function and a variety of inflammatory indicators. This paper reviews the immune and inflammatory indicators of OSAHS patients to increase the understanding of OSAHS immunity and improve the attention to OSAHS.

Keywords

Obstructive Sleep Apnea-Hypopnea, Intermittent Hypoxia, Interleukin 6, Tumor Necrosis Factor *α*, Cellular Immunity, Humoral Immunity, Inflammatory Indicators

1. 引言

阻塞性睡眠呼吸暂停低通气综合征(OSAHS)是一种临床症状，其主要特征是在睡眠中反复出现上气道部分或完全的塌陷，导致肺泡通气改变，间歇性低氧血症伴随呼吸强度增加和胸腔内负压波动，并出现高碳酸血症，从而出现夜间憋醒、睡眠结构紊乱等，继而导致一系列并发症。阻塞性睡眠呼吸暂停低通气综合征这种反复的缺氧及复氧，导致全身炎症反应及免疫功能异常。

2. 细胞因子水平变化与 OSAHS

1) 白细胞介素 6 (IL-6)属于细胞因子家族，包括多种因子，且这些因子可与糖蛋白 130 (gp130)结合，作为 β 受体激活细胞内信号级联，这些级联通常由 gp130 的同源或异源二聚体组成与其他细胞因子受体结合[1]。间歇性缺氧和睡眠结构紊乱可引起脂肪组织炎症，继而导致 IL-6 释放升高[2]，并可能通过脂肪细胞衍生的介质如 IL-6 与内皮细胞发生交联，促进内皮功能障碍[3]。此外，血浆 IL-6 水平与内皮功能障碍及动脉粥样硬化的程度相关，并且还可预测 2 型糖尿病和肥胖症的发病率[4] [5]，因此，IL-6 可以作为 OSAHS 存在或 OSAHS 相关发病率风险的可靠指标。另外 OSAHS 的标志性特征是间歇性缺氧，而间歇性缺氧会诱发巨噬细胞的极化从而增加 IL-6 的产量[6]。有研究表明，有 OSAHS 和没有 OSAHS 的肥胖患者的血浆中包括 IL-6 在内的各种促炎细胞因子的组织表达和循环水平大幅增加，且 CPAP 治疗 6 个月后这些促炎细胞因子水平明显降低[7]。并且通过减少睡眠延迟记录的成年 OSAHS 和过度嗜睡的患者白天和夜间 IL-6 血浆水平显著升高，如果没有过度嗜睡时这一变化就不存在[8]。已发表的 OSAHS 成人报告汇总显示，CPAP 治疗前 IL-6 的血浆水平在 1.2~131.66 pg/mL 之间，在 CPAP 治疗后显著降至 0.45~66.04 pg/mL 之间($p < 0.05$)，但也不排除存在显著的个体间异质性[9]，在 OSAHS 患儿的 IL-6 水平中也检测到类似的异质性[10] [11] [12] [13]，可能与 IL-6 和 CRP 基因的遗传变异有关[13]。

2) 肿瘤坏死因子-α (TNF-α)是一种经典的促炎细胞因子其与调节睡眠有关[14] [15] [16]。全身应用 TNF-α 可促进生理性睡眠状态的概率和深度，特别是增加非快速眼动睡眠(NREM)阶段的时间。此外，TNF-α 水平表现出昼夜节律模式，在睡眠剥夺后会增强，而中枢神经系统中的肿瘤坏死因子-α 受体的靶向破坏或抑制将导致自发性 NREM 睡眠的抑制[17]，另外，TNF-α 传统上会导致 NF 通路的激活，进而激活一氧化氮合酶、环氧合酶 2 和腺苷 A1 受体，而这些都与睡眠调节有关[14] [15] [16]。睡眠结构紊乱模式模拟了 OSAHS 睡眠中断这一特征，诱导小鼠中枢神经系统和其他组织 TNF-α 表达大幅上调，伴随着睡眠倾向的增加以及认知和情绪障碍，甚至在睡眠时间不受限制的情况下[17] [18]。此外，在受分段睡眠影响的野生型小鼠中使用 TNF-α 中和抗体治疗，或在将相同的睡眠干扰应用于双 TNF-α 受体缺失小鼠时，增加的睡眠倾向明显减弱，睡眠中断引起的认知和行为障碍也明显减弱[19] [20]。除了在小鼠和人类实验中证明的睡眠紊乱和 TNF-α 之间的关系外，在小鼠中的类似研究集中于 OSAHS 的慢性间歇性缺氧，进一步证明了 TLR-4-NF-κB 通路的募集以及细胞内外 TNF-α 水平的增加，从而进一步证实了肿瘤坏死因子在 OSAHS 中的病理生理作用[19]-[24]。除了 OSAHS 或其内在成分促进促炎状态并表现为 TNF-α 循环水平升高外，这种相互关系也可能有利于上气道功能障碍的出现或其他促进 OSAHS 发病的机制，例如，间歇性缺氧可在颈动脉体产生炎症过程，进而转化为免疫调节的改变以及呼吸控制的干扰，可能会促进睡眠时呼吸不稳定的倾向[25]，此外，虽然缺乏与上气道肌肉组织相关的具体研究，但在其他条件(如肥胖)下，TNF-α 的增加可能促进肌肉功能障碍，从而增加上气道功能障碍的可能性[26]。由于白天过度嗜睡(EDS)是成年人 OSAHS 常见的临床特征[20]，在肥胖儿童[21] [22] [23] OSAHS 中，EDS 和 TNF-α 之间的相关性已经被提出[27]。这些研究表明，无论是独立于肥胖的成人 OSAHS 患者，还是儿童，循环 TNF-α 升高水平都不一致。事实上，在迄今发表的 37 项成人研究中，27 项显示 TNF-α 水平较高，8 项未检测到 TNF-α 水平升高的证据，OSAHS 患者的循环浓度，另有两项研究报告结果模棱两可，这些结果的差异可能是由于被招募的受试者数量不足、OSAHS 严重程度的差异、并发肥胖的分布差异以及潜在的种族差异[28]。一项 Meta 分析表明，OSAHS 患者血浆 TNF-α 水平总体升高，尽管幅度不大，甚至被提议作为 OSAHS EDS 的生物标志物[29]。OSAHS 患者全身 TNF-α 浓度升高存在显著差异，提示 OSAHS 直接效应可能受到以下因素的增强(如 TNF-α 基因多态性)或减弱(如饮食、体力活动)，从而支持了 OSAHS 背景下的全身炎症程度是疾病发生并发症的主要决定因素。

3. 免疫功能变化与 OSAHS

参与 OSAHS 的免疫细胞种类较多，其中以 T 淋巴细胞最为重要，T 淋巴细胞按照其分化抗原可分为两大类，分别为：$CD4^+$辅助 T 细胞和 $CD8^+$细胞毒 T 细胞，T 淋巴细胞的功能主要是介导细胞免疫，另外 T 淋巴细胞也对体内免疫应答起到关键的调节作用[30]。$CD4^+$辅助 T 细胞的主要功能是通过其分泌的淋巴因子，增强和扩大免疫应答过程，而 $CD8^+$细胞毒 T 细胞的功能为抑制 T 淋巴细胞和 B 淋巴细胞的功能，从而抑制免疫应答过程，以保持免疫功能的平衡[30]。有研究表明 OSAHS 患者外周血中 $CD8^+$明显升高，而 $CD4^+$及 $CD4^+$与 $CD8^+$比值降低，但另一些研究表明 OSAHS 患者血 $CD4^+$和 $CD8^+$细胞计数增加，表明存在差异性，但不可否认的是，OSAHS 患者的免疫功能是下降的[31]。且 $CD8^+$T 细胞的数目改变与特定疾病相关，如 CD8+T 细胞数目增加已被证实与动脉粥样硬化密切相关，而 $CD8^+$T 细胞的减少与上皮组织的细胞毒性降低、结肠炎症的预防和肿瘤诱导的免疫抑制等有关[31]。B 细胞的功能是体液免疫，许多证据表明，B 细胞在抑制和调节免疫反应中起着非常重要的作用，它是通过释放白细胞介素 10 (IL-10)和表达可诱导 T 细胞凋亡的程序性死亡配体 1，2 (PD-1，PD-2)、Fas-L 和颗粒细胞 B 起作用的，Domagaia-Kulawik 等发现 OSAHS 患者中 B 细胞比例减低、数量减少，并首次观察到 OSAHS 患者外周血 B 细胞数量减少与代谢紊乱和肥胖密切相关并且 B 细胞的耗竭可能促进了 OSAHS 的全身性炎症[32]。

4. 部分炎症指标与 OSAHS

OSAHS 的特征表现为反复发生的间歇性缺氧，并伴有炎症发生。且 OSAHS 与炎症相关已被大量研究所证实，已发现 OSHAS 患者的炎症指标升高，且升高程度与疾病严重程度以及缺氧时间有关[33]。

1) 中性粒细胞：中性粒细胞与淋巴细胞比率(neutrophil-to-lymphocyte ratio NLR)是一个新的指标，可反应机体的炎症情况，并且比较稳定。有研究发现 0SAHS 患者 NLR 较健康体检者升高，并且 NLR 与 OSAHS 的严重程度存在显著相关性，且 NLR 与冠心病独立相关[34]，同时亦有研究者发现 OSAHS 患者进行 CPAP 治疗后 NLR 值显著降低[35]。

2) C 反应蛋白：C 反应蛋白(CRP)参与慢性炎症，且动脉粥样硬化形成有关，但 CRP 与 OSAHS 疾病之间是否存在相关性，争议较大，且研究结果不一致。有一项 Meta 分析显示，OSAHS 患者血清 CRP 水平高于健康对照组，最高体重指数与 AHI 和 CRP 值之间存在相关性[36] [37]。Yokoe 等人观察到 30 例 OSAHS 患者 CRP 水平高于健康受试者[38]。

3) 血沉：目前血沉也作为炎症活动的表现因子，但由于有关血沉与 OSAHS 疾病及其严重程度的研究较少，所以其作用也不清楚。但有研究显示 OSAHS 患者血沉水平明显高于对照组，而血沉水平升高与炎症反应的发生密切相关，血沉是炎症发生的重要标记物，这表明 OSAHS 患者存在炎症反应，血沉升高可能与 OSAHS 患者反复的血氧不足和睡眠障碍引起的组织炎症有关[39]。

4) 降钙素原 PCT：是一种无激素活性的蛋白质，在血浆中稳定，健康人体内含量低(<0.1 ng/ml)，脂多糖和其它多种炎症因子诱导 PCT 的产生，PCT 可能是一种次级炎症因子，它本身不能启动炎症反应，但可放大并加重炎症反应过程，全身细菌或真菌感染时显著升高，但病毒或局部感染时正常或轻微升高，对鉴别感染、判断感染严重程度和预后有重要意义，研究发现 OSAHS 组 PCT 较对照组略有所增高[40]，提示 PCT 在 OSAHS 患者的诊断中有一定的价值，但具体机制尚需进一步探讨。

5. 结论

综上，OSAHS 主要表现以慢性缺氧为特征，且机体的免疫功能失调，进而导致一系列全身炎症反应，一些炎症因子升高，但由于目前有关 OSAHS 免疫及炎症的研究尚少，且结果缺乏一致性，所以还需进一步研究。且有研究表明，OSAHS 患者发生动脉粥样硬化的可能性较高，但具体机制尚不清楚，有待进一步研究。

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