

# IL-17在系统性红斑狼疮中的作用

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## 摘要

SLE是一种全身多器官受累的慢性自身免疫性疾病, 其具体发病机制尚不明确, 目前越来越多的研究表明IL-17及其相关细胞因子参与SLE的发病, 本文就IL-17在SLE发病机制及治疗中的相关研究进行综述。

## 关键词

系统性红斑狼疮, 白介素17, 机制, 治疗

# Role of IL-17 in Systemic Lupus Erythematosus

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## Abstract

SLE is a chronic autoimmune disease with multiple organ involvement, and the specific pathogenesis is still unclear. At present, more and more studies show that IL-17 and its related cytokines are involved in the pathogenesis of SLE. Therefore, this paper reviews the related studies of IL-17 in the pathogenesis and treatment of SLE.

## Keywords

Systemic Lupus Erythematosus, Interleukin 17, Mechanism, Treatment

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## 1. 引言

系统性红斑狼疮(Systemic lupus erythematosus, SLE)是一种典型的系统性自身免疫性疾病,其特征为免疫耐受的丧失和自身抗体的持续产生,临床症状具有异质性,范围从轻度皮疹到更严重的多器官多系统受累。SLE好发于育龄期女性,流行病学研究表明,该病的发病率和患病率在不同种族人群中具有一定的差异,在亚洲及太平洋地区,SLE的年发病率为(2.5~9.9)/10万,患病率为(3.2~97.5)/10万,我国SLE的患病率为(30~70)/10万[1]。目前认为,遗传易感个体的环境因素促进了抗原的耐受性丧失,随后激活先天性和适应性免疫反应[2]。SLE中的慢性免疫激活导致大量炎症细胞因子的产生,并促进局部炎症和组织损伤,因此炎症通路对于开发新的靶向生物疗法非常重要[3]。近年来,白介素17(IL-17)在SLE中的作用受到越来越多的关注,因此在本篇文章中,我们将主要从机制及治疗方面对这一问题展开综述。

## 2. IL-17

IL-17是一种与人类自身免疫性疾病的发生发展密切相关的细胞因子。同时,对人类和小鼠的研究也阐明了IL-17在SLE中功能失调,并有助于疾病的进展。IL-17细胞因子组由6个不同的配体(IL-17A、IL-17B、IL-17C、IL-17D、IL-17E和IL-17F)和5个不同的受体(IL-17RA~IL-17RE)组成[4],其可促进T细胞的激活和多种细胞因子的产生,从而导致炎症,同时,它也会促进炎症细胞,如单核细胞和中性粒细胞,被招募到炎症器官[5],目前研究最多的为IL-17A和IL-17F,两者有50%的同源性,而IL-17B、IL-17C、IL-17D的功能尚不清楚,IL-17E被证明参与二型免疫反应。IL-17A与受体结合后,可通过MAP激酶途径和核转录因子 $\kappa$ B(nuclear factor  $\kappa$ B, NF- $\kappa$ B)途径发挥其生物学作用。虽然IL-17A主要由Th17细胞产生,但IL-17A也可由其他类型的细胞产生,包括 $\gamma\delta$ T细胞、自然杀伤T细胞(NKT细胞)、CD8<sup>+</sup>T细胞和3型先天淋巴细胞(ILC3s)等[6]。

IL-17A和IL-17F均与自身免疫性疾病相关,一方面IL-17A和IL-17F通过触发促炎反应来促进组织介导的先天免疫,另一方面IL-17A/F与其他细胞因子如肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )、IL-1 $\beta$ 和干扰素- $\gamma$ 的联合作用可协同增强不同靶细胞的促炎反应。Zúñiga等发现IL-17A也与代谢性疾病相关的炎症有关,阻断IL-17A可减少动脉粥样硬化模型中的病变大小、脂质堆积和细胞浸润[7]。有研究指出IL-17-A通过促进血管生成和肿瘤细胞从原位灶点的释放,促进肿瘤的生长,此外,它也促进了抗肿瘤细胞毒性T淋巴细胞反应,致使肿瘤消退。IL-17F能显著抑制人内皮细胞的血管生成,诱导内皮细胞产生IL-2、TGF- $\beta$ 和MCP-1,有抗血管生成的保护性功能。另外还有研究显示IL-17A可促进破骨细胞生成,同时也促进了成骨细胞分化、骨再生和重塑[8]。IL-17A还可调控造血功能,在诱导造血干细胞的增殖和分化中起作用[9]。

## 3. IL-17及其相关细胞因子在SLE中的作用

已有多项研究表明,与健康对照相比,SLE患者血清中IL-17A水平显著升高[10],但其是否与狼疮疾病活动度有关目前存在不同的意见,有研究发现SLE患者血清中IL-17水平与疾病活动度显著相关,但也有部分研究认为二者无明显相关性[10][11]。Ebrahimi Chaharom等通过病例对照研究发现SLE患者血清IL-17A水平与肾脏及神经系统受累相关[12]。此外,有报道称,SLE患者尿液中IL-17和IL-23相关基因的表达增加,并与LN的活动性相关[13]。Sipl等发现SLE合并关节炎患者滑膜内IL-17A水平升

高, 使用 IL-17 阻断后关节炎症状得到改善[14]。

IL-23 可与 IL-23R 结合, 通过 Janus 激酶 2 (JAK2)和酪氨酸激酶 2 (TYK2)促进信号转导和转录激活因子 3 (STAT3)的磷酸化。它还能增强维甲酸相关核孤儿受体  $\gamma$ t (ROR $\gamma$ t)的表达, ROR $\gamma$ t 参与了 IL-17 和其他 Th17 细胞因子的表达[15]。因此, IL-23 可通过促进 Th17 细胞介导的组织炎症, 在小鼠模型[16]和人类[17]的各种自身免疫性疾病的发展中发挥了重要作用。已有研究表明, 在 IL-23 受体缺乏的狼疮易发小鼠中, 使用抗 IL-23 抗体治疗后, LN 的临床和病理结果可以减轻[18]。SLE 患者肾组织中 IL-23 表达的升高进一步证明了 IL-23 在 SLE 中发挥重要作用。

#### 4. IL-17 及其相关细胞因子在 SLE 治疗中的作用

目前一些靶向 IL-17 或 IL-17R 的生物制剂已被批准用于一些免疫介导的炎症性疾病, 如银屑病[19]、银屑病关节炎[20]和强直性脊柱炎[21]。尽管针对 IL-17A 的抑制剂已被证明对狼疮易发小鼠的治疗有效, 但目前仅有部分病例报道描述了 IL-17A 抑制剂在 SLE 患者中的疗效[22], 未来还需进一步的临床试验来评估 IL-17 抑制剂在 SLE 患者中的长期疗效和安全性。

乌司奴单抗(ustekinumab)是一种抗 IL-12/23 p40 中和性单克隆抗体, 目前已有研究报道了其在亚急性性皮肤狼疮[23]、银屑病[24]和银屑病关节炎[25]患者中的有效性和安全性。近年来, 一项 II 期随机双盲临床研究表明, 乌司奴单抗对于活动性 SLE 患者具有较好的疗效和安全性[26]。但遗憾的是其 III 临床试验因未取得预期疗效而提前终止。

#### 5. 总结及展望

综上所述, IL-17 与 SLE 的发病密切相关, 但由于 SLE 是一种具有高度异质性的自身免疫性疾病, 单纯 IL-17 阻断可能不适用于所有患者, 未来寻找对 IL-17 抑制剂有较好治疗反应的临床标志物尤为重要。同时, 还需更多的随机临床试验来证明 IL-17 抑制剂在 SLE 治疗中的确切价值。

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