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I型干扰素在系统性红斑狼疮中的研究进展

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摘　要

系统性红斑狼疮(SLE)是一种慢性、多系统、炎症性自身免疫性疾病，具有复杂的发病机制和遗传易感性。随着对这种疾病的不断了解，发现SLE与干扰素基因特征有关，尤其I型干扰素对先天免疫系统和适应性免疫系统都有影响，本文就I型干扰素在系统性红斑狼疮中的研究进展进行综述。

关键词

系统性狼疮狼疮，I型干扰素，干扰素-α，干扰素-β，干扰素-κ，治疗靶点

Research Progress of Type I Interferon in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory autoimmune disease with complex pathogenesis and genetic susceptibility. With the increasing understanding of this disease, it has been found that SLE is associated with interferon gene characterization, especially type I interferon, which has an effect on both the innate and adaptive immune systems, and this article provides a review of the progress of type I interferon research in SLE.

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Keywords

Systemic Lupus Erythematosus, Type I Interferons, Interferon-*α*, Interferon-*β*, Interferon-*κ*, Therapeutic Targets

1. 引言

系统性红斑狼疮(SLE)是一种典型的自身免疫性疾病，可影响全身的各种组织和器官。系统性红斑狼疮的特征是免疫系统过度激活，导致自身抗体和免疫复合物增加以及器官功能障碍[1]。随着测序技术的不断发展，SLE 患者高度的 I 型 IFN 上调基因，称为干扰素刺激基因(ISG)。这些基因最初被测量为外周血细胞中的 mRNA 转录表达，具有独特的干扰素(IFN)基因特征[2]，50%的 SLE 患者血液中 I 型干扰素(IFN)水平长期持续升高[3]。IFN 特征已被提议作为 SLE 特定发病率的标志物[4]。此外，I 型干扰素阻断疗法为 SLE 新的治疗靶点提供支持，现综述如下。

2. I 型干扰素的概述

IFN-I 家族由 IFN-*α*、IFN-*β*、IFN-*ε*、IFN-*κ* 和 IFN-*ω* 组成[5]。IFN-*α* 和 IFN-*β* 都会触发信号级联反应，通过激活 JAK1、TYK2、STAT1 和 STAT2，启动 IFN 刺激基因(ISG)的基因转录。值得注意的是，其他 STAT 家族成员和 IFN 反应因子(IRF)也有助于激活 IFN 反应[6]。一项针对 SLE 患者的转录组分析研究确定了 STAT1 和 STAT2 等位基因相关的长链非编码 RNA (lncRNA) linc00513 的过表达，这种升高的 linc00513 通过促进 STAT1 和 STAT2 的磷酸化增加，是 I 型 IFN 信号通路的正调节因子[7]。影响 I 型 IFN 通路上游事件的基因中的 SNP 的分析揭示了 IRF 转录因子家族中许多遗传风险多态性，这些多态性与狼疮患者的高 I 型 IFN 水平相关。IRF1、IRF5、IRF7 和 IRF8 被认为是 I 型 IFN 产生的主要诱导剂，介导主要模式识别受体(PRR)的信号通路，两种主要的 PRR 信号通路可识别 DNA：Toll 样受体和环 GMP-AMP 合酶(cGAS)-干扰素基因刺激因子(STING) [8]。当通过 PRR 激活时，I 型 IFN 主要由浆细胞样树突状细胞(pDC)产生，每个 pDC 可以在 12 小时内产生多达 10^9IFN-*α* 分子[9]，pDC 中 I 型 IFN 产生的早期阶段由 Toll 样受体(主要是 TLR7 和 TLR9)产生内源性核酸[10]。在机制上，pDCs 通过内体膜中 TLR7 或 TLR9 的表达，通过受体介导的内吞作用感知病原体的 RNA 或 DNA，并启动涉及髓系分化因子和下游转录因子的激活链，最终诱导 I 型 IFNs 的表达[11] [12]。IRF5 在 IFN-*α* 和 IFN-*β* 的产生中起着关键作用，IRF5 表达水平升高与 SLE 患者的抗 RNA 结合蛋白(抗 RBP)或抗双链 DNA (抗 dsDNA)自身抗体阳性相关[13]。患者的双链 DNA (dsDNA)和免疫复合物(IC)刺激 TLR9 会导致 IFN-I 过量产生[14]。事实上，IRF5 和 STAT4 的 SLE 相关风险变异中的许多 SNP 被发现与抗 dsDNA 自身抗体的水平相关，因此表明这些基因和增强的 I 型 IFN 反应可能通过促进自身抗体的产生来增加 SLE 的风险。IRF5 的相同风险等位基因在健康供体中存在时，与先天免疫细胞(如 pDC 和中性粒细胞)的激活增加、可检测的自身抗体和 I 型 IFN 通路富集有关，因此表现为症状前 SLE [15]。小鼠中 TLR7 的过度表达和男性 SLE 患者中 TLR7 转录增加的遗传变体，易患 SLE [16]。外周血单核细胞(PBMC)中环状 GMP-AMP 合酶(cGAS)和干扰素-I 诱导蛋白 16 (IFI16)的高表达水平与疾病活动度密切相关。cGAS 识别胞质双链 DNA 可诱导 cGAMP 的产生并激活 IFN 基因刺激因子(STING)。cGAS 在 DNA 刺激的 IFN-*β* 产生中起关键作用，并导致与 ISG 高表达相

关的疾病，尤其是 SLE [17]。IFI16 不仅作为促炎分子和内皮细胞凋亡的诱导剂，而且通过与 STING 相互作用导致 IFN-I 的产生，作为病毒感染和全身性自身免疫性疾病炎症的重要介质[18]，外周血单核细胞(PBMC)中环状 GMP-AMP 合酶(cGAS)和干扰素-I 诱导蛋白 16 (IFI16)的高表达水平与疾病活动度密切相关。cGAS-STING 轴的阻断代表了 SLE 的一个有前途的治疗靶点。内源性逆转录元件(如 LINE-1)也可以激活 SLE 中的 I 型 IFN 系统[19]，作为额外的核酸刺激。

I 型干扰素(IFN)是系统性红斑狼疮(SLE)的主要致病因素。IFN-I 通过对内皮细胞的作用直接促进内皮功能障碍，即过量 IFN-I 引起的 EPC 耗竭可能与 SLE 患者的内皮功能障碍和心血管风险增加有关[20]。Tie2 是血管稳定所必需的受体，I 型 IFN 通过抑制 Tie2 信号传导在内皮细胞(EC)的稳定性中发挥重要作用[21]。I 型干扰素还促进 NK 细胞和细胞毒性 T 细胞的细胞溶解活性，可增加组织损伤和抗原过载，这是 SLE 发展的主要因素之一[22]。虽然 I.型干扰素被认为是 SLE 发病机制中的关键干扰素，但不同类别的 I 型干扰素似乎在 SLE 的调控中具有不同的功能。

3. I 型干扰素在系统性红斑狼疮中的作用

1) 干扰素-α (IFN-α)：IFN-α 是自身免疫反应的关键调节因子，IFN-α 可能由所有白细胞产生，但浆细胞样树突状细胞(pDC)是主要来源。NK 细胞在含 RNA 的免疫复合物刺激下可诱导 pDCs 分泌 IFN-α，而单核细胞则起抑制作用[23]。此外，重组 IFN-α 作为恶性肿瘤或肝炎感染患者的治疗药物时，可诱发 SLE。中性粒细胞胞外陷阱(NETs)提供内源性 I 型 IFN 通路刺激，从而能够分泌高水平 IFN-α [24]。IFN-α 可加速内皮细胞(EC)凋亡和破坏内皮祖细胞(EPC) [25]，也可改变内皮祖细胞(EPC)和髓样循环血管生成细胞(CAC)介导的血管修复之间的平衡，IFN-α 对狼疮血管生成的有害影响通过抑制 IL-1 依赖性途径来干扰 SLE 的血管修复[26]。IFN-α 也可使平滑肌祖细胞(SMPC)维持未成熟状态，从而产生巨噬细胞并最终产生泡沫细胞[27]，这会导致 SLE 患者的内皮功能障碍和过早心血管风险(CVD)的显著增加。血清 IFN-α 水平升高与 SLE 疾病活动性和发热、关节痛、皮疹和白细胞减少等特定临床表现相关[28]。高剂量 IFN-α 治疗可诱导多种神经精神不良反应，脑脊液中检测到较高水平的 IFN-α，但当狼疮精神病的表现消退时，IFN-α 水平下降[29]。在最近比较 SLE 患者与健康对照的微阵列研究中，IFN-α 诱导基因的过度表达是 SLE 患者外周血单核细胞中最主要的发现之一[30] [31]。SLE 家族队列中年轻个体的血清 IFN-α 活性较高，这种与年龄相关的 IFN-α 活性模式可能导致成年早期 SLE 发病率的增加[32]。IFN-α 是自身免疫反应的关键调节因子。

2) 干扰素-β (IFN-β)：成纤维细胞和上皮细胞及 B 细胞，会产生 IFN-β [33]，在狼疮中，IFN-β 在发育中的 B 细胞中的过度表达可能会促进自身反应性成熟 B 细胞的产生[34]。在 SLE 小鼠模型中，B 细胞内在产生的 IFN-β 不依赖于环境，是 TLR7 信号增强和自身反应性 B 细胞发育的固定特征[35]。SLE 患者 PBMC 中 cGAS 和 IFI16 的表达与 IFN-β 相结合可能作为早期诊断和监测 SLE 疾病活动的潜在生物标志物[36]。SLE 患者循环 B 细胞中 IFN-β 水平升高，在非裔美国肾病患者和自身抗体患者中明显更高[37]，有肾脏疾病史的 SLE 受试者在过渡和幼稚 B 细胞中也表现出 IFN-β 的显著增加。系统性红斑狼疮骨髓间充质干细胞基于涉及先天信号分子线粒体抗病毒信号蛋白的正反馈回路产生更多的干扰素 β，IFN-β 信号转导抑制人 SLE 骨髓的成骨[38]。

3) 干扰素-κ (IFN-κ)：在 SLE 患者中，狼疮角质细胞产生 IFN-κ，IFN-κ 是一种多功能 I 型 IFN，当在小鼠胰岛的 β 细胞中转基因表达时，可诱导自身免疫[39]，也会导致 IL-6 的过量产生[40]，因此，IFN-κ 被认为是参与人类和小鼠模型 SLE 的光敏性和其他皮肤表现的关键介质，也是预防皮肤红斑狼疮(CLE)靶向治疗的潜在新靶点[41] [42]。在 SLE 皮肤病变中，I 型 IFN 的产生增加，浆细胞样树突状细胞在皮肤狼疮病变中积聚[43]。

4) 干扰素-ε 和干扰素-ω 在系统性红斑狼疮的作用尚不明确。

4. IFN-I 通路的靶向治疗

目前 SLE 的标准治疗包括使用皮质类固醇和免疫抑制剂[44]，I 型 IFN 被认为是减少 SLE 慢性炎症和终末器官损伤的潜在靶点。两种最常用的系统性红斑狼疮药物羟氯喹(HCQ)和糖皮质激素会影响 I 型 IFN 系统并下调 I 型 IFN 特征。HCQ 通过阻断核酸的 TLR7/9 结合表位[45]以及可能通过干扰内源性核酸来干扰 TLR7 和 TLR9 激活。最近，还表明 HCQ 抑制 IFN-β 诱导的 DNA 传感器 cGAS [46]。糖皮质激素具有许多免疫抑制作用，包括高剂量使用时 pDC 的消耗[47]。

现已经开发出抗 IFN-α 抗体(rontalizumab、sifalimumab 及 AGS-009)、抗 I 型 IFN 受体抗体(anifrolumab)和诱导抗 IFN-α 抗体(IFN-α 激酶)的疫苗制剂。罗他利珠单抗(Rontalizumab)是一种中和 IFN-α 的人源化 IgG1 单克隆抗体，在给予 rontalizumab 后，在 3 mg/kg 和 10 mg/kg 队列中观察到 IRGs 表达的快速下降，并且这种效果可以通过重复给药来维持[48]。西法木单抗(Sifalimumab)是一种全人源 IgG1 单克隆抗体，可中和 IFN-α。但 IFN 特征的抑制程度是中度疾病患者高于疾病活动性更强的患者，西伐单抗 I 期研究的结果显示，与安慰剂相比，治疗后 IFN 信号具有显著的剂量依赖性抑制，并且未报告严重不良事件[49]。AGS-009 是一种人源化 IgG4 单克隆抗 IFN-α 抗体，AGS-009 已成功完成 Ia 期安全性试验。阿尼鲁单抗(Anifrolumab)是一种全人源 IgG1κ 单克隆抗体，可与 IFNAR 结合并阻止所有 I 型 IFN 的信号传导。Anifrolumab 在中度至重度 SLE 患者的多个临床终点显著降低了疾病活动度[50]。免疫治疗疫苗干扰素 α 激肽(IFN-K)诱导中和抗 IFN-α2b 抗体，显著降低 IFN 基因特征，耐受性好，免疫原性好，安全性可接受[51]。

5. 小结与展望

综上所述，随着科研工作不断进展，IFN-I 越来越被认为是 SLE 患者的一种中枢致病介质。不同类型的 I 型干扰素被人类发现，成为研究的热点。I 型干扰素在狼疮的发生发展中占据着不可或缺的地位，针对 IFN 和 IFN 信号通路的新的治疗策略正在开发中，但进展有限，需要我们进一步的研究，提供更具体、更有效的靶向治疗，并最终为 SLE 提供个性化的治疗方法。

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