IL-37与自身免疫性疾病

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摘要 由调节性T细胞和免疫抑制因子提供的负反馈调控是免疫反应中的重要组成部分. 白介素37 (IL-37) 是最近发现的具有广泛免疫抑制活性的免疫抑制因子. 在炎症反应和自身免疫性疾病的发生发展中, IL-37被激活并保持较高水平的表达. 被激活的IL-37具有较强的炎症抑制作用. 在多种小鼠(*Mus musculus*)炎症模型中, 表达IL-37的转基因小鼠具有较低水平的炎症反应. IL-37可以与IL-18受体结合并激活下游信号通路, 进而表达和激活或抑制相关细胞因子, 从而达到免疫抑制的作用. 本文将首先对免疫抑制细胞和因子进行概述, 然后详细阐述IL-37的发现历史、表达调控机制, 以及其在自身免疫性疾病中的作用.

关键词 IL-37, 自身免疫性疾病, 白介素37

免疫系统为机体提供一系列保障, 使机体免于寄生虫、病毒、细菌、真菌以及其他外源有毒物质的侵害. 这对于免疫系统具有极大的挑战性, 因为免疫系统要能够区分哪些是对机体有利的, 哪些是对机体有害的. 在人体内, 有部分微生物对于机体是有利的, 它们帮助人类消化食物、产生维生素、抑制有害菌生长以及调控免疫系统的发育. 正常的免疫系统必须能够保证这些有利于机体的外源物质和自身物质不被攻击, 而有害的物质则必须被彻底清除. 因此, 免疫系统必须具备识别特定外源有害物质的效应分子, 同时也要具备由调节性T细胞(Treg)和免疫抑制因子提供的负反馈调控, 从而使机体免于遭到过度激活免疫系统的攻击^[1-4]. 免疫抑制作用是由Treg细胞和免疫抑制因子(IL-2, IL-10, IL-27, IL-35, IL-37和转化生长因子 β

(transforming growth factor- β , TGF β)等)提供^[3-5].

1 免疫抑制细胞和因子

1.1 调节性T细胞

目前共发现了3种CD4⁺的Treg细胞, 其中两种表达转录因子Foxp3. Foxp3阳性Treg细胞又可以根据其定位分为天然Treg细胞和可诱导Treg细胞. 天然Treg细胞定位于胸腺而可诱导Treg细胞存在与外周血系统. 第3种Treg细胞是Tr1细胞, 它不表达Foxp3, 但在抗原刺激下可分泌IL-10和TGF β ^[6,7]. Foxp3阳性细胞在调节免疫系统平衡中起着重要作用, 具有Foxp3基因突变的病人患有严重的自身免疫性疾病^[8,9]. Foxp3可以通过调控特定转录因子的表达或激活特定转录因子来

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调控效应细胞,其作用形式类似与其他辅助性T细胞,如Th1, Th2和Th17. 根据不同的表面分子标记, Foxp3阳性Treg可以进一步分为不同的细胞亚型^[10-12]. 根据趋化因子受体CCR6, CCR3, CCR4和CCR10的表达情况,可以将Foxp3阳性Treg细胞分为4种不同的类型^[13]. 根据CD45RA的表达情况, Foxp3阳性细胞也可以分为两种不同类型: CD45RA⁺Foxp3^{low}代表原始或静息Treg细胞和CD45RA⁺Foxp3^{hi}代表效应或激活的Treg细胞;而CD45RA⁺Foxp3^{low}则代表非Treg细胞^[14].

Treg细胞可通过细胞接触和分泌细胞因子两种方式介导其免疫抑制作用. Treg细胞可以分泌IL-10, TGF β , IL-35, granzyme和perforin; 可通过其表面分子CD25 (IL-2受体 α 链)结合IL-2进而清除效应T细胞; 可以通过ectonucleotidases降解ATP; 通过表达抑制性受体CTLA4, 与效应细胞表达的激活受体CD28竞争性结合抗原呈递细胞表达的激活分子CD80和CD86^[15-17]. 自身免疫性疾病通常伴有Treg细胞比例和功能的变化^[18].

1.2 IL-2

早期研究发现, IL-2可以在体外刺激活化T细胞的增殖, 因此曾经认为IL-2是促炎症因子^[19]. 但IL-2基因敲除小鼠(*Mus musculus*)却表现出严重的自身免疫性疾病^[20,21]. 后续研究发现, 具有免疫抑制功能的Treg细胞高表达IL-2的受体分子CD25, 从而可以被IL-2激活并抑制免疫活性^[22]. IL-2可以激活CD4⁺Foxp3⁺ Treg细胞, 因此IL-2具有抑制免疫的活性^[23]. 此外, IL-2还可以通过干扰IL-6信号通路来抑制Th17细胞的分化, 从而达到控制炎症反应的效果. IL-2可以在转录激活结合位点用STAT5替换STAT3, 进而降低IL-6受体和其他参与Th17分化的细胞因子的表达^[24,25]. 敲除或沉默IL-2可以明显提高IL-17的表达^[24,26]. 此外, 过量Foxp3阳性Treg细胞可以过度消耗IL-2, 从而有利于促进Th17细胞的分化^[27,28]. IL-2还可以影响滤泡辅助性T细胞的发育. 滤泡辅助性T细胞是一类调控体液免疫反应的辅助性T细胞, 它们定位于生发中心并表达CXCR5和分泌IL-21, 帮助B细胞进行体细胞突变和亚型转换^[29-32]. 但IL-2对于滤泡辅助性T细胞的影响是间接性的, 因为IL-2只影响滤泡辅助性T细胞的分化, 但并不影响已经分化的滤泡辅助性T细胞^[33-35]. 所以, IL-2可以通过降低Th17和滤泡辅助性T细胞的数量, 增加Treg细胞的数量来起到免疫抑制的作用, 以防止过度炎症反

应的发生.

1.3 IL-10

IL-10广泛表达于各种免疫细胞中, 包括树突状细胞、巨噬细胞和粒细胞^[36]. IL-10主要调控机体感染过程中的免疫反应, 以防止过度免疫反应对机体自身的损害^[37]. IL-10的表达可以从多方面进行调控, 包括染色质结构、转录因子和转录后调控^[38,39]. 在小鼠和人上, IL-10缺失或突变都可导致严重的自身免疫性疾病^[40,41]. IL-10可以通过调控多种免疫细胞, 在免疫反应的不同阶段抑制免疫系统的过度激活. IL-10抑制树突状细胞、巨噬细胞和单核细胞分泌各类促炎症因子; 抑制主要组织相容性复合体和各类激活因子的表达; 激活多种免疫抑制因子的表达和相关受体的表达. 此外, IL-10可以抑制Th17细胞的增殖^[42,43], 促进Treg细胞的存活和功能^[44,45], 促进B细胞分化和抗体分泌^[46,47]. IL-10表达异常与多种疾病相关, 其中包括自身免疫性疾病^[48].

1.4 TGF β

TGF β 属于一个包含多种成员的基因家族. 其中TGF β 1在胚胎发育、免疫系统发育和免疫调控中起着重要作用^[49-52]. 敲除TGF β 1的小鼠患有严重的自身免疫性炎症疾病^[53]. TGF β 1可以促进Foxp3阳性细胞的发育; 促进Th17细胞的发育; 抑制Th1和Th2细胞的发育; 调控抗体亚型转换和分泌^[54-58].

1.5 IL-27

IL-27由p28 (IL30)和EBI3两个亚单位组成, 主要在巨噬细胞和树突状细胞中表达^[59]. IL-27缺失的小鼠更加容易死于过度激活的免疫攻击^[60,61]. IL-27可以将被激活的、具有促炎症功能的CD4⁺ T细胞转变为表达IL-10的Th1或Tr1细胞^[62]. IL-27可以在T细胞中上调转录因子AhR, 并与转录因子c-Maf协同作用, 共同激活IL-10和IL-21, 最终导致Tr1细胞的产生^[63]. IL-27在多种炎症反应中也抑制Th2和Th17细胞的产生^[62].

1.6 IL-35

IL-35由EBI3和p35 (IL-12)两个亚单位组成, 主要在Treg细胞中表达^[64,65]. IL-35可以将促炎症CD4⁺ T细胞转变为Treg细胞并表达IL-35但不表达Foxp3, TGF β

和IL10 (iTreg35细胞). 这种细胞可以有效抑制多种自身免疫性疾病的发生和发展^[66].

1.7 IL-37

IL-37是最近发现的具有广泛免疫抑制活性的免疫抑制因子. 在炎症反应和自身免疫性疾病的发生发展中, IL-37被激活并保持较高水平的表达. 被激活的IL-37具有较强的炎症抑制作用. 在多种小鼠炎症模型中, 表达IL-37的转基因小鼠具有较低水平的炎症反应. IL-37可以与IL-18受体结合并激活下游信号通路, 进而表达和激活或抑制相关细胞因子, 从而达到免疫抑制的作用.

2 白介素37

2.1 IL-37的基因结构和表达调控

早在2000年, 有3个不同实验室分别报道了IL-37基因的克隆和鉴定^[67-69]. 在正式命名IL-37之前, 它拥有多个别名(表1). 人类IL-37基因位于IL-1基因家族区域内, 临近IL-1 α 和IL-1 β , 定位于染色体2q12-13^[72]. IL-37共有5个不同的转录本(IL-37a~e). 但是其各自的作用, 组织分布并不清楚. 如图1所示, IL-37亚型a, b和d都含有外显子4, 5和6, 该区域负责IL-37细胞外活性功能域的编码. 而外显子1, 2和3编码的蛋白质, 在完成细胞分泌后被切除, 但其具体作用和负责蛋白切除的相关酶并不清楚. 目前还没有在小鼠和黑猩猩(*Pan troglodytes*)上发现IL-37的同源基因, 但在大猩猩和其他灵长类动物中都发现了该基因的同源基因^[73]. 现在还不清楚IL-37在小鼠和黑猩猩基因组中缺失的原因. IL-37的第一个外显子可以在小鼠的基因组中找到, 但

并不具有完整的编码区. 此外, 人类IL-37具有较高的突变频率, 目前共发现了14个不同的变异体^[74]. 因此, IL-37的基因位置可能是个基因突变热点. 序列分析显示, IL-37并没有前导肽序列, 仅在外显子1的位置(蛋白序列第20位, 即天冬氨酸)有一个caspase1的切割位点^[75]. IL-37在体内具有多种不同的N端序列, 并且缺失N端45个氨基酸的重组蛋白比野生型IL-37具有更高的活性, 说明IL-37在体内具有由多种酶参与的活化过程, 但其具体机制目前尚不清楚^[69,76,77].

通过免疫组化分析, IL-37在人类外周血液单核细胞、组织巨噬细胞、关节液细胞、扁桃体B细胞、浆细胞、肿瘤细胞以及皮肤、肾脏和小肠的上皮细胞中表达^[78]. 健康人体细胞中的IL-37表达量非常低, 但其可被Toll样受体激活剂和促炎症因子所激活, 如IL-1 β , TNF α 和IFN γ ^[79]. 即使在IL-37被激活后, 其蛋白含量仍然很低, 这是由于其mRNA半衰期较短^[79]. 在转基因小鼠中, 尽管IL-37是由组成型启动子CMV驱动表达, 其mRNA水平依然很低^[77,80-82]. 在人外周血单核细胞被激活后, 其IL-37的蛋白含量也只能达到10~20 pg/百万细胞. 尽管其产量较低, 但其活性很高. 在体外实验中, pg级的IL-37已经具有很好的免疫抑制作用; 而在小鼠

表1 IL37别名

别名	亚型	参考文献
<i>FIL1ζ</i>	<i>IL-37a</i>	[70]
<i>IL-1H4</i>	<i>IL-37b</i>	[67]
<i>IL-1RP1</i>	<i>IL-37c</i>	[68]
<i>IL-1HL</i>	<i>IL-37b</i>	[69]
<i>IL-1HS</i>	<i>IL-37c</i>	[69]
<i>IL-1F7</i>	<i>IL-37b</i>	[71]

图1 人IL-37基因结构和转录本亚型(网络版彩图)

体内, 注射 μg 级的IL-37已经具有炎症抵抗作用^[76,83-85].

2.2 IL-37的作用机制

IL-37可以被LPS, Pam3CSK4, CpG, IL-1 β , IL-18, TNF α , IFN γ 和TGF β 激活, 被IL-12, IL-32, GM-CSF和IL-4抑制^[80]. 此外, triptolide和triptonide^[86], hBD3^[87], β -defensin 3^[87], flagellin^[87], peptidoglycan^[87], lipoarabinomannan^[88]和poly (I:C)^[87]也可以诱导IL-37的表达.

在小鼠(RWA细胞系)和人(THP-1细胞系)的巨噬细胞系中高表达IL-37, 可以有效降低由LPS或IL-1 β 诱导的细胞因子分泌(如TNF α , IL-1 α , IL-1 β , IL-6, GM-CSF, IL-23和可溶性ICAM-1)和信号通路分子活性(如FAK, STAT3, mTOR, p53, STAT1, p38, paxillin, Syk, SHP-2和AKT)^[75,80,89,90]. 在人类单核细胞的原代细胞中沉默IL-37, 会导致TNF α , IL-1 α , IL-1 β , IL-6, G-CSF和GM-CSF的表达量增加^[80,89]. 此外, 在LPS刺激人类单核细胞的同时利用IL-37抗体中和IL-37可以增加TNF α , IL-1 β 和IL-6的表达量^[76]. 此外, 这一现象也存在于树突状细胞、巨噬细胞中^[76,91]. 而且IL-37还具有抑制Th1和Th17细胞分化的功能^[91]. 这些证据都表明IL-37具有抑制免疫反应的作用(图2).

在没有IL-37蛋白的情况下, IL-18可以在细胞表面结合其受体IL-18R α 并招募其共受体IL-18R β 形成完整的IL-18受体分子^[92]. 位于IL-18R α 和IL-18R β 的TIR结构域从而可以结合在一起, 并进一步招募其配体分子MyD88, 进而激活一系列的促炎症分子信号. 在有IL-37存在的情况下, IL-37也可以结合IL-18R α 并阻止IL-18R β 与IL-18R α 的结合, 从而抑制了下一步的促炎症信号^[69,78,92,93]. IL-37结合IL-18R α 后招募其共受体IL-1R8. IL-1R8仅含有一个具有突变的TIR结构域(TIRb), 降低了MyD88的结合活性, 从而降低了促炎症反应信号^[94,95]. 尽管IL-18R α 在多数细胞中都表达, 但

并不是所有细胞都可以响应IL-18的刺激, 因为还需要IL-18R β 的表达^[96]. 但所有细胞都表达IL-1R8, 因此可以响应IL-37的刺激并行使其免疫抑制功能^[97,98]. 敲除或沉默IL-18R α 或IL-1R8可以抵消IL-37的抗炎作用^[76,89]. 但IL-37/IL-18R α /IL-1R8信号通路并不能完全解释IL-37的作用, 因为IL-1R8的TIRb结构域仍然有少部分结合MyD88的活性, 所以不能完全抑制炎症反应^[99].

此外, 也有研究表明, IL-37可以结合IL-18BP蛋白. IL-18BP可以招募IL-18R β 并阻断其与IL-18R α 的结合, 从而起到抗炎作用^[100]. IL-37结合IL-18BP后, 可以提高IL-18BP的抗炎作用^[93].

IL-37除了被释放到细胞外, 并通过IL-18信号通路起到抗炎作用外, 它还可以直接进入细胞核内, 参与转录调控作用^[75]. IL-37的核转移作用依赖于caspase1活性, 抑制caspase1活性可以阻止其核定位和抗炎作用^[90]. SMAD3是TGF β 信号通路中的重要一员, 并在TGF β 介导的抗炎作用中起着重要作用. 有研究表明, IL-37可以与磷酸化SMAD3相结合, 并且抑制SMAD3活性可以抑制IL-37的抗炎作用(图3)^[80]. 但其核定位的调控机制以及其在细胞核内的具体作用, 目前尚不清楚.

3 IL-37在自身免疫性疾病发生、发展中的作用

自身免疫性疾病是一类由免疫系统异常引起的免疫系统攻击自身细胞和组织, 进而导致自身细胞和组织受到损伤并且其功能受到严重影响甚至损害的疾病. 研究发现, IL-37在多种自身免疫性疾病中都表达异常, 包括系统性红斑狼疮(systemic lupus erythematosus, SLE)^[101,102]、类风湿性关节炎(rheumatoid arthritis, RA)^[103-106]、炎症肠炎(inflammatory bowel disease, IBD)^[107-109]、强直性脊柱炎(ankylosing spondylitis, AS)^[110]、牛皮癣(psoriasis)^[111]、吉兰-巴雷综合征(Guillain-Barré syndrome)^[112]、异位性皮炎(atopic dermatitis)^[113]、糖尿病(obesity)^[114,115]和甲状腺功能亢进(Graves' disease, GD)^[82]. 此外, IL-37还直接参与了这些自身免疫性疾病的发生和发展^[116].

与健康个体相比, 自身免疫病(包括RA、牛皮癣、AS, GD和SLE)病人的血清和外周血单核细胞中都有

图2 IL-37的抗炎作用(网络版彩图)

图3 IL-37的抗炎机制(网络版彩图)

较高水平的IL-37表达, 以及其他炎症因子, 如 $\text{TNF}\alpha$, IL-6和IL-17^[82,101~103,106,111,117]. 血清中的IL-37水平与炎症因子和疾病活性指数呈正相关性^[82,101~103,117].

4 利用IL-37治疗自身免疫性疾病的潜在前景

在葡聚糖硫酸酯钠(dextran sulfate sodium, DSS)诱导的小鼠肠炎模型中, IL-37转基因小鼠具有显著降低的发病率、淋巴细胞浸润和炎症因子表达^[81]. 在体外, 用IL-37处理AS, GD和SLE病人的外周血单核细胞, 可以明显降低炎症因子 $\text{TNF}\alpha$, IL-6和IL-17的表达水平^[82,102,117]. IL-37在小鼠中的显著抗炎作用和在外周血IL-37对人外周血细胞的免疫抑制作用, 使得IL-37成为一个潜在的、具有广泛应用前景的抗炎药物和自身免疫性疾病的治疗药物. 但在大规模临床研究之前, IL-37的具体作用机制以及其他动物模型中的效果

和安全性都需要进一步研究.

5 结论与展望

IL-37作为一种新出现的免疫抑制因子, 在治疗自身免疫性疾病中具有潜在的应用前景. 但目前对于IL-37的具体作用机制仍然不是十分清楚. 有几个问题是亟待解决的: (i) 为什么在小鼠和黑猩猩的基因组中没有发现IL-37的同源基因, 这是不是意味着IL-37是冗余的? 还是IL-37参与了进化选择? (ii) IL-37不同转录本之间有什么差异, 其具体的转录调控机制是如何的? (iii) IL-37是如何进入细胞核内和释放到细胞外的? (iv) IL-37蛋白水平的剪切和修饰是如何进行的? (v) IL-37在细胞核内的具体作用机制是什么? 最后一点是IL-37在其他动物模型中的作用是目前最为需要研究的, 因为现在大部分研究都是基于小鼠模型而小鼠却缺乏IL-37基因.

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Interleukin-37 and autoimmune diseases

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Anti-inflammatory factors and regulatory T cells function as negative feedback circuit in immune responses. Interleukin-37 (IL-37) has been characterized as the anti-inflammatory factor recently and it is activated in inflammatory responses and autoimmune diseases. The activated IL-37 has high anti-inflammatory activities. In the IL-37 transgenic mice, there is a very low level of inflammatory factors when the mice are stimulated with antigens. IL-37 could bind to IL-18 receptor and activate downstream pathways, resulting in anti-inflammatory factors' activation and immune suppression. In this review, we first discuss the regulatory T cell and cytokines involved in immune suppression and second discuss IL-37, including the history, mechanism of regulation and its role in the development of autoimmune diseases.

IL-37, autoimmune diseases, interleukin-37

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