

HLA-B关联转录因子3在免疫相关疾病中的作用

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Role of HLA-B associated transcript 3 in immune diseases

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Abstract

HLA-B associated transcript 3 (BAT3/Scythe/BAG6) is a member of the BAG protein

family which can regulate the cell cycle. Recently, BAT3 has also been identified to have immunoregulatory function through kinds of mechanisms. First, BAT3 can promote the maturation of dendritic cells (DCs), the activity of macrophages and the expression of major histocompatibility complex (MHC)-II on antigen presenting cells (APCs) to regulate chronic inflammation. Second, BAT3 can suppress T cell immunoglobulin and mucin domain 3 (Tim-3)-mediated cell death and exhaustion of T helper cell type 1 (Th1) to exacerbate autoimmune diseases. Finally, BAT3 can regulate the cytotoxicity of natural killer cells (NKs) in a NKp30-dependent manner to play a part in tumor immune evasion and tumor rejection. Further details about BAT3 and its involvement in immunity and immunity-associated diseases will benefit the novel strategy for treatment of immune diseases.

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Key Words: BAT3; Inflammation; Autoimmune disease; Tumor immunity

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摘要

HLA-B关联转录因子3(HLA-B associated transcript 3, BAT3/Scythe/BAG6)是BAG蛋白家族一员。近几年发现他除调控细胞周期

■背景资料

HLA-B关联转录因子3(HLA-B associated transcript 3, BAT3/Scythe/BAG6)是BAG蛋白家族的一员,过去研究普遍认为他在调控凋亡、细胞周期、细胞内质量控制、蛋白质折叠和基因损伤修复中发挥作用。而最近的研究发现BAT3以多种机制在免疫调节方面也发挥了重要的作用。

■同行评议者

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■ 研究前沿

免疫相关疾病一直是近年研究的热点, 这一类疾病与免疫失调密切相关。而BAT3可介导的辅助性T细胞(T helper cells, Th)1凋亡, 并调节Tim-3(T cell immunoglobulin and mucin domain 3)/半乳糖素-9(galactin-9, Gal-9)通路。而与炎症性肠病等很多慢性炎症相关的BAT3/Tim-3/Gal-9通路可能成为今后免疫和炎症领域的研究热点。BAT3也与多种肿瘤免疫逃逸相关, 肿瘤患者BAT3变异的存在有望为肿瘤早期诊断提供帮助。

外还以多种机制参与机体免疫调控, 通过促进树突状细胞(dendritic cells, DCs)成熟、巨噬细胞的活性及抗原提呈细胞(antigen presenting cells, APCs)上主要组织相容性复合体(major histocompatibility complex, MHC)-II的表达来调节慢性炎症; 细胞内表达的BAT3抑制Tim-3(T cell immunoglobulin and mucin domain 3)介导的辅助性T细胞(T helper cells, Th)1凋亡, 加重自身免疫性疾病; 肿瘤细胞分泌的BAT3依赖天然杀伤细胞(natural killer cell, NK)p30调节NKs的毒性, 参与肿瘤细胞免疫逃逸和肿瘤排斥。进一步了解BAT3及其与免疫调控和免疫相关疾病的研究进展有利于为免疫相关疾病的治疗带来新的方法。

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关键词: BAT3; 炎症; 自身免疫性疾病; 肿瘤免疫

核心提示: 近年发现HLA-B关联转录因子3(HLA-B associated transcript 3, BAT3/Scythe/BAG6)可调控免疫: 促进树突状细胞(dendritic cells, DCs)成熟、巨噬细胞的活性和抗原提呈细胞(antigen presenting cell)主要组织相容性复合体(major histocompatibility complex)-II的表达, 调节机体炎症; 与Tim-3(T cell immunoglobulin and mucin domain 3)结合, 抑制其介导的Th1细胞凋亡, 也加重了实验性自身免疫性脑脊髓膜炎等自身免疫性疾病; 以天然杀伤细胞(natural killer cell, NK)p30依赖的方式参与肿瘤免疫逃逸和肿瘤排斥。

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0 引言

机体免疫系统分为相互联系的固有免疫和适应性免疫, 固有免疫细胞如天然杀伤细胞(natural killer cells, NKs)、树突状细胞(dendritic cells, DCs)和巨噬细胞等; 适应性免疫细胞如T细胞和B细胞^[1]。其中DCs和巨噬细胞参与抗原入侵后的抗原提呈^[1,2]; 调节性T细胞(regulatory T cell, Treg)和辅助性T细胞(T helper cells, Th)参与机体免疫稳定; NKs是免疫监视的主力军。这些免疫细胞作为炎

症反应的执行者, 其功能和状态与感染、自身免疫性疾病、肿瘤密切相关^[3]。1989年Spies等^[4]发现染色体6p21.3位点与HLA-B结合并命名为HLA-B关联转录因子(HLA-B associated transcript), 其编码的蛋白称为BAG蛋白家族。HLA-B关联转录因子3(HLA-B associated transcript 3, BAT3/Scythe/BAG6)是BAG蛋白家族的一员, 由*bat3*编码, 早期研究发现他可以调控凋亡、细胞周期、细胞内蛋白的质量控制及基因修复^[5-8]。而近期发现BAT3可以通过促进DCs成熟和巨噬细胞的活性及二者主要组织相容性复合体(major histocompatibility complex, MHC)-II的表达来调节机体免疫防御, 与结核病等炎症有关; BAT3抑制Tim-3(T cell immunoglobulin and mucin domain 3)介导的Th1细胞凋亡, 打破免疫自稳, 加重小鼠实验性脑脊髓炎等自身免疫性疾病; 肿瘤细胞分泌的BAT3通过NKs细胞表面的毒性受体调节NKs的毒性, 参与肿瘤细胞免疫逃逸和肿瘤排斥^[9-13]。这为慢性炎症、自身免疫性疾病和肿瘤的治疗带来契机, BAT3有望成为新的治疗靶点。现就BAT3与免疫调控间的研究现状作一综述。

1 BAT3结构和功能

人BAT3全长1126个氨基酸, 约140 kDa, 由C-末端的BAG域(BAG domain)、BAG域上游的二联体核定位信号(nuclear localization signal, NLS)和N-末端的泛素结构域(ubiquitin-like domain, UBL domain)组成, 这些结构域排列在富含脯氨酸的TXSEEX重复序列上^[14]。BAG域由250个氨基酸组成, 是已发现的BAG家族蛋白BAG1-9共有的保守序列^[14]。单核细胞、DCs和NKs等免疫细胞及HeLa和肝癌细胞等肿瘤细胞中检测到BAT3^[15]。其细胞内定位广泛, 细胞核中的BAT3可以调节组蛋白的翻译后修饰和基因表达; 其NLS序列突变可诱导BAT3从核内排出, 在胞质中与UBLA4, TRC35结合成三聚体负责疏水蛋白的组装, 蛋白酶的降解, 参与细胞蛋白的定位及对多肽链的质量控制; Derlin2可将细胞质中的BAT3招募到内质网膜, 指导错构蛋白从内质网排出和降解^[7,16-18]。最近发现DCs和肿瘤细胞可释放含有BAT3的外泌体, 参与对肿瘤细胞的免疫监视; DCs细胞膜上的BAT3可以通

过与NKp30和NKp44结合激活NKs的细胞毒性, 调节DCs成熟^[9,11].

2 BAT3与炎症

当外来细菌和病毒等入侵机体时, 固有免疫作为第一道防线, 抗原提呈细胞(antigen presenting cell, APC), 如DCs和巨噬细胞, 摄取外来抗原加工处理后, 通过MHC-II提呈到细胞表面, 识别和激活适应性免疫细胞, 通过体液免疫和细胞免疫杀死入侵的病菌^[1]. 在这个过程中, DCs和巨噬细胞的功能状态与免疫防御密切相关^[19]. 而研究发现BAT3可调节DCs和巨噬细胞的活性.

2.1 BAT3促进DCs成熟 当受到各种炎症因子和细菌分泌的脂多糖等刺激时未成熟树突状细胞(imature dendritic cells, iDCs)分化为成熟树突状细胞(mature dendritic cells, mDCs), 表达更多的MHC-I, 发挥更强的抗原提呈作用, 分泌更多的炎症因子激活NKs; 反过来, NKs识别并杀死iDCs, 促进DC成熟^[20,21]. 但在诱导DCs成熟的过程中, DCs和NKs的通讯机制未明, 直到最近发现iDCs除分泌BAT3外, 细胞核、细胞膜上也分布有BAT3, 且膜上的BAT3与MHC-I共定位, 可作为NKp30的配体激活NKs, 启动细胞毒作用杀伤iDCs, 而mDCs表达的大量MHC-I从而避免了凋亡^[20]. 推测iDCs和mDCs上表达的MHC-I类分子数量不同或结构不同, 影响了BAT3与MHC-I共表达在细胞膜上, 从而导致BAT3介导的NKp30依赖的iDCs的凋亡. 此外, 当iDCs与NKs共培养时可诱导CD86的上调, 而加入可溶性的BAT3会使上调的CD86减少, 这说明BAT3对NKs介导的DCs的成熟有密切影响^[9]. 通过诱导iDCs的凋亡, 选择了一类更有效的DCs群, 发挥更有力的免疫防御作用^[22]. 但是关于BAT3如何结合在DCs细胞膜上仍是未知数.

2.2 BAT3调节APC上MHC-II表达 MHC-II由HLA-II编码, 将细胞内吞噬的外源性抗原加工处理后以肽段的形式提呈到细胞表面^[23]. γ 干扰素(interferon- γ , IFN- γ)诱导的II类分子反式激活因子(class II transactivator, CII TA)促进启动子组蛋白乙酰化, 在转录水平上诱导MHC-II的表达, 而在表达MHC-II的肿瘤细胞及原代人类巨噬细胞中, IFN- γ 刺激同步上调CII TA和BAT3的表达, 同时在荧光镜下

观察到了CII TA和BAT3的共移位^[24]. 然而, BAT3调节CII TA的分子机制不明, 且BAT3的过表达不会改变CII TA的表达.

2.3 BAT3调节巨噬细胞活性 在体外研究^[11]中发现热休克的巨噬细胞合成并分泌BAT3, 反过来可以下调IFN- γ 和脂多糖(lipopolysaccharide, LPS)诱导的一氧化氮和炎症因子的分泌. 在结核杆菌感染的巨噬细胞发生早期分泌性抗原靶-6(early secreted antigenic target-6, ESAT-6)诱导的凋亡, 同时诱导一过性BAT3表达, BAT3与抗凋亡蛋白B细胞淋巴瘤基因-2(B cell lymphoma 2, BCL-2)作用, 拮抗ESAT-6诱导的凋亡^[10].

2.4 抑制核因子- κ B(nuclear factor- κ B, NF- κ B)信号通路 NF- κ B信号通路参与结肠炎等多种炎症调控, 该信号通路被激活后, 导致大量促炎因子和炎症介质的分泌, 加重炎症^[25-28]. 研究^[29]发现BAT3抑制NF- κ B通路的DNA结合能力, 显著抑制肿瘤坏死因子(tumor necrosis factor, TNF)依赖的白介素-6(interleukin 6, IL-6)、MCP1和A20的转录. 此外, BAT3 rs3117582单核苷酸多态性(single nucleotide polymorphism, SNP)的编码序列的可变性与肺结核和川崎病的遗传易感性相关^[30,31].

3 BAT3与自身免疫性疾病

Tim-3是表达在Th1和Tc1等免疫细胞膜上的抑制性受体, 诱导T细胞免疫耐受, 与Th1介导的疾病密切相关^[32]. BAT3可与Tim-3的胞内段尾部 Δ 271-281结合, 抑制半乳糖素-9(galectin-9, Gal-9)介导的Th1死亡, 促进Th1增殖和促炎因子合成. Gal-9可通过Tim-3尾部第256和263个残基的磷酸化作用介导BAT3从Tim-3的尾部释放, 且在不表达Tim-3的细胞中BAT3的表达量远低于表达Tim-3的细胞, 推测Tim-3可诱导BAT3的表达^[12]. 将BAT3过表达的Th1细胞转给Rag^{-/-}小鼠导致IFN- γ 和IL-2增多, 此外, 将Bat3^{-/-}小鼠胎肝细胞转给Rag^{-/-}小鼠可显著缓解小鼠的实验性自身免疫性脑脊髓膜炎(experimental autoimmune encephalomyelitis, EAE), 且BAT3缺失导致外周血中出现Tim-3^{high}IFN- γ ^{low}CD4⁺细胞(耗竭型T细胞), IFN- γ 和IL-2降低, Tim-3和IL-10升高.

研究^[33]表明BAT3与多发性硬化(multiple

■ 相关报道

Rangachari等研究发现, 在实验性脑脊髓膜炎小鼠中BAT3可以通过抑制Tim-3介导的T细胞凋亡和耗竭, 促进T细胞免疫反应和自身免疫性疾病的发生. 这可能预示着一新的调节免疫反应的通路-BAT3/Tim-3/Gal-9通路.

■ 创新盘点

针对最近几年BAT3在免疫调节方面的研究进行了整理总结, 并提炼概括为在炎症、自身免疫性疾病和肿瘤中发挥调节作用的具体机制, 对这些疾病的基础研究和临床诊治提供了新思路。

sclerosis, MS)的临床分型密切相关。MS是由自我攻击的髓磷脂碱性蛋白(myelin basic protein, MBP)特异的T细胞介导的中枢神经系统的炎症和脱髓鞘。在良性多发性硬化中, Gal-9/Tim-3相互作用促进MBP特异性的T细胞的凋亡; 而在进展型多发性硬化中, BAT3与Tim-3的作用减缓了T细胞的凋亡。预示着BAT3可能致使该病由良性向进展性转变; 而BAT3的封闭则可能促进疾病向良性转变。各种体内外和临床实验都表明, BAT3可以抵抗Gal-9/Tim-3的抑制作用, 促进Th1介导的各种炎症反应。BAT3与Tim-3的相互作用有望成为多种自身免疫性和炎症性疾病的治疗靶点。

此外, 在小鼠雄性不育模型中观察到BAT3诱导PXT1恢复定位到核中, 抑制胚胎细胞凋亡^[34]。除之前研究^[21,35]发现的BAT3与风湿性关节炎、重症肌无力和1型糖尿病之间的关系外, 最近研究^[36]发现BAT3与帕金森病的发病率有关。此外, 在发生造血干细胞移植后的排斥反应的患者存在BAT2和BAT3位点的多形性, 推测BAT3与移植排斥反应的发生有关^[37]。Etokebe等^[38]发现大关节(髋、膝)骨性关节炎与6号染色体上BAG6 rs3117582 SNP和FAM46A基因的第二个外显子的VNTR的多形性有关。Yang等^[39]在替考拉宁和万古霉素连续治疗引起的Steven-Johnson综合征的患者中发现存在MUC21 rs2844682和BAG6 rs750332的变异。

4 BAT3与肿瘤

NKs是固有免疫系统的关键组成, 通过其表面的激活型和抑制型受体与靶细胞表面特异性配体的结合来对这些细胞进行识别和防御功能, 从而抵抗肿瘤, 病毒和细菌感染的细胞, 这个过程称为免疫监视^[40-42]。肿瘤细胞免疫逃逸的机制之一便是肿瘤细胞分泌可溶性配体, 结合并激活NKs和T细胞上的NK细胞受体成员2D(natural killer group 2, member D, NKG2D)受体, 使这些细胞对肿瘤细胞不敏感^[43,44]。最近研究^[45]发现重组的可溶性片段MULT1, 作为NKG2D的高亲和力受体却引起了NKs的激活和肿瘤排斥。除NKG2D受体外, 自然细胞毒性受体(natural cytotoxicity receptors, NCRs)是NKs表面激活型受体的一小类, 由NKp30、NKp44及NKp46组成^[46]。多发性骨髓

瘤模型中发现肿瘤细胞分泌的BAT3可以激活NKp30依赖的细胞毒性, 引起肿瘤排斥^[9]。而慢性淋巴细胞白血病模型中肿瘤细胞释放的BAT3, 其C-端BAG域与NKs表面NKp30受体结合, 却抑制NKs的细胞毒性作用, 导致了肿瘤免疫逃逸^[21,47]。这看似相反的作用, 可能与BAT3、NKG2D及NKp30的修饰有关。概括来说, BAT3调控NKs的细胞毒性, 参与肿瘤免疫逃逸和免疫监视。在全基因组关联分析中发现15q6p(BAT3-MSH5)和肺癌风险相关, 另一项Meta分析表明BAT3 rs1052486和rs3117582的基因多态性与肺癌风险有关^[48,49]。染色体6p21.33和6p22.1的变异与中国人人群中非吸烟者小细胞肺癌有关^[50]。最近的一项实验^[51]发现, 挪威人的非吸烟者小细胞肺癌患者有BAT3 rs3117582 SNP变异, 且去除年龄和性别的影响后, BAT3的多形性可以作为挪威人和克罗地亚-挪威人的非小细胞肺癌的预测因子。这预示着研制针对BAT3的肿瘤疫苗可能成为新的肿瘤治疗靶点。

5 结论

近年发现BAT3可调控免疫, 膜结合型的BAT3可促进DCs的成熟、巨噬细胞的活性和APC上MHC-II的表达, 调节机体对病菌的防御能力和炎症; 细胞内的BAT3与Tim-3结合, 抑制其介导的Th1细胞凋亡, 也加重了EAE和MS等自身免疫性疾病; 可溶性和分泌性的BAT3以NKp30依赖的方式参与肿瘤免疫逃逸和肿瘤排斥。然而关于BAT3的表达调控、如何在各种亚细胞结构中穿梭、在肿瘤研究中出现的矛盾结果等都需要进一步研究解决。而BAT3与慢性炎症、自身免疫性疾病、肿瘤的关系还需要更多更深入的研究来证实和阐释, 有望成为新的治疗靶点。

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应用要点

本文中提到的BAT3在慢性炎症、自身免疫性疾病和肿瘤中发挥的作用, 都很有应用价值, 有望成为治疗这些疾病的新靶点。进一步研究BAT3有关的机制和开发相关药物, 对临床诊断和治疗有指导意义。

■名词解释

免疫调节: 本文中
指体内外各种信
号分子通过不同
的信号通路调节
免疫分子、免疫
细胞的活性, 从而
调节机体免疫力的
过程;
Tim-3/Gal-9通路:
近年来发现的, 在
Th1等细胞内存在
的一条免疫调节
通路, 细胞外
表达Gal-9, 识别
结合Th1膜上的
Tim-3, 启动Th1细
胞的耗竭和凋亡;
肿瘤免疫逃逸:
肿瘤细胞以各种
不同于普通细胞
的机制逃避了机
体的免疫监视作
用, 无法通过机
体免疫监视识别
和清除。

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同行评价

本文内容较新颖, 阐述清晰, BAT3 为目前研究热点, 尤其是其在免疫方面的作用, 对临床诊治有帮助.

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•消息•

《世界华人消化杂志》栏目设置

本刊讯 本刊栏目设置包括述评, 基础研究, 临床研究, 焦点论坛, 文献综述, 研究快报, 临床经验, 病例报告, 会议纪要. 文稿应具科学性、先进性、可读性及实用性, 重点突出, 文字简练, 数据可靠, 写作规范, 表达准确.