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过表达 XB130 抑制哮喘小鼠气道高反应性和气道炎症

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摘要 目的:研究 XB130 在哮喘小鼠气道高反应(airway hyperresponsiveness,AHR)和气道炎症中的作用。**方法:**36 只 C57 小鼠分为 4 组：正常对照组（Control,CON）、哮喘组（Asthma,AS）、腺病毒载体组（Ad-vector+AS）和腺病毒过表达 XB130 组（Ad-XB130+AS）。采用卵白蛋白（ovalbumin,OVA）建立小鼠过敏性哮喘模型，后两组小鼠分别尾静脉注射 Ad-vector 和 Ad-XB130。最后一次雾化吸入后 24 小时进行气道高反应试验,收集支气管灌洗液(bronchi alveolar lavage fluids,BALF)。采用 RT-PCR 和 Western blotting 方法检测 XB130 表达。ELISA 法检测血清中 OVA 特异性 IgE 的含量。直接计数法计算 BALF 中嗜酸性粒细胞(eosinophile granulocyte,EOS)数量。ELISA 方法用于检测 BALF 和肺组织中 IL-4、IL-5、IL-13 和 IFN-γ 的分泌。**结果:**哮喘小鼠肺组织中 XB130 表达减少，过表达 XB130 其 mRNA 和蛋白表达水平显著升高。过表达 XB130 降低醋甲胆碱(methacholine,Mch)诱导的气道高反应。与载体对照组(48± 3)相比,XB130 过表达(17± 4)EOS 数量显著减少。同时,过表达 XB130(0.051± 0.002)较载体对照组(0.128± 0.007)IgE 含量减少。此外,XB130 抑制哮喘小鼠中 IL-4、IL-5 和 IL-13 并促进 IFN-γ 分泌。**结论:**过表达 XB130 可抑制哮喘模型小鼠气道高反应性和炎症反应。

关键词:XB130;哮喘;气道高反应;气道炎症

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Overexpression of XB130 Inhibited the Airway Inflammation and Hyperresponsiveness in a Murine Asthmatic Model

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ABSTRACT Objective: To investigate the effect of XB130 on the airway inflammation and hyperresponsiveness in a murine asthmatic model. **Methods:** C57 mice were randomly divided into 4 groups with 9 mice each: control group (CON), Asthma group (AS), Adenovirus contral group (Ad-vector+AS) and XB130 overexpression group (Ad-XB130+AS). A murine asthmatic model was induced by ovalbumin (OVA) administration. Ad-vector and Ad-XB130 were injected intravenously. After the last antigen challenge for 24 h, the bronchi alveolar lavage fluids (BALF)have been collected. Airway hyperresponsiveness to methacholine (Mch) was measured. The expression of XB130 in lung tissues was evaluated using RT-PCR and Western blotting respectively. The content of OVA-specific IgE in serum was detected using ELISA. The cell counts of eosinophile granulocyte (EOS) were calculated. The secretion of IL-4, IL-5, IL-13 and IFN-γ were determined using ELISA. **Results:** XB130 was reduced in the lung tissue of asthma mice. The mRNA and protein expression of XB130 were increased in Ad-XB130 asthmatic mice. Overexpression XB130 reduced the airway hyperresponsiveness induced by methacholine (Mch). The number of EOS in Ad-XB130+AS group (17± 4) was decreased compared with Ad-vector+AS group (48± 3). Moreover, forcing expression of XB130 (0.051± 0.002) reduced the content of OVA-specific IgE compared with vector control group (0.128± 0.007). In addition, XB130 inhibited the secretion of IL-4, IL-5 and IL-13, promoted the production of IFN-γ in BALF and lung tissues. **Conclusion:** Overexpression of XB130 inhibited the airway inflammation and hyperresponsiveness in asthmatic mice.

Key words: XB130; Asthma; Airway hyperresponsiveness; Airway inflammation

Chinese Library Classification (CLC): Q95-3; R562.25 Document code: A

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前言

支气管哮喘(简称哮喘)是发病率较高的慢性气道疾病,且逐年上升[1]。其主要由免疫、遗传和环境等多种因素共同作用,表现为粘液分泌增多、气道炎症反应及气道高反应性[2]。过敏性哮喘又称外源性哮喘,多见于儿童和青少年[3]。其中 OVA 是过敏性哮喘模型中最常用的过敏原。

XB130 是 Hann 等人在克隆人类 AFAP 过程中发现的一种新型接头蛋白，命名为 AFAP1L-2 (actin filament associated protein1-like2)，由于其编码一种 818 个氨基酸组成的蛋白质,且分子量大小是 130 kDa,所以称 XB130[4]。文献报道,XB130 在信号转导的调控中起重要作用,调控癌细胞增殖、转移和侵袭[5,6]。XB130 在其他病理生理过程中也发挥一定作用,如气道

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损伤和修复,过表达 XB130 促进 NKK 诱导气道上皮细胞的迁移,有助于气道上皮修复[7],敲除 XB130 小鼠气道上皮损伤面积增大[8]。但 XB130 对哮喘小鼠的作用还少见报道,因此本研究通过建立过敏性哮喘探讨 XB130 对气道炎症和高反应性的作用,为 XB130 对哮喘及其他呼吸系统疾病的防治提供理论依据。

1 材料和方法

1.1 材料

SPF 级 C57 雄性小鼠(6 周龄,体重 22~25g,上海斯莱克实验动物有限公司);OVA(Sigma 公司,美国);IL-4、IL-5、IL-13 和 IFN-γ 酶联免疫测定试剂盒(R&D 公司,美国);醋甲胆碱(Sigma,美国);TRIzol 试剂(Invitrogen,美国);逆转录试剂盒(Promega 公司,美国);XB130 和 β-actin 抗体(Abcam 公司,美国);小鼠 IgE 试剂盒(优宁维,上海)。

1.2 方法

1.2.1 小鼠分组及哮喘模型建立 小鼠哮喘动物模型的建立参照文献[9]后略加改动。小鼠随机分成 4 组:正常对照组(Control,CON)、哮喘组(Asthma,AS)、腺病毒载体组(Ad-vector+AS)和腺病毒过表达 XB130 组(Ad-XB130+AS),每组 9 只。在第 0 天、第 14 天,CON 组腹腔注射等量的生理盐水,其他三组注射 0.2 mL 的 OVA。Ad-vector+AS 和 Ad-XB130+AS 组小鼠分别在第 19 天静脉注射 50 μL Ad-vector 和 Ad-XB130[10]。第 22~25 天,每天雾化吸入 1% OVA 磷酸缓冲液(7 mL),次日取血浆、肺泡灌洗液(bronchoalveolar lavage fluid,BALF)。

1.2.2 气道高反应性测定 小鼠在最后一次滴鼻 OVA 24 h 后,采用 1%的戊巴比妥钠(100 mg/kg)进行麻醉,分离肌肉,小心剥离气管并剪开一个小口,将插管插入并固定,连接至动物肺功能仪上,设置通气参数:呼吸频率 90 次 /min、潮气量 6 mL/kg。待基线平稳每隔 5 min 分别注射 Mch 25、50、75 和 100 mg/mL,并记录每次注射 1 min 后的最大气道阻力。

1.2.3 血清中 IgE 的测定 实验结束时采集血清,IgE 的含量采用 ABC-ELISA 法检测,操作严格按照试剂盒的说明书进行。

1.2.4 支气管肺泡灌洗液(BALF)收集及 EOS 计数 小鼠最后一次 OVA 雾化吸入后 24 h,麻醉后颈部切开皮肤暴露气管,在气管上方做一个切口,插入自制插管,用 1 mL 注射器注入 0.5 mL 的 PBS 于肺组织中,然后抽出,置于离心管中,重复三次,收集到的 BALF 经离心,取上清用于 EOS 的计数及炎症因子检测。

1.2.5 炎症相关因子检查 小鼠 BALF 和肺组织中的 IL-4、IL-5、IL-13、IFN-γ 均采用 ELISA 方法检测,按照说明书操作。

1.2.6 实时定量 PCR 采用 TRIzol 试剂提取各组小鼠肺组织 mRNA,将 mRNA 逆转录为 cDNA,进行实时定量 PCR 检测目的基因表达量。引物序列如下:XB130:Forward: 5'-TCAGCATCTCCAGAC-3',Reverse: 5'-GGCTGTTTC CTCTCT-3';β-actin:Forward: 5'- GGCTGTATTCCCC-TCCATCG-3',Reverse: 5'- CCAGTTGGTAACAATGCCATGT-3'。

1.2.7 Western blotting 提取各组小鼠肺组织中总蛋白,50 μg/ 孔上样量于 SDS-PAGE 分离、转膜,5%的牛奶室温封闭 1 h,4℃过夜孵育抗 XB130 和 β-actin 抗体,TBST 洗膜 3 次,室温孵育二抗 1 h。采用化学发光液进行显色,扫描胶片,ImageJ 用于统计各个条带的 OD 值。

1.3 统计学分析

采用 SPSS 11.0 软件包分析所有数据,采用单因素方差分析数据,P<0.05 为差异具有显著性。

2 结果

2.1 肺组织中 XB130 的表达

小鼠经注射过表达 XB130 的腺病毒 Ad-XB130 后雾化 OVA 诱发哮喘,提取肺组织 mRNA 和蛋白,检测 XB130 表达。结果如图 1A 所示,与 CON 组相比,哮喘组 XB130 的 mRNA 表达下降。与 Ad-Vector+AS 组相比,过表达 XB130 其 mRNA 表达增加 6.51± 0.19 倍。图 B 显示,与 CON 组比,哮喘组 XB130 蛋白表达显著下降,Ad-XB130+AS 组的蛋白水平是载体对照组的 3.35± 0.26 倍。

2.2 XB130 降低哮喘小鼠气道高反应性

如图 2 所示,与 CON 组相比,哮喘组小鼠气道阻力显著增加,过表达 XB130 降低 Mch 诱导哮喘小鼠的气道高反应(P < 0.05)。

2.3 XB130 降低哮喘小鼠 EOS 细胞数量

与 CON 组相比,哮喘小鼠 BALF 中 EOS 数量较正常组显著增多(46± 5,P<0.05)。与载体对照组(48± 3)相比过表达 XB130EOS 数量减少(17± 4),有显著性差异(P<0.05)。结果表明,XB130 使哮喘小鼠 BALF 中 EOS 数量减少。

2.4 XB130 降低血清中 OVA 特异性 IgE 含量

采用 ELISA 方法检测各组小鼠血清中 OVA 特异性 IgE 含量。结果表明,与 CON 组(0.032± 0.005)相比,哮喘组 IgE 含量(0.131± 0.012)升高(P<0.05)。过表达 XB130(0.051± 0.002)较载体对照组(0.128± 0.007)中 OVA 特异性 IgE 含量减少(P<0.05)。

2.5 XB130 减少哮喘小鼠 IL-4、IL-5 和 IL-13 分泌

哮喘小鼠 BALF 中 IL-4(图 5A)、IL-5(图 5B)和 IL-13(图 5C)分泌量较正常组显著增加,过表达 XB130 后其分泌量减少,具有显著性差异(P<0.05)。此外,过表达 XB130 也显著抑制肺组织中 IL-4(图 5A)、IL-5(图 5B)和 IL-13(图 5C)的分泌。

2.6 XB130 促进 IFN-γ 的分泌

如图所示,与 CON 组(78.83± 8.22)相比,哮喘组(21.35± 3.58)BALF 中 IFN-γ 的分泌量显著下降(P<0.05)。与载体组(18.53± 2.29)相比,过表达 XB130(65.83± 5.48)BALF 中 IFN-γ 分泌量增加(P<0.05)。

3 讨论

哮喘小鼠肺部可见炎性细胞浸润,以嗜酸性粒细胞为主,气道粘液异常增多及 Th1/Th2 细胞因子分泌失衡[11]。AHR 是指哮喘患者对多种刺激物的反应性异常增高,主要表现为敏感的气道在吸入各种刺激性物质后,较正常气道易出现支气管平滑肌收缩、粘液分泌增多及炎性介质释放[12],从而表现出气道阻力急速短暂或者较长时间的上升、肺通气功能下降的一种现象[13,14]。Mch 是直接引起气道平滑肌收缩的刺激剂,诱发 AHR[15]。本研究发现,过表达 XB130 有效抑制 Mch 诱发的 AHR。

过敏性哮喘发生机制与 T 淋巴细胞的分化失衡联系密切,

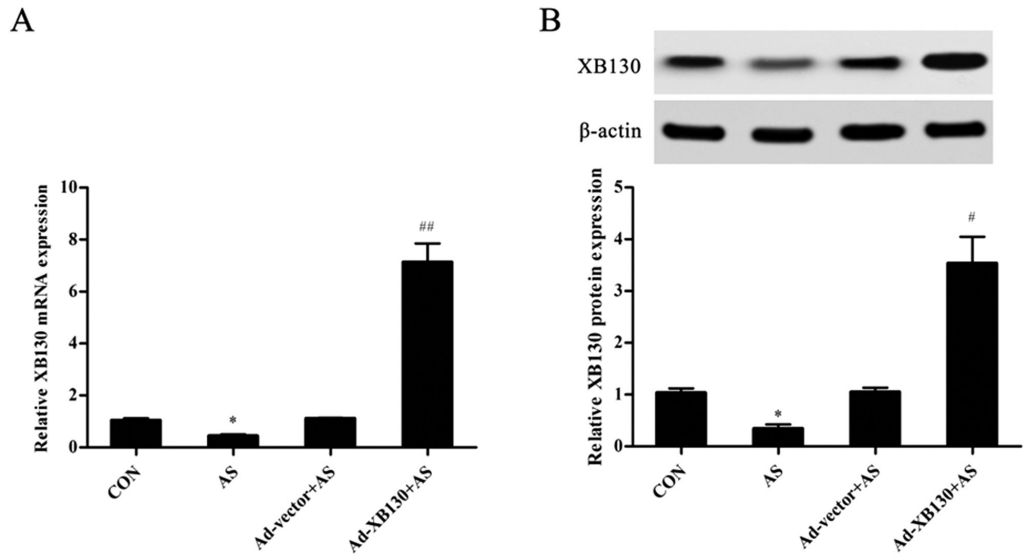

图 1 XB130 在肺组织中的表达

A. 实时定量 PCR 检测 XB130 mRNA 表达水平；B. Western blotting 检测 XB130 蛋白表达。CON：对照组；AS：哮喘组；与 CON 组相比，*P<0.05；与 Ad-vector+AS 组相比，#P<0.05，##P<0.01

Fig. 1 The expression of XB130 in lung

A. The mRNA expression of XB130 was assayed using RT-PCR. B. The protein expression of XB130 was detected using Western blotting. CON: control; AS: asthma; *P<0.05 compared with CON group; #P<0.05, ##P<0.01 compared with Ad-vector+AS group.

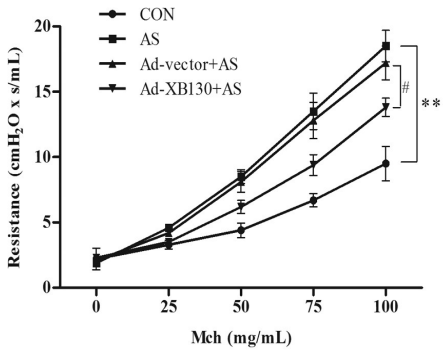

图 2 XB130 降低 Mch 诱导哮喘小鼠气道高反应。Mch：醋甲胆碱；与 CON 组相比，**P<0.01；与 Ad-vector+AS 组相比，#P<0.05

Fig. 2 XB130 reduced the airway hyperresponsiveness induced by Mch. Mch: methacholine; **P<0.01 compared with CON group; #P<0.05 compared with Ad-vector+AS group.

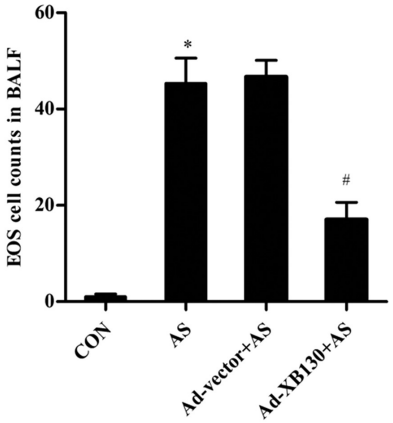

图 3 过表达 XB130 降低 BALF 中 EOS 数量。与 CON 组相比，*P<0.05；与 Ad-vector+AS 相比，#P<0.05

Fig. 3 Overexpression of XB130 decreased the number of EOS in BALF. *P<0.05 compared with CON group; #P<0.05 compared with Ad-vector+AS group

辅助性 T 淋巴细胞能够分化为 Th1 和 Th2 细胞[16]，Th1 细胞主要分泌 IFN-γ，Th2 细胞主要分泌 IL-4、IL-5 和 IL-13[17,18]。Th1/Th2 失衡，在哮喘中发挥关键性作用[19]。生理状态下，Th1/Th2 处于平衡状态，哮喘发生时 Th2 细胞异常增加，导致 IL-4、IL-5 和 IL-13 分泌增多，Th1 细胞减少，IFN-γ 分泌减少[20,21]。XB130 参与调控 LPS 诱导肺损伤，敲除 XB130 小鼠血清中 TNF-α、MCP-1、IL-6 和 IL-10 升高，支气管肺泡灌洗液中 IL-6 和 IL-10 分泌增加[22]。本研究证实，过表达 XB130 抑制 Mch 诱导的气道高反应，降低血清中 OVA 特异性 IgE 的含量。此外，XB130 抑制 BALF 和肺组织中 IL-4、IL-5 和 IL-13 的分泌，同时促进 IFN-γ 分泌。

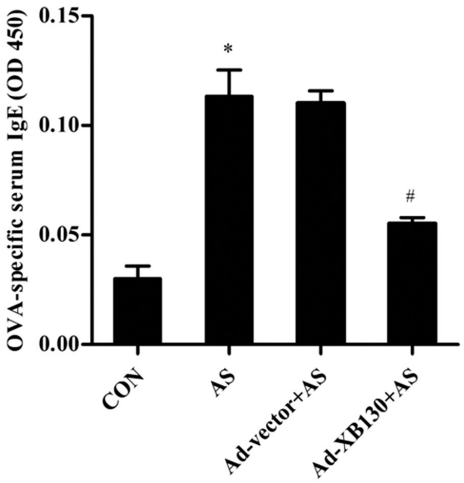

图 4 XB130 降低血清中 IgE 的含量。与 CON 组相比，*P<0.05；与 Ad-vector+AS 组相比，#P<0.05

Fig.4 XB130 declined the content of IgE in serum. *P<0.05 compared with CON group; #P<0.05 compared with Ad-vector+AS group.

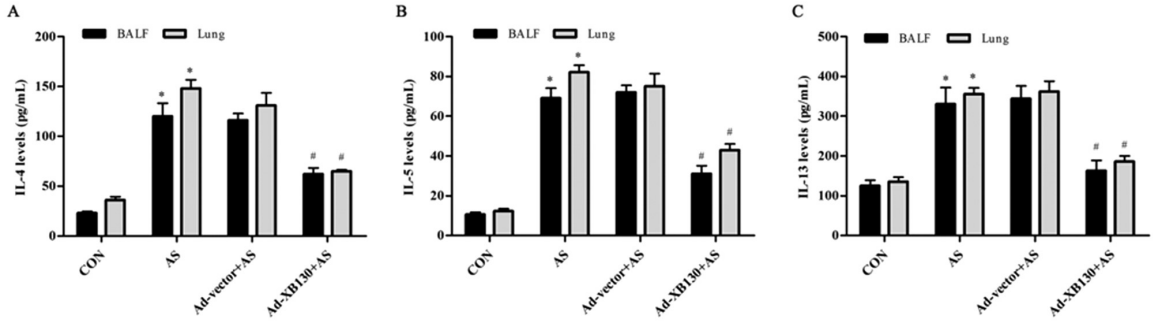

图 5 过表达 XB130 抑制 IL-4、IL-5 和 IL-13 分泌

A. IL-4 的分泌量；B. IL-5 的分泌；C. IL-13 的分泌。与 CON 组相比，*P<0.05；与 Ad-vector+AS 组相比，#P<0.05

Fig.5 Overexpression of XB130 inhibited the secretion of IL-4, IL-5 and IL-13

A. The secretion of IL-4. B. The secretion of IL-5. C. The secretion of IL-13.

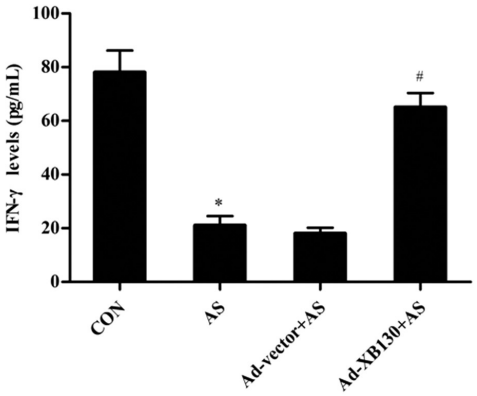

图 6 过表达 XB130 促进 IFN-γ 泌

与 CON 组相比，*P<0.05；与 Ad-vector+AS 组相比，#P<0.05

Fig. 6 Overexpression of XB130 promoted the secretion of IFN-γ

*P<0.05 compared with CON group. #P<0.05 compared with Ad-vector+AS group

综上所述，过表达 XB130 显著抑制 Mch 诱发的 AHR、降低血清中 OVA 特异性 IgE 的含量并减少 BALF 中 EOS 数量。此外，XB130 抑制 BALF 和肺组织中 IL-4、IL-5 和 IL-13 产生并促进 IFN-γ，表明 XB130 主要是通过调节 Th1/Th2 平衡参与调控哮喘的发生发展。这些结果提示 XB130 可能作为哮喘防治的靶分子，对呼吸系统疾病的防治具有重要的意义。

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