姜黄素通过抑制p38 MAPK和AKT活化改善幼鼠过敏性气道炎症

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摘 要：【目的】选择幼龄小鼠模拟3~12岁儿童的过敏性气道炎症，探索膳食补充姜黄素对幼龄小鼠过敏性气道炎症的防治作用。【方法】4周幼龄雌性BALB/c小鼠随机分为3组(每组n=8)，分别是空白对照组，过敏性气道炎症模型组，姜黄素干预组。在末次卵清白蛋白激发24 h后，观察各组小鼠的症状，测定肺泡灌洗液(BALF)中的炎症细胞数，全血细胞分析白细胞亚型的数量，用HE染色观察肺部支气管周围炎症细胞浸润情况，用过碘酸-雪夫染色观察杯状细胞增生情况，酶联免疫吸附法测定BALF中的细胞因子IL-4、IL-5、IL-13以及血浆中的总IgE水平，western blot技术检测肺组织磷酸化p38丝裂原活化蛋白激酶(p-p38 MAPK)/p38 MAPK，p-AKT/AKT蛋白表达情况。【结果】与过敏性气道炎症模型组相比，饲料添加姜黄素的干预组可以明显改善幼鼠的反复抓挠鼻子、点头呼吸、体质量减轻等症状，外周血中嗜酸性粒细胞降低具有统计学差异(P<0.05)，肺泡灌洗液和肺支气管周围的炎症细胞以及肺泡灌洗液中IL-4，IL-5，IL-13的水平降低(P<0.05)，支气管上皮杯状细胞增生减轻，此外，肺组织的磷酸化p38 MAPK和磷酸化AKT水平降低，组间差异有统计学意义(P<0.05)。【结论】膳食添加姜黄素可以抑制幼龄小鼠过敏性气道炎症，其机制可能与抑制肺组织的p-38 MAPK和AKT信号传导有关。

关键词：幼鼠；姜黄素；过敏性气道炎症；哮喘；p38 MAPK；AKT
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Curcumin Attenuates Allergic Airway Inflammation of Young Mice through Inhibiting the Activation of p38 MAPK and AKT

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Abstract:【Objective】To investigate the effects of dietary curcumin on the prevention and treatment of allergic airway inflammation in young mice for simulating the allergic airway inflammation of 3-12 years old children.【Methods】The 4 weeks young female BALB/c mice were randomly divided into three groups (n=8): Control group, Model group and curcumin group (800 mg curcumin/ kg diet). 24 h after the last OVA challenge, the symptoms of mice in each group were observed, the inflammatory cells in the bronchoalveolar lavage fluid (BALF) were measured, various kinds of blood cells were detected, the inflammatory cells around the peribronchial areas stained by H & E and the goblet cell hyperplasia in the lungs stained by PAS were analyzed. Additionally, the IL-4, IL-5, IL-13 in the BALF and the total IgE level in the plasma were detected by ELISA, and the activation of p38 MAPK and AKT was measured by western blot.【Results】The mice of model group showed the symptoms of allergic airway inflammation, such as repeatedly scratched the noses, showed nodding breath, notably, the weight of model mice was decreased significantly during the OVA challenge

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phase, while the symptoms mentioned above were alleviated in curcurmin group. The blood cells test found that the curcumin could inhibit the elevation of the eosinophils significantly (P<0.05). Dietary curcumin treatment significantly decreased the inflammatory cells in the BALF and peribronchial areas, and the IL-4, IL-5, IL-13 levels in the BALF were significantly inhibited (P<0.05). The goblet cell hyperplasia was attenuated by curcumin treatment, and the dietary curcumin inhibited the activation of p38 MAPK and AKT signaling.【Conclusions】Dietary curcumin can alleviate the allergic airway inflammation of young mice, which may through inhibiting the transduction of p-38 MAPK and AKT signaling.

Key words: young mice; curcumin; allergic airway inflammation; asthma; p38 MAPK; AKT

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全球大约有20%左右的人口患有过敏性疾病,造成了严重的健康负担。过敏性哮喘主要发生在儿童期,影响了大概5%~10%的学龄儿童[1]。最近有调查发现,中国儿童哮喘和过敏性鼻炎的患病率大约为3.3%和9.8%,并有不断上升的趋势[2]。目前临床常用哮喘治疗药物不能很好地控制哮喘的全部症状,并且经常使用药物糖皮质激素对儿童患者的生长发育有不良影响[3-4]。因此,研究过敏性鼻炎或哮喘对儿童的特殊性影响和其机制,以及寻求副作用少而有效的药物或有益的膳食补充剂等具有重要的意义,对于生长发育阶段的儿童尤为重要。过敏性鼻炎和过敏性哮喘同属于过敏性气道炎症,具有相似的发病机制,并且许多哮喘患者同时患有过敏性鼻炎[5-6]。过敏性哮喘的特征包括血浆中免疫球蛋白IgE升高,Th2细胞分泌的细胞因子如白介素(IL)-4、IL-5、IL-13增多,伴随有炎症细胞趋化至肺支气管周围的气道炎症表现[7-8]。黏液分泌过多和气道高反应性(AHR)也是哮喘的标志[9]。已有研究发现,部分膳食或其活性成分可以调控机体的免疫系统和肺部炎症[10],例如越来越多的研究证据表明,植物性食物及代谢物,对过敏性气道炎症具有有益的调节作用[11-13]。姜黄素是姜黄属根茎的一种多酚类成分,研究表明姜黄素在慢病防治上具有一定的生物活性,其中包括对气道疾病如慢阻肺(COPD)、哮喘、肺纤维化等[14-16]。虽已有姜黄素对过敏性鼻炎或哮喘小鼠的作用的研究报道,但研究对象多为成年小鼠[17-18],至今暂未见姜黄素是否能通过膳食干预的方式缓解幼龄小鼠的过敏性气道炎症。由于幼龄儿童处在生长发育阶段,与成年人可能存在不同的免疫反应情况[19],因此,本研究拟通过膳食添加姜黄素的方式,研究其对过敏性气道炎症幼龄小鼠的防治作用,以及可能的作用机制。此研究可为姜黄素防治儿童的过敏性鼻炎和(或)哮喘提供理论依据,具有一定的临床应用前景。

1 材料与方法

1.1 实验动物

24只雌性SPF级BALB/c纯系小鼠,鼠龄4周,体质量13~16 g,购于广东省医学实验动物中,许可证号:SCXK(粤)2013-0002。饲养于中山大学公共卫生学院SPF级动物房。动物实验操作符合中山大学动物实验伦理学规定。

1.2 主要试剂及仪器

IL-4,IL-13 ELISA试剂盒(Arigo,台湾),IL-5和总IgE的ELISA试剂盒(eBioscience),p38MAPK及其磷酸化抗体,AKT和p-AKT抗体,β-actin以及二抗(Cell signaling Technology),Diff-quick染液(Baso Diagnostics),OVA(Sigma A5503纯度5级),氢氧化铝(Sigma A8222),AIN 93G普通饲料(江苏美迪森公司),姜黄素纯品(纯度≥99%)(Sigma),压缩空气式雾化器(鱼跃,江苏),荧光酶标仪(瑞士TECAN公司),全自动多物种五分类动物血液分析仪(HEMAVET 950)。

1.3 幼鼠过敏性气道炎症模型的建立

在实验的第1、7、14天,小鼠腹腔注射0.2 mL的致敏液(OVA 40 μg+4 mg氢氧化铝)。腹腔注射致敏后,间隔1周,从第21天开始,将小鼠置于雾化吸入箱进行激发,通过压缩空气式雾化器雾化吸入5%的OVA溶液,每次30 min。30 min后,用40 μg/mL的OVA溶液滴入小鼠鼻腔,每侧鼻腔各10 μL,即每侧鼻腔滴入400 μg OVA,每天激发一次,连续5 d,即第21、22、23、24、25天[20]。

1.4 动物分组和姜黄素干预

幼鼠随机分为3组,每组8只小鼠,分别为空

白对照组（Control group），模型组（Model group）和姜黄素干预组（Cur group）。姜黄素干预组小鼠的造模与模型组一致。空白对照组小鼠采用PBS作为安慰剂代替OVA进行致敏和激发实验。空白对照组和模型组的饲料为AIN 93G普通饲料，姜黄素干预组按照800 mg/kg饲料添加姜黄素，剂量选择参照相关文献[21]。各组小鼠单笼饲养，自由饮水和自由食用对应的饲料，每天固定时间更换新配置的饲料，并称量记录剩食和洒食。记录最后一次OVA激发后10 min内各组小鼠总抓挠鼻子次数，并重复三次观察记录。

1.5　收集血样和肺泡灌洗液

小鼠最后一次OVA激发24 h后，麻醉后心脏采集ACD抗凝血。采血后马上切开小鼠颈部皮肤，暴露气管，行气管插管，用1 mL预冷PBS灌洗肺部，回吸得到肺泡灌洗液（BALF）。每个血样取20 μL用血液分析仪测定血中嗜酸性粒细胞。离心得到血浆并保存在−80 ℃中待测。肺泡灌洗液在2000 r/min（r=8 cm），4 ℃，5 min中条件下离心，吸取上清冻存−80 ℃待测，沉淀细胞用200 μL体积的PBS重悬，用血球计数板计数重悬液中白细胞总数，并用重悬液涂片，diff-quick染色对白细胞分类计数，每个样本共计数200个细胞。

1.6　细胞因子测定

肺泡灌洗液中Th2细胞因子IL-4、IL-5和IL-13以及血浆中总IgE水平用酶联免疫吸附试验方法（ELISA）测定。操作步骤按说明书进行。

1.7　肺组织切片染色观察及半定量分析

小鼠心脏采血后，及时分离出完整的左肺与右肺，各组小鼠右肺放入冻存管中，并冻存于−80 ℃留待western blot检测。各组小鼠左肺放在标记好的包埋盒里，浸泡于10%的新鲜甲醛溶液中24 h后石蜡包埋，并常规切片做HE染色和PAS染色，然后镜下观察（200×）。各组小鼠HE染色的炎症评分和PAS染色的阳性细胞百分比参照文献进行分析[22]。

1.8　免疫印迹法检测

肺组织中的p-p38/p38，p-AKT/AKT蛋白的测定采用western blotting技术。提取肺组织蛋白，经BCA方法蛋白定量后，总蛋白进行SDS-PAGE电泳，然后转移至PVDF膜上。用5%脱脂牛奶室温封闭1.5 h后，加入相应一抗，4 ℃摇床过夜；TBST洗膜3次，每次10 min，加入二抗，室温摇床孵育1.5 h后TBST洗膜三次后ECL显影，最后放入成像系统完成显影，并分析蛋白条带。

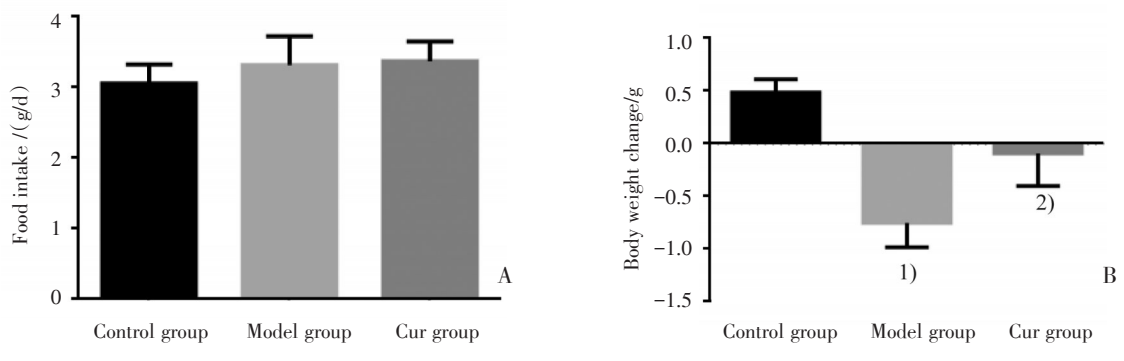
1.9　统计学分析

采用SPSS20.0软件进行统计学处理，计量资料以表示。多组计量资料采用单因素方差分析（ANOVA），多组比较有统计学差异以后采用SNK-q检验进行两两比较，统计分析采用双侧检验，$P<0.05$认为差异具有统计学意义。

2　结　果

2.1　小鼠摄食量和OVA激发前后体质量变化

小鼠体质量监测发现，模型组小鼠体质量在OVA激发前后体质量减轻，而姜黄素干预组小鼠体质量减轻得到了抑制，与模型组相比组间差异



A: Food intake during the experiment showed no significant difference between each group; B: the body weight change during the OVA challenge period showed that the Model group had a significant body weight reduction compared to the Control group, while the curcumin treatment inhibited the reduction significantly. n=8/group, F=7.429, P=0.0018. 1)$P<0.01$ vs Control group; 2) $P<0.05$ vs Model group by SNK-q test after ANOVA.

图1　小鼠摄食量和OVA激发前后体质量改变

Fig.1　Food intake and body weight change during OVA challenge phase in mice

具有统计学意义(P<0.05;图1),小鼠每日摄食量各组间无统计学差异。

2.2 OVA激发后小鼠行为表现的改变

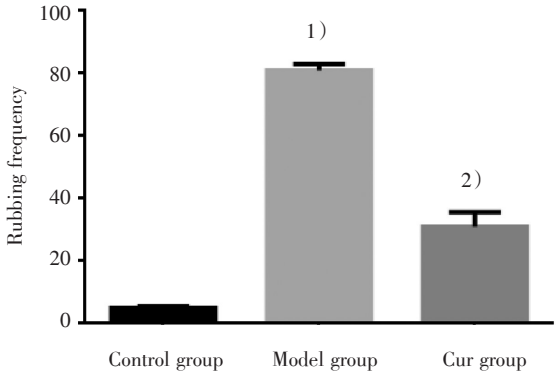
在最后一次OVA激发后,观察发现空白对照组小鼠活动正常,毛发光滑柔顺,无异常表现,而模型组小鼠出现弓背直立,前肢缩抬,反复抓挠鼻子和头面,烦躁不安或者静止不动,点头呼吸,毛发散乱等过敏性气道炎症的症状。而这些异常行为在姜黄素干预组得到了明显改善,各组小鼠挠鼻次数定量分析发现,姜黄素组小鼠的挠鼻次数明显比模型组少,组间差异有统计学意义(P<0.01;图2)。

2.3 小鼠全血中嗜酸性粒细胞,中性粒细胞与淋巴细胞比值(NLR)改变情况

血常规测定结果发现模型组小鼠嗜酸性粒细胞所占白细胞总数的百分比(Eo%)较正常对照组增加(P<0.05),而姜黄素干预组的嗜酸性粒细胞百分比较模型组降低,组间差异具有统计学意义(P<0.05)。此外,模型组的中性粒细胞与淋巴细胞比值(NLR)比空白对照组的升高具有统计学意义(P<0.01),而此比值在姜黄素干预组较模型组降低(P<0.05;图3)。

2.4 肺泡灌洗液中白细胞总数和分类的改变

模型组肺泡灌洗液细胞总数比空白对照组增多,而膳食性姜黄素干预后降低(P<0.01)。Diff-quick染色后镜下观察发现,空白对照组几乎无可见的嗜酸性粒细胞,而模型组的嗜酸性粒细胞显著增加,但姜黄素干预组的嗜酸性粒细胞较模型组降低,组间差异有统计学意义(P<0.01;图4)。



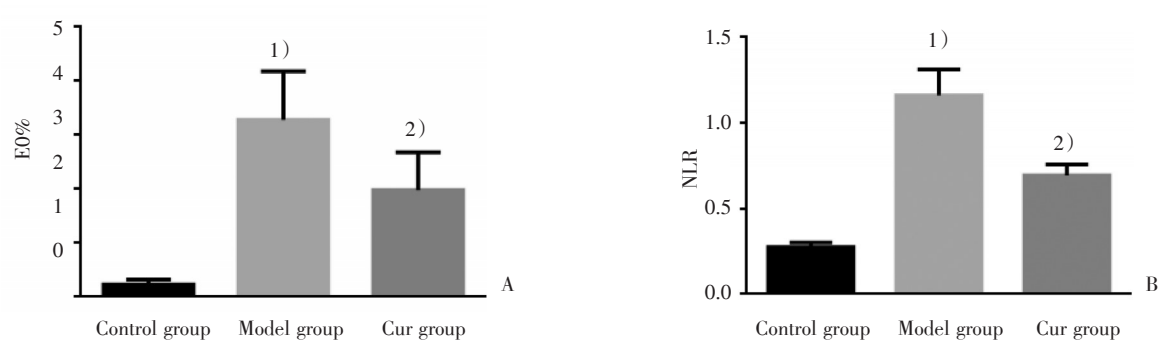
Model group showed a significant increase of rubbing frequency compared to the Control group, while the curcumin treatment showed a reduction in rubbing frequency compared to the Model group. n=8/group, F=165.778, P<0.0001. 1)P<0.01 vs Control group; 2)P<0.01 *vs* Model group by SNK-q test after ANOVA.

图2 各组小鼠OVA激发后挠鼻次数的比较

Fig.2 Rubbing frequencies around noses comparison in mice

2.5 姜黄素对肺泡灌洗液中的IL-4、IL-5、IL-13以及血浆中总IgE水平的影响

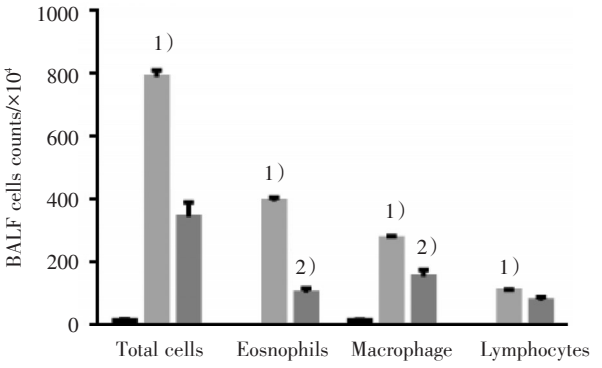
模型组肺泡灌洗液中IL-4、IL-5、IL-13水平相比空白对照组均明显升高,组间差异有统计学意义(P < 0.01),而姜黄素干预组较模型组此三者



A: Eosinophils percentage (Eo%) analysis in the blood, the Model group showed a significant increase of Eo% compared to Control group, while the curcumin treatment inhibited the increase significantly, n=8/group, F=4.063, P=0.0252. 1) P<0.05 *vs* Control group; 2)P<0.05 *vs* Model group by SNK-q test after ANOVA; B: NLR analysis in the blood, the Model group showed a significant elevation of NLR compared to the Control group, while the curcumin treatment decreased the elevation significantly, n=8/group, F=15.734, P<0.0001. 1)P<0.01 vs Control group; 2)P<0.05 *vs* Model group by SNK-q test after ANOVA.

图3 各组小鼠全血嗜酸性粒细胞百分比和NLR的比较

Fig.3 Comparison of Eo% and NLR in whole blood between each group



BALF cells were stained by Diff-quick and divided into different kinds of cells. The analysis showed that the total cells, eosinophils and macrophages of the BALF in the Model group increased significantly compared to the Control group, while their elevations were both inhibited significantly by the curcumin treatment. n=8/group, 1) P<0.01 *vs* Control group; 2)P<0.01 vs Model group by SNK-q test after ANOVA.

图4　各组小鼠肺泡灌洗液细胞分类计数

Fig.4　The classification of inflammatory cells in the BALF of mice

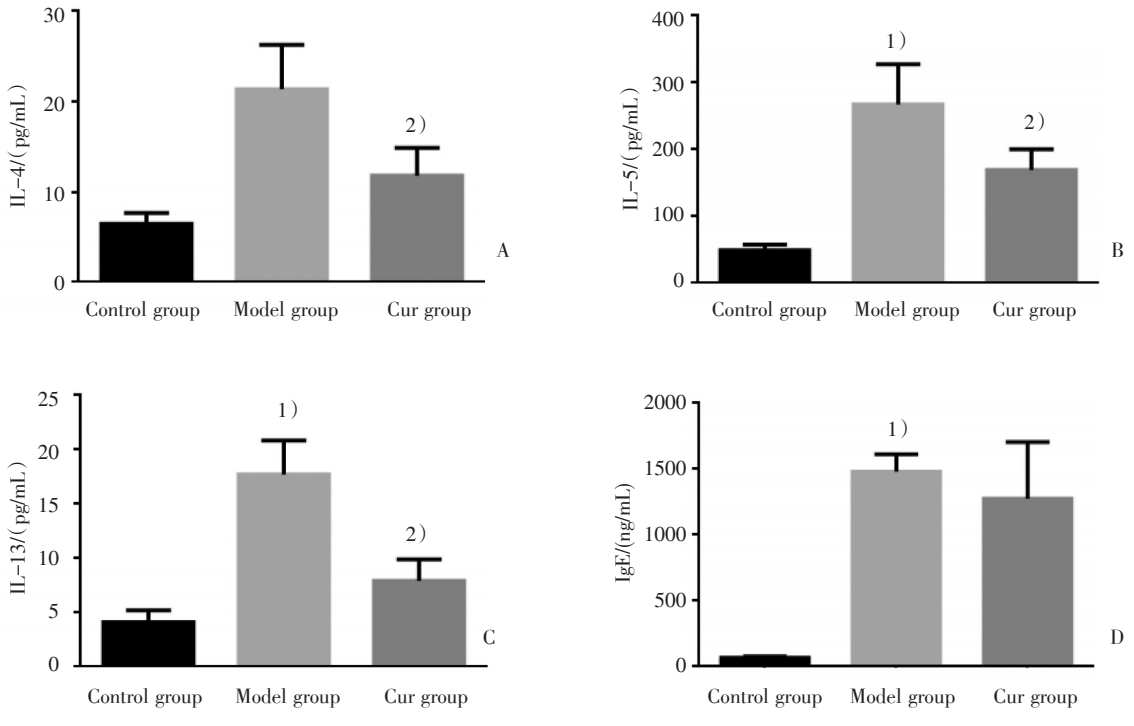
水平均降低(P<0.05)。模型组血浆的总IgE水平明显比空白对照组高，组间差异有统计学意义(P<0.01)，但姜黄素干预组与模型组相比，无明显下降，无统计学差异(P>0.05；图5)。

2.6　姜黄素对肺部炎症细胞浸润、杯状细胞增生和黏液分泌的影响

肺组织切片HE染色后，镜下观察到模型组支气管与血管周围有大量的炎症细胞浸润，而姜黄素干预后炎症细胞浸润明显减少。PAS染色可见，模型组支气管杯状细胞增生显著，黏液分泌增多，但姜黄素干预后杯状细胞增生受到明显抑制，黏液分泌减少(图6)。

2.7　姜黄素对肺组织p-p38MAPK/p38MAPK和p-AKT/AKT的影响

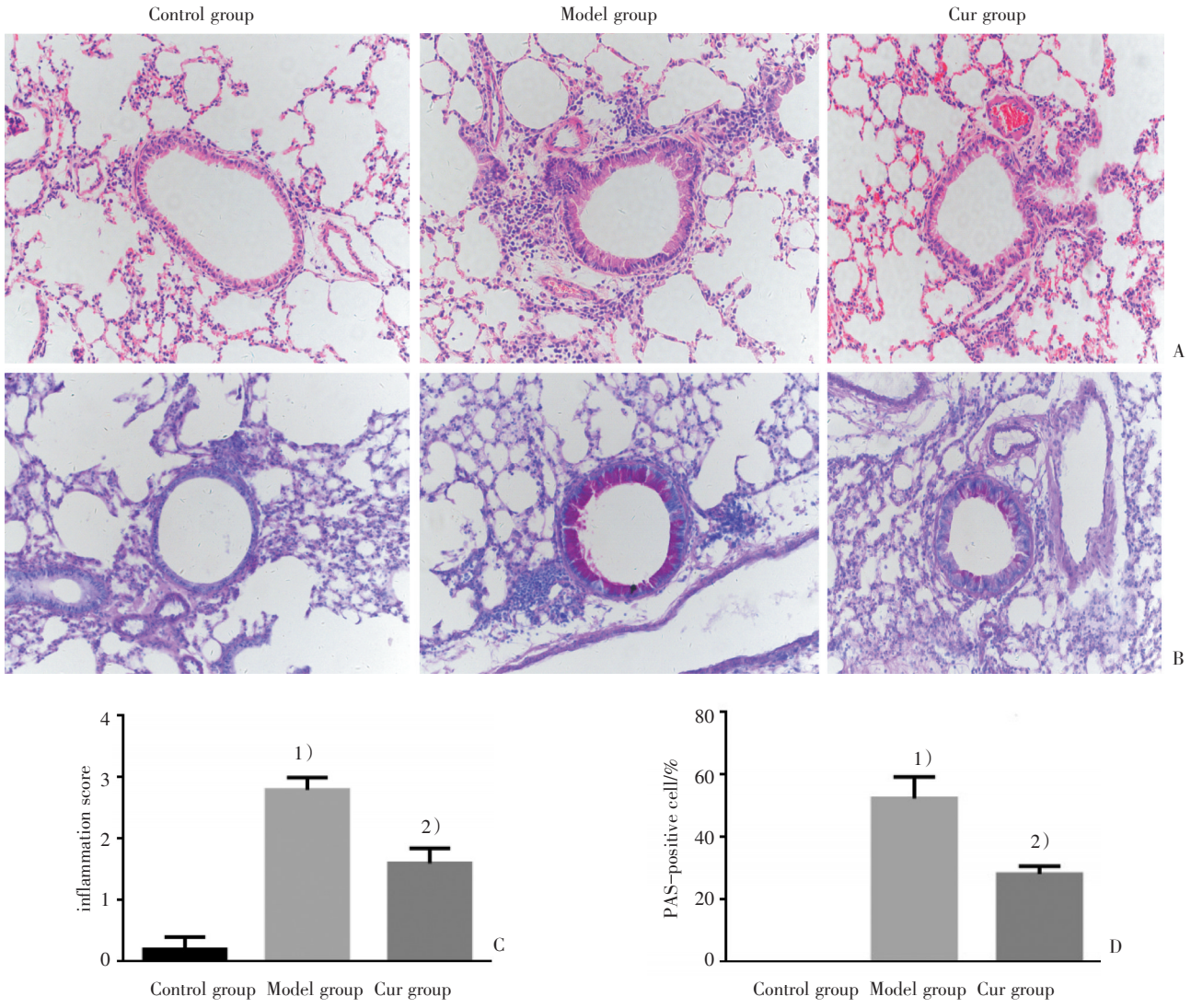
经图像分析发现，模型组的小鼠肺组织磷酸化p38丝裂原活化蛋白激酶(p38 MAPK)和磷酸



A: Model group showed a significant elevation of IL-4 levels in the BALF compared to the Control group, while the curcumin treatment inhibited the elevation of IL-4 significantly n=8/group, F=7.042, (P=0.0076). 1)P<0.01 vs Control group; 2)P<0.05 vs Model group by SNK-q test after ANOVA; B: Model group showed a significant elevation of IL-5 levels in the BALF compared to the Control group, while the curcumin treatment inhibited the elevation of IL-5 significantly. n=8/group, F=10.612, (P=0.0019). 1)P<0.01 vs Control group; 2)P<0.05 vs Model group by SNK-q test after ANOVA; C: Model group showed a significant elevation of IL-13 levels in the BALF compared to the Control group, while the curcumin treatment inhibited the elevation of IL-13 significantly. n=8/group, F=9.548, (P=0.0028). 1)P<0.01 vs Control group; 2)P<0.05 vs Model group by SNK-q test after ANOVA; D: though the model group showed a significant increase of IgE(D)levels in the plasma, the curcumin did not inhibited the elevation significantly, n=8/group, F=23.327, (P<0.0001). 1)P<0.05 vs Control group by SNK-q test after ANOVA.

图5　各组小鼠肺泡灌洗液中IL-4，IL-5，IL-13及血浆中总IgE水平的比较

Fig.5　IL-4, IL-5, IL-13 levels in the BALF and the total IgE level in the plasma in mice



A: Representative photographs of HE-stained lung sections from each group, which showed that the Model group had a significant increase in inflammatory cells infiltration around the bronchi compared to the Control group, while curcumin treatment attenuated the inflammatory cells infiltration; B: Representative photographs of PAS-stained lung sections from each group, which showed that the Model group had a significant increase of mucus accumulation at the luminal surface of the bronchi compared to the Control group, while curcumin treatment inhibited the mucus accumulation significantly; Original magnification × 200; C: inflammation scores for the inflammatory cells infiltration, n=8/group, F=36.286, (P<0.0001). 1)P< 0.01 vs Control group; 2)P<0.01 vs Model group by SNK-q test after ANOVA; D: PAS analysis showed that the model group had a significant increase in PAS-positive cells compared to the Control group, while curcumin treatment significantly inhibited the increase. n=8/group, F=134.403, (P<0.0001). 1)P<0.01 vs Control group; 2)P<0.01 vs Model group by SNK-q test after ANOVA.

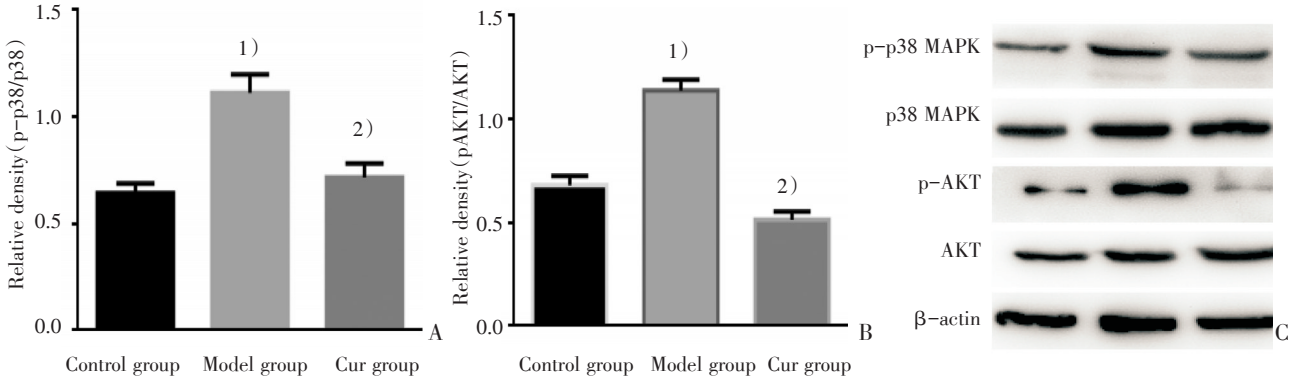
图6 小鼠肺组织切片观察炎症细胞浸润和杯状细胞增生与黏液分泌改变

Fig.6 The inflammatory infiltration, goblet cell hyperplasia and the mucous secretion in mice lungs

化AKT的表达较空白对照组明显增加,组间差异有统计学意义(P < 0.01),而姜黄素干预组的磷酸化p38 MAPK和磷酸化AKT的表达较模型组有明显降低,组间差异有统计学差异(P < 0.01;图7)。

3 讨 论

已知Th2细胞因子IL-4,IL-5和IL-13主要由活化的CD4+ T细胞产生,它们在过敏性鼻炎和哮



A: Western blotting results showed that protein expression of p-p38 MAPK was significantly enhanced in the Model group compared to the Control group, while curcumin treatment significantly inhibited the expression of p-p38 MAPK compared to the Model group. n=3/group, F=73.62, (P=0.0003). 1)P<0.01 vs Control group; 2)P<0.01 vs Model group by SNK-q test after ANOVA; B: Western blotting results showed that protein expression of p-AKT was significantly enhanced in the Model group compared to the Control group, while curcumin treatment significantly inhibited the expression of p-AKT compared to the Model group. n=3/group, F=50.42, (P=0.0002). 1)P<0.01 vs Control group; 2)P<0.01 vs Model group by SNK-q test after ANOVA; C: the representative graphs of three independent experiment for each protein measurement by western blotting.

图7　各组小鼠肺组织磷酸化p38MAPK以及磷酸化AKT表达的变化

Fig.7　The expression of phosphorylated p38 MAPK and phosphorylated AKT in the mice lungs

喘的病理过程中起到关键作用。IL-4诱使B细胞生成IgE，后者与IgE受体交联时介导肥大细胞脱颗粒。IL-5促使嗜酸性粒细胞前体细胞分化和增殖以及嗜酸性粒细胞的活化[23]。IL-13在哮喘症状中也起到至关重要的作用，比如AHR、气道炎症、杯状细胞增生[24]。此外，近期人群研究资料显示哮喘和过敏性鼻炎儿童的血液中中性粒细胞与淋巴细胞比值(NLR)较正常人群高[25-27]。在过敏性哮喘患者和OVA诱导的小鼠模型中，嗜酸性粒细胞被趋化至肺部，嗜酸性粒细胞表达高亲和力的FceR与过敏原特异性IgE结合，作为嗜酸性粒细胞活化和炎症介质释放的前提。因此，为了减少嗜酸性粒细胞在气道的活化和释放炎症细胞因子，减少嗜酸性粒细胞的生成以及趋化至肺部的数量是改善气道炎症的可行的方式。本研究结果显示，姜黄素干预可显著降低血液中以及肺泡灌洗液中的嗜酸性粒细胞的数量，并且与IL-5水平的降低相一致。模型组小鼠的NLR比空白对照组显著增加，而姜黄素干预组NLR较模型组显著降低。姜黄素干预后IL-4、IL-5、IL-13水平均降低显著，小鼠症状和病理也有改善。这些结果均提示，姜黄素膳食干预后可有效性地控制幼龄小鼠的过敏性气道炎症。

本次研究发现，姜黄素干预组的小鼠血浆总IgE与模型组无统计学差异，这一结果提示姜黄素干预后可能对IgE的生成的影响不大。已有文献报道IgE水平经常和症状不成正相关，因为症状的严重程度不仅与IgE抗体相关，还与其他介质的释放以及靶器官对介质的反应有关[6]。

p38丝裂原活化蛋白激酶(p38 MAPK)在哮喘模型小鼠的炎症因子的产生中起到了关键的作用，而下调p38 MAPK表达可以减轻哮喘症状[28-30]。本实验结果显示在过敏性气道炎症小鼠肺组织中p38 MAPK磷酸化(活化形式)增加，而膳食中添加姜黄素干预可以抑制p38 MAPK的磷酸化。

在监测小鼠的一般状态和症状时，我们发现OVA激发后，过敏性气道炎症模型小鼠体质量有明显的降低，呈现消瘦的状态，而空白对照组小鼠体质量正常增加。膳食中添加姜黄素后体质量的下降得到了抑制。在探究此现象的可能机制中，我们发现肺组织的AKT信号蛋白的磷酸化水平在各组间有显著的差异，即过敏性气道炎症模型组小鼠肺组织的AKT磷酸化水平明显较空白对照组高，而姜黄素干预组的AKT磷酸化水平得到了显著抑制。有研究显示IL-4可通过影响AKT活性调节细胞和器官的能量代谢，AKT的活化增加可以提高胰岛素的敏感性，AKT的过

度活化影响小鼠的生长发育[31]。AKT活化促使葡萄糖转运至免疫细胞内,供免疫细胞进行能量代谢,对CD4+ T细胞增殖分化也起到了重要调控作用[32-33]。因此,姜黄素对过敏性气道炎症幼龄小鼠体质量的恢复性调控可能与AKT的活化程度受到抑制有关,进一步的机制研究值得深入探讨。

本研究使用的姜黄素剂量为每天800 mg/kg饲料,按照小鼠每日摄食量为3 g计算,每只小鼠实际摄入量为2.4 mg,经过安全系数换算后,相当于人每日摄入姜黄素的量为240 mg,已有文献报道,在经常食用富含姜黄素的膳食的人群中,每日摄食姜黄素的数量可达260 mg[34]。因此接近于常食用富含姜黄素的膳食人群的每日摄入量。

综上所述,本实验证明了膳食性姜黄素可以改善幼龄小鼠的过敏性气道炎症的症状,并且对过敏性气道炎症的幼龄小鼠的生长起到良性的改善作用,而此作用可能与姜黄素同时抑制p38 MAPK和AKT介导的信号传导有关。

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