

STAT6在肺部疾病发生发展中的生物学功能

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【摘要】 信号转导和转录激活因子(signal transducers and activators of transcription, STAT)是转录因子家族的成员, STAT6主要由IL-4和IL-13激活,发挥重要的免疫调节作用。STAT6参与调节肺部炎症反应和免疫调控,包括气道嗜酸性粒细胞增多、Th2细胞分化以及B细胞生成IgE等。STAT6不仅是哮喘发展的关键因素之一,还参与调节肺部抗病毒反应,并涉及肺纤维化的调控。此外,STAT6还参与IL-4/IL-13诱导的肿瘤相关巨噬细胞的信号通路。本文总结了STAT6在肺部疾病中的作用及其相关机制的研究进展。

【关键词】 STAT6; 哮喘; 急性呼吸窘迫综合征(ARDS); 肺癌

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Biological function of STAT6 in the development of lung diseases

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【Abstract】 Signal transducer and activator of transcription (STAT) proteins are members of transcription factors family that activate gene transcription in response to a number of different cytokines. STAT6 is activated by cytokines IL-4 and IL-13, and plays important immune regulatory roles. Recent work suggests that STAT6 regulates many immune responses in animal models, including Th2 cell differentiation and IgE production from B cells. STAT6 participates in the progression of asthma, pulmonary antiviral responses and pulmonary fibrosis. Additionally, STAT6 is involved in the differentiation of IL-4/IL-13-induced tumor-associated macrophages (TAM). In this review, we summarize the recent advances in the effects of STAT6 on inflammatory lung diseases and underlying molecular and immunological mechanisms.

【Key words】 STAT6; asthma; acute respiratory distress syndrome (ARDS); lung cancer

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信号转导和转录激活因子(signal transducers and activators of transcription, STAT)属于转录因子家族,其主要表达在细胞质中,通过Janus激酶(Janus kinase, JAK)进行酪氨酸磷酸化反应,激活后可转入细胞核内与DNA结合,具有信号转导和转录的双重功能^[1]。JAK-STAT信号通路是细胞因子发挥生物学功能的主要通路,该通路机能的失调可引起免疫系统紊乱,甚至导致肿瘤的发生。

STAT6是STAT家族成员之一,近年的研究表明STAT6在多种肺部疾病的发生和发展中有重要的调控作用。STAT6可介导IL-13诱导的肺气道高感性(airway hyperresponsiveness, AHR)和黏液的生成^[2-3]。STAT6还参与调节动物模型中的许多病理反应,包括气道嗜酸性粒细胞的增多、上皮细胞黏液的生成、平滑肌的变化、Th2细胞分化以及B细胞产生IgE等^[4-5]。STAT6不仅是哮喘发展的一

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个关键因素,还参与肺部抗病毒反应及肺纤维化的发展。另外,STAT6与IL-4/IL-13诱导的肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)的分化密切相关。本文总结了STAT6信号通路在这些肺部疾病中作用和机制的最新研究进展。为进一步深入和系统了解STAT6在生理和病理条件下的生物学功能,探索以STAT6为靶点的靶向治疗提供新的理论基础和思路。

STAT6的信号通路 STAT6属于STAT家族,由847个氨基酸构成,在第641位氨基酸残基的酪氨酸发生突变的情况下,STAT6将丧失结合DNA和转录活性。STAT6由IL-4和IL-13激活^[1]。IL-4以高亲和力与IL-4受体 α 链(IL-4R α)和伽玛链(γ c)组成的I型受体复合物结合,激活JAK-STAT6通路^[5]。IL-13与IL-4R α 和IL-13R α 1组成的II型受体复合物结合,激活JAK-STAT6通路。STAT6单体被磷酸化和同源二聚化后,被转运到细胞核,与相关基因的启动子结合,诱导特异基因的表达。

STAT6与哮喘 支气管哮喘的发生和发展由多种细胞参与,包括嗜酸性粒细胞、肥大细胞、T淋巴细胞、巨噬细胞、中性粒细胞和气管上皮细胞等。这些细胞产生和分泌多种细胞因子,诱导气道慢性炎症和气道高反应性。IL-4和IL-13是哮喘的主要炎症因子,主要由CD4+Th2细胞和交替激活或抗炎作用的M2型巨噬细胞产生,在过敏性哮喘的发生和发展中具有重要作用^[6-7]。在过敏性气道疾病(allergic airway disease, AAD)小鼠模型中,IL-4/IL-13升高,诱导气管上皮细胞表达STAT6^[1,8]。当STAT6基因敲除时,卵清蛋白(ovalbumin, OVA)诱导AAD小鼠模型的肺部炎症和AHR明显减轻^[9-10],肺泡灌洗液(bronchoalveolar lavage fluid, BALF)的嗜酸性粒细胞明显降低^[3, 11],表明STAT6参与Th2细胞的分化,及其诱导的过敏性肺部炎症反应^[1, 12]。过继性输入野生型抗原特异性Th2细胞到该抗原诱导的STAT6-/-小鼠哮喘模型后,并不能增加该模型肺嗜酸性粒细胞数量、黏液生成和AHR,表明肺上皮细胞的STAT6信号通路在哮喘的诱导和发展中具有重要影响^[13]。

Rankin等^[14]进一步研究了IL-4和IL-13在哮喘中的潜在作用,发现IL-4在肺组织内过表达可增加肺部炎症反应,主要表现为上皮细胞肥大、巨噬细

胞、淋巴细胞、嗜酸性粒细胞和中性粒细胞等浸润。IL-13在肺组织内过表达也可引起单核和嗜酸性细胞炎症反应、黏液细胞增生、Charcot-Leyden样晶体沉积、气道纤维化、嗜酸性粒细胞趋化因子生成、气道阻塞和非特异性AHR^[15]。哮喘患者的痰和支气管活检中不仅可检测到过表达的IL-4和IL-13^[16],其气道平滑肌中肥大细胞来源的IL-4和IL-13含量也增加^[17],患者支气管活检组织中的STAT6表达明显升高^[18],进一步表明IL-4、IL-13和STAT6与哮喘易感性的关系^[19]。

因此,IL-4/IL-13/STAT6信号通路在过敏性哮喘的发生和发展中具有重要作用,可作为哮喘治疗的靶点,目前已经出现STAT6抑制肽、抗IL-13单克隆抗体和IL-4受体拮抗剂,并用于临床前期治疗^[4, 20]。STAT6-IP是新研发的一种抑制STAT6转录因子的细胞穿透肽,已经证实可以抑制小鼠哮喘模型的Th2细胞分化、黏液分泌、肺部炎症和AHR^[21]。STAT6反义核苷酸和显性负肽等动物实验治疗效果尚不明确^[20]。近期的一项II期临床试验表明,IL-4R α 拮抗剂可明显减轻哮喘的临床症状^[22],IL-13单克隆抗体lebrikizumab也有类似的治疗效果^[23]。

STAT6与急性呼吸窘迫综合征 急性肺损伤(acute lung injury, ALI)是一种严重的弥漫性肺部疾病,其严重形式是急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS),目前尚无特效治疗方法。ALI的主要特征是炎症损伤、肺水肿和难治性低氧血症,其中炎症损伤主要是组织和细胞损伤。异常激活的巨噬细胞、中性粒细胞的浸润以及过量的炎症细胞因子共同导致炎症反应发生。肺部炎症反应程度与巨噬细胞表型的多样性密切相关^[24]。巨噬细胞表型可分为M1(典型激活或促炎)或M2(交替激活或抗炎)型。巨噬细胞可从急性炎症时期为主的M1表型转变为恢复时期的M2表型,这一过程有助于肺组织损伤的修复^[25]。M2巨噬细胞主要通过IL-4/IL-13/STAT6信号通路发挥抗炎功能^[1]。IL-4和IL-13与相应的受体结合,促进STAT6磷酸化、二聚化并转运到细胞核,从而触发靶基因的表达。IL-4在脂多糖诱导的小鼠ALI模型中表达明显增加,具有免疫抑制和保护性作用^[26]。给予IL-4可明显减轻无菌性和感染性肺部炎症,并改善肺功能,目前认为IL-4通过增加巨噬

细胞STAT6的表达和激活,抑制炎症基因的转录和减轻肺炎反应^[27]。

STAT6与肺纤维化 研究发现特发性肺纤维化患者有高水平的IL-4和IL-13^[28],同时在特发性间质性肺炎患者的肺活检组织中过表达IL-4R α 和IL-13R α 2受体亚基^[29]。此外,特发性间质性肺炎和普通间质性肺炎患者来源的肺成纤维细胞株中也有高水平的IL-4R α 、IL-13R α 1及IL-13R α 2表达。目前认为IL-13与肺纤维化密切相关,参与哮喘和间质性肺炎的气道纤维化和平滑肌增生^[30]。IL-4和IL-13还涉及组织重塑,刺激人肺成纤维细胞分化,增加 α -平滑肌肌动蛋白和胶原的表达^[31]。IL-4和IL-13水平在博来霉素诱导的小鼠肺纤维化动物模型中明显升高,但阻断IL-4/IL-13信号通路后,STAT6激活减低,可明显减轻肺间质纤维化^[32]。IL-4/IL-13/STAT6通路在肺纤维化的发生发展中具有重要作用,可作为肺纤维化的有效治疗靶点。

STAT6在肺部抗病毒中的作用 干扰素基因刺激蛋白(stimulator of interferon genes,STING)是一种内质网驻留的膜蛋白,在天然病毒免疫中有重要作用。STING被环状二核苷酸激活后,转移到高尔基体,激活下游TANK结合激酶1(TANK-binding kinase 1, TBK1)^[33]。不同于IL-4/IL-13诱导的典型JAK/STAT6信号通路^[34],病毒感染免疫细胞后,STING被激活,将STAT6招募到内质网,由TBK1促进STAT6的磷酸化和形成二聚体,并转至细胞核内,诱导特定目标基因的表达和免疫细胞趋化转移^[34]。病毒感染成纤维细胞、骨髓来源的巨噬细胞和腹腔巨噬细胞后,STAT6被激活,通过产生相关抗病毒淋巴因子,抑制病毒在细胞内的增殖^[34],而在STAT6^{-/-}小鼠模型中,也证实STAT6信号通路与细胞的抗病毒作用有关,因为STAT6^{-/-}小鼠更易受到病毒的感染和诱导呼吸道症状。虽然呼吸道病毒感染通过诱导STAT6激活,增加哮喘发病的敏感性,但STAT6同时具有抗病毒作用,因此STAT6在哮喘和病毒免疫之间有双刃剑的作用^[35]。

STAT6与肺癌 STAT6不仅参与哮喘和肺部抗病毒反应,在肺癌的发生和发展也有重要作用^[36]。TAM是一种在肿瘤组织中浸润的巨噬细胞,在肿瘤侵袭转移、免疫逃避、血管及淋巴管生成等过程中都有重要作用。TAM在肿瘤微环境中可被极化为M2型巨噬细胞,刺激非小细胞肺癌(non-

small cell lung cancer, NSCLC)的血管生成,促进癌症进展和转移^[37-38]。甘露糖受体1(macrophage mannose receptor 1, MRC1)和精氨酸酶1(arginase-1, Arg1)是M2细胞标记性表达蛋白。肿瘤来源的巨噬细胞中MRC1和Arg1的表达明显增加,表明肿瘤微环境中M2细胞增多,可能不同程度参与肿瘤侵袭转移和免疫逃避^[39]。Th2细胞分泌的IL-4和IL-13通过激活STAT6,促进TAM细胞向M2细胞极化^[40]。肺癌患者过表达的STAT6的mRNA水平,提示其可能在M2细胞极化和免疫逃避中起到重要作用。体外实验也证实STAT6对癌细胞生长的促进作用,NSCLC患者的STAT6和pSTAT6水平显著升高^[41],但沉默肺癌细胞内的STAT6后,肺癌细胞凋亡显著增加^[41-42]。此外,pSTAT6在NSCLC组织类型之间的表达也存在一定的差异^[41],表明STAT6在肺癌发生中具有重要作用,pSTAT6可作为NSCLC各组织类型的潜在生物标记物。

癌细胞的基本特征包括基因突变、有丝分裂、血管生成、凋亡、转移和免疫抑制等,与环氧合酶-2(cyclooxygenase-2, COX-2)驱动的前列腺素表达水平密切相关^[41,43]。肺癌中COX-2的表达增加,促进肿瘤的发生、侵袭和肿瘤免疫^[44]。在NSCLC中STAT6的表达也明显升高^[9]。Cui等^[45]认为,STAT6可通过增加COX-2表达,减少NSCLC细胞的凋亡,沉默STAT6后,COX-2的表达下降,NSCLC细胞凋亡减少^[45]。STAT6在肺癌细胞增殖和侵袭中发挥重要作用^[46]。

细胞因子信号转导抑制因子(suppressor of cytokine signaling, SOCS)是JAK/STATs信号通路的负调控因子。SOCS蛋白功能丧失会增加癌变风险,研究证实肺癌等诸多肿瘤组织内的SOCS3表达较低或缺失^[47]。恢复SOCS3表达后,癌细胞凋亡增加,细胞侵袭性减低^[41]。高水平的SOCS3可提高NSCLC细胞对放疗的敏感性^[48]。由于肿瘤组织内的SOCS3和STAT6表达水平呈负相关^[41],提示SOCS3的抗肿瘤作用与STAT6表达密切相关,SOCS3可能通过抑制STAT6信号通路发挥抗肺癌作用。

结语 STAT6在多种肺部疾病的发生和发展过程中起关键的调控作用,包括哮喘、ALI、肺纤维化、肺部抗病毒作用和肺癌等。鉴于STAT6在这

些疾病进展中的重要作用,STAT6可能成为这些肺部疾病的有效治疗靶点。

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参 考 文 献

- [1] GOENKA S, KAPLAN MH. Transcriptional regulation by STAT6[J]. *Immunol Res*, 2011, 50(1): 87-96.
- [2] KUPERMAN DA, HUANG X, KOTH LL, *et al*. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma [J]. *Nat Med*, 2002, 8(8): 885-889.
- [3] KUPERMAN DA, SCHLEIMER RP. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma [J]. *Curr Mol Med*, 2008, 8(5): 384-392.
- [4] INGRAM JL, KRAFT M. IL-13 in asthma and allergic disease: asthma phenotypes and targeted therapies [J]. *J Allergy Clin Immunol*, 2012, 130(4): 829-842.
- [5] WALFORD HH, DOHERTY TA. STAT6 and lung inflammation [J]. *Jakstat*, 2013, 2(4): e25301.
- [6] QIAN X, GAO Y, YE X, *et al*. Association of STAT6 variants with asthma risk: a systematic review and meta-analysis [J]. *Hum Immunol*, 2014, 75(8): 847-853.
- [7] VENKAYYA R, LAM M, WILLKOM M, *et al*. The Th2 lymphocyte products IL-4 and IL-13 rapidly induce airway hyperresponsiveness through direct effects on resident airway cells [J]. *Am J Respir Cell Mol Biol*, 2002, 26(2): 202-208.
- [8] MULLINGS RE, WILSON SJ, PUDDICOMBE SM, *et al*. Signal transducer and activator of transcription 6 (STAT-6) expression and function in asthmatic bronchial epithelium [J]. *J Allergy Clin Immunol*, 2001, 108(5): 832-838.
- [9] PASTUSZAK-LEWANDOSKA D, DOMANSKA-SENDEROWSKA D, ANTCZAK A, *et al*. The expression levels of IL-4/IL-13/STAT6 signaling pathway genes and SOCS3 could help to differentiate the histopathological subtypes of non-small cell lung carcinoma [J]. *Mol Diagn Ther*, 2018, 22(5): 621-629.
- [10] DOHERTY TA, KHORRAM N, CHANG JE, *et al*. STAT6 regulates natural helper cell proliferation during lung inflammation initiated by *Alternaria* [J]. *Am J Physiol Lung Cell Mol Physiol*, 2012, 303(7): L577-L588.
- [11] KRISHNAMURTHY P, KAPLAN MH. STAT6 and PARP family members in the development of T cell-dependent allergic inflammation [J]. *Immune Netw*, 2016, 16(4): 201-210.
- [12] MATHEW A, MACLEAN JA, DEHAAN E, *et al*. Signal transducer and activator of transcription 6 controls chemokine production and T helper cell type 2 cell trafficking in allergic pulmonary inflammation [J]. *J Exp Med*, 2001, 193(9): 1087-1096.
- [13] CHAPOVAL SP, DASGUPTA P, SMITH EP, *et al*. STAT6 expression in multiple cell types mediates the cooperative development of allergic airway disease [J]. *J Immunol*, 2011, 186(4): 2571-2583.
- [14] RANKIN JA, PICARELLA DE, GEBA GP, *et al*. Phenotypic and physiologic characterization of transgenic mice expressing interleukin 4 in the lung: lymphocytic and eosinophilic inflammation without airway hyperreactivity [J]. *Proc Natl Acad Sci U S A*, 1996, 93(15): 7821-7825.
- [15] ZHU Z, HOMER RJ, WANG Z, *et al*. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production [J]. *J Clin Invest*, 1999, 103(6): 779-788.
- [16] SAHA SK, BERRY MA, PARKER D, *et al*. Increased sputum and bronchial biopsy IL-13 expression in severe asthma [J]. *J Allergy Clin Immunol*, 2008, 121(3): 685-691.
- [17] BRIGHTLING CE, SYMON FA, HOLGATE ST, *et al*. Interleukin-4 and -13 expression is co-localized to mast cells within the airway smooth muscle in asthma [J]. *Clin Exp Allergy*, 2003, 33(12): 1711-1716.
- [18] CHRISTODOULOPOULOS P, CAMERON L, NAKAMURA Y, *et al*. TH2 cytokine-associated transcription factors in atopic and nonatopic asthma: evidence for differential signal transducer and activator of transcription 6 expression [J]. *J Allergy Clin Immunol*, 2001, 107(4): 586-591.
- [19] TAMURA K, SUZUKI M, ARAKAWA H, *et al*. Linkage and association studies of STAT6 gene polymorphisms and allergic diseases [J]. *Int Arch Allergy Immunol*, 2003, 131(1): 33-38.
- [20] OH CK, GEBA GP, MOLFINO N. Investigational therapeutics targeting the IL-4/IL-13/STAT-6 pathway for the treatment of asthma [J]. *Eur Respir Rev*, 2010, 19(115): 46-54.
- [21] MCCUSKER CT, WANG Y, SHAN J, *et al*. Inhibition of experimental allergic airways disease by local application of a cell-penetrating dominant-negative STAT-6 peptide [J]. *J Immunol*, 2007, 179(4): 2556-2564.
- [22] WENZEL S, WILBRAHAM D, FULLER R, *et al*. Effect of an interleukin-4 variant on late phase asthmatic response

- to allergen challenge in asthmatic patients: results of two phase 2a studies[J].*Lancet*,2007,370(9596):1422-1431.
- [23] CORREN J, LEMANSKE RF, HANANIA NA, *et al.* Lebrikizumab treatment in adults with asthma[J].*N Engl J Med*,2011,365(12):1088-1098.
- [24] MANTOVANI A, BISWAS SK, GALDIERO MR, *et al.* Macrophage plasticity and polarization in tissue repair and remodelling[J].*J Pathol*,2013,229(2):176-185.
- [25] HEROLD S, MAYER K, LOHMEYER J. Acute lung injury: how macrophages orchestrate resolution of inflammation and tissue repair [J]. *Front Immunol*, 2011,2:65.
- [26] D'ALESSIO FR, CRAIG JM, SINGER BD. Enhanced resolution of experimental ARDS through IL-4-mediated lung macrophage reprogramming [J]. *Am J Physiol Lung Cell Mol Physiol*,2016,310(8):L733-L746.
- [27] CZIMMERER Z, DANIEL B, HORVATH A, *et al.* The Transcription factor STAT6 mediates direct repression of inflammatory enhancers and limits activation of alternatively polarized macrophages[J].*Immunity*,2018,48(1):75-90.
- [28] HANCOCK A, ARMSTRONG L, GAMA R, *et al.* Production of interleukin 13 by alveolar macrophages from normal and fibrotic lung [J]. *Am J Respir Cell Mol Biol*, 1998,18(1):60-65.
- [29] JAKUBZICK C, CHOI ES, KUNKEL SL, *et al.* Augmented pulmonary IL-4 and IL-13 receptor subunit expression in idiopathic interstitial pneumonia [J]. *J Clin Pathol*,2004,57(5):477-486.
- [30] DOHERTY T, BROIDE D. Cytokines and growth factors in airway remodeling in asthma [J]. *Curr Opin Immunol*, 2007,19(6):676-680.
- [31] DOUCET C, BROUTY-BOYE D, POTTINCLE-MENCEAU C, *et al.* Interleukin (IL)-4 and IL-13 act on human lung fibroblasts. Implication in asthma [J]. *J Clin Invest*,1998,101(10):2129-2139.
- [32] JAKUBZICK C, CHOI ES, JOSHI BH, *et al.* Therapeutic attenuation of pulmonary fibrosis via targeting of IL-4- and IL-13-responsive cells[J].*J Immunol*,2003,171(5):2684-2693.
- [33] ISHIKAWA H, MA Z, BARBER GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity[J].*Nature*,2009,461(7265):788-792.
- [34] CHEN H, SUN H, YOU F, *et al.* Activation of STAT6 by STING is critical for antiviral innate immunity [J]. *Cell*, 2011,147(2):436-446.
- [35] HOLTZMAN MJ. Asthma as a chronic disease of the innate and adaptive immune systems responding to viruses and allergens[J].*J Clin Invest*,2012,122(8):2741-2748.
- [36] TARIQ M, ZHANG JQ, LIANG GK, *et al.* Gefitinib inhibits M2-like polarization of tumor-associated macrophages in Lewis lung cancer by targeting the STAT6 signaling pathway[J].*Acta Pharmacol Sin*,2017,38(11):1501-1511.
- [37] QIAN BZ, POLLARD JW. Macrophage diversity enhances tumor progression and metastasis [J]. *Cell*, 2010,141(1):39-51.
- [38] DAI F, LIU L, CHE G, *et al.* The number and microlocalization of tumor-associated immune cells are associated with patient's survival time in non-small cell lung cancer[J].*BMC Cancer*,2010,10:220.
- [39] MARTINEZ FO, HELMING L, GORDON S. Alternative activation of macrophages: an immunologic functional perspective[J].*Annu Rev Immunol*,2009,27:451-483.
- [40] GENSEL JC, ZHANG B. Macrophage activation and its role in repair and pathology after spinal cord injury [J]. *Brain Res*,2015,1619:1-11.
- [41] PASTUSZAK-LEWANDOSKA D, DOMANSKA-SENDEROWSKA D, KORDIAK J, *et al.* Immunoexpression analysis of selected JAK/STAT pathway molecules in patients with non-small-cell lung cancer[J].*Pol Arch Intern Med*,2017,127(11):758-764.
- [42] DUBEY R, CHHABRA R, SAINI N. Small interfering RNA against transcription factor STAT6 leads to increased cholesterol synthesis in lung cancer cell lines[J]. *PLoS One*,2011,6(12):e28509.
- [43] HARRIS SG, PADILLA J, KOUMAS L, *et al.* Prostaglandins as modulators of immunity [J]. *Trends Immunol*,2002,23(3):144-150.
- [44] HIDA T, YATABE Y, ACHIWA H, *et al.* Increased expression of cyclooxygenase 2 occurs frequently in human lung cancers, specifically in adenocarcinomas [J]. *Cancer Res*,1998,58(17):3761-3764.
- [45] CUI X, ZHANG L, LUO J, *et al.* Unphosphorylated STAT6 contributes to constitutive cyclooxygenase-2 expression in human non-small cell lung cancer [J]. *Oncogene*,2007,26(29):4253-4260.
- [46] MA Y, BAO C, KONG R, *et al.* MicroRNA3615p suppresses cancer progression by targeting signal transducer and activator of transcription 6 in nonsmall cell lung cancer[J].*Mol Med Rep*,2015,12(5):7367-7373.
- [47] OGATA H, KOBAYASHI T, CHINEN T, *et al.* Deletion of the SOCS3 gene in liver parenchymal cells promotes hepatitis-induced hepatocarcinogenesis[J].*Gastroenterology*, 2006,131(1):179-193.
- [48] LIN YC, LIN CK, TSAI YH, *et al.* Adenovirus-mediated SOCS3 gene transfer inhibits the growth and enhances the radiosensitivity of human non-small cell lung cancer cells [J].*Oncol Rep*,2010,24(6):1605-1612.

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