中南大学学报(医学版) 2010, 35(3) 209-214 DOI: 10.3969/j.issn.1672-7347.2010. ISSN: 1672-7347 CN: 43-1427/R

论著

SH2B1调控JAK2/IRS2在肥胖症发病中的分子机制

段朝军1, 2， 汤参娥1, 2， 廖岚3， 李萃2， 苏涛1， 陈主初2

中南大学湘雅医院1.卫生部肿瘤蛋白质组学重点实验室, 长沙410008；
2.医学实验研究中心, 长沙 410008； 3.内分泌科, 长沙 410008

摘要：

目的：研究JAK2接头蛋白SH2B1调控JAK2/IRS2在肥胖症发病中的作用及其分子机制。方法：采用高效稳定表达瘦素受体的细胞株HEK239LRb和SH2B1基因缺失小鼠，Western 印迹、［γ-32P］-ATP体外激活分析法分析瘦素信号通路关键分子JAK2和IRS2的酪氨酸磷酸化水平；ELISA法测定小鼠血清瘦素水平；检测出生后至27周小鼠体质量。结果：在高效稳定表达瘦素受体细胞株HEK239LRb中，SH2B13显著增强瘦素刺激的JAK2激酶活性和IRS2磷酸化；在SH2B1基因缺失小鼠中，瘦素刺激JAK2激酶活性和IRS2酪氨酸磷酸化水平均显著降低；无论空腹还是随机给食，SH2B1基因缺失小鼠血清瘦素水平均升高并发展为高瘦素血症，其血清瘦素水平与同窝野生型小鼠相比分别增加3.2倍和5.1倍。5 周后，SH2B1基因缺失小鼠体质量逐渐增加，21周龄时，大约为同窝野生型小鼠2倍。结论：JAK2接头蛋白SH2B1是内源性瘦素敏感性增强子，通过瘦素JAK2/IRS2信号通路参与瘦素对体质量的调节，SH2B1基因缺失小鼠易发展为高瘦素血症及肥胖。

关键词： SH2B1 肥胖症 胰岛素受体底物-2 瘦素信号通路

Molecular mechanism of SH2B1 in regulating JAK2/IRS2 during obesity development

DUAN Chaojun1,2, TANG Can’e1,2, LIAO Lan3, LI Cui2, SU Tao1, CHEN Zhuchu2

1.Key Laboratory of Cancer Proteomics, Ministry of Health of China, Xiangya Hospital, Central South University,
Changsha 410008; 2.Medical Research Center, Xiangya Hospital, Central South University,
Changsha 410008; 3.Department of Endocrinology, Xiangya Hospital,
Central South University, Changsha 410008, China

Abstract:

ObjectiveIn order to investigate the effect of SH2B1 on leptin signal transduction JAK2/IRS2 and its biological function.MethodsVitro kinase assay and Western blot were used to analyse tyrosine phosphorylatin of key molecule JAK2 and insulin receptor substrate-2 (IRS2). ELISA was used to measure the plasma leptin levels in mice. The postnatal growth of mice was monitored over 27 weeks. ResultsSH2B1 dramatically enhanced the leptin-stimulated tyrosine phosphorylation of JAK2 and IRS2 in HEK293 cells stably expressing LRb (HEK239LRb). Leptin-stimulated activation of hypothalamic JAK2 and phosphorylation of hyphothalamic IRS2 were significantly impaired in SH2B1-/- mice. The deletion of SH2B1 led to leptin resistance,and fasting and randomly fed plasma leptin levels were respectively 3.2 times and 5.1 times higher in SH2B1-/- males than wild-type littermates at 15 weeks of age. SH2B1-/- males gained body weight rapidly and exceeded wild-type littermates from 5th week. SH2B1-/- (at 21 weeks) was approximately twice heavier than wild-type littermates.ConclusionSH2B1 is an endogenous enhancer of leptin sensitivity and required for maintaining normal bodyweight in mice via leptin JAK2/IRS2 pathway.

Keywords: SH2B1;obesity;insulin receptor substrate-2;leptin signal pathway SH2B1;obesity;insulin receptor substrate-2;leptin signal pathway

收稿日期 2009-06-29 修回日期 网络版发布日期

DOI: 10.3969/j.issn.1672-7347.2010.

基金项目:

通讯作者: 段朝军

作者简介:

作者Email: duancjxy@126.com

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