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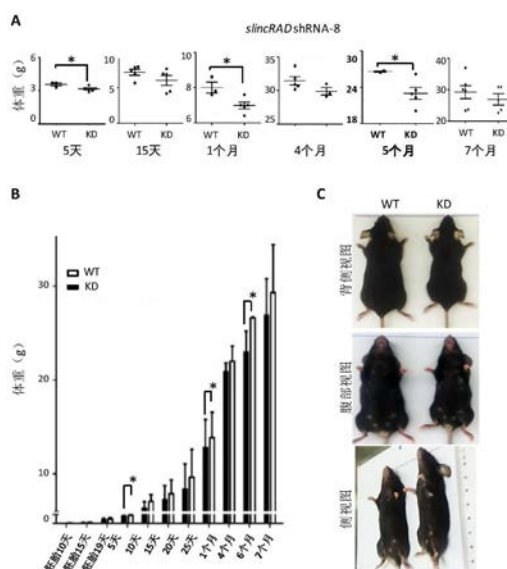
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(54) 发明名称

一种脂肪细胞分化相关的长非编码RNA及其应用

(57) 摘要

本发明提供了一种与脂肪细胞分化相关的长非编码RNA slincRAD,该RNA通过与DNMT1蛋白结合,利用PPARγ等信号通路调节脂肪细胞的分化和脂肪组织的发育。利用靶向slincRAD的siRNA或shRNA,可以抑制slincRAD的表达,进而特异性地抑制脂肪的分化进程。敲低slincRAD的转基因小鼠表现出更好的血糖耐受性,对血脂代谢也有积极的作用。



1. 一种抑制长非编码RNA *slincRAD* 表达的小干扰核糖核酸分子,所述小干扰核糖核酸分子的序列如SEQ ID No 1-12所示。

2. 一种抑制长非编码RNA *slincRAD*表达的小发夹结构核糖核酸分子,所述小发夹结构核糖核酸分子的序列如SEQ ID No 21-24所示。

3. 权利要求1或2所述的核糖核酸分子在制备抑制脂肪细胞分化的制剂或药物中的应用。

4. 权利要求1或2所述的核糖核酸分子在制备*slincRAD*低表达模型动物中的应用,其特征在于将模型动物脂肪组织*slincRAD*的表达水平降低至野生型动物脂肪组织*slincRAD*表达水平的60%及以下。

5. 根据权利要求4所述的应用,其特征在于所述模型动物选自小鼠、大鼠或恒河猴。

6. 一种制备*slincRAD*低表达模型动物的方法,包括以下步骤:

1) 获得编码*slincRAD*-shRNA 表达框的DNA片段;

2) 利用显微注射将DNA片段导入动物受精卵的原核中,然后将受精卵移植到假孕的同种动物体内,使其发育成成体动物;

3) 鉴定获得基因组中整合*slincRAD*-shRNA的转基因动物;

4) 将转基因动物与同种野生型动物进行交配,获得子代动物;

5) 鉴定获得基因组中整合*slincRAD*-shRNA的子代动物即为*slincRAD*敲低的转基因动物。

7. 敲低*slincRAD*表达的转基因动物模型在脂肪代谢相关疾病药物筛选中的应用。

8. 根据权利要求7所述的应用,其特征在于所述脂肪代谢相关疾病选自代谢综合症、肥胖症、高血糖、高血脂、糖尿病。

一种脂肪细胞分化相关的长非编码RNA及其应用

技术领域

[0001] 本发明涉及生理和生物学领域,具体涉及一种具有脂肪细胞分化调节功能的长链非编码RNA及其应用。

背景技术

[0002] 长链非编码RNA (lncRNA) 是一类转录本长度大于200bp,具有相对较长的核苷酸链的非编码RNA。lncRNA具有类型多、作用模式多和数量多等特点,因此它蕴含的信息十分丰富,其参与表达调控的分子机制也多种多样,主要从表观遗传学、转录水平以及转录后水平三个层面实现对基因表达的调控。lncRNA可能主要具有以下几个方面的功能:(1)通过在蛋白编码基因上游启动子区发生转录,干扰下游基因的表达;(2)通过抑制RNA聚合酶I I或者介导染色质重构以及组蛋白修饰,影响下游基因表达;(3)通过与蛋白编码基因的转录本形成互补双链,进而干扰mRNA的剪切,从而产生不同的剪切形式;(4)通过与蛋白编码基因的转录本形成互补双链,进一步在Dicer酶作用下产生内源性的siRNA,调控基因的表达水平;(5)通过结合到特定蛋白质上,lncRNA转录本能够调节相应蛋白的活性;(6)作为结构组分与蛋白质形成核酸蛋白质复合物;(7)通过结合到特定蛋白上,改变该蛋白的胞质定位;(8)作为小分子RNA,如miRNA、piRNA的前体分子转录。正因为lncRNA可以从转录和转录后水平参与蛋白质编码基因的调控,这些基因包括疾病发生相关基因及发育相关基因等,通过参与调控蛋白质编码基因,lncRNA既能影响细胞内信号转导途径,也能影响生物体发育过程中的信号转导通路。目前已报道lncRNA会对多种疾病的发生和发展产生影响,包括神经系统的疾病,心血管疾病以及多种肿瘤癌症等疾病。

[0003] 近年来对长非编码RNA的研究引起了广泛关注,而与脂肪细胞分化相关的lncRNA研究尚非常有限。探索新的在脂肪分化中扮演重要角色的lncRNA,不仅会揭示调控脂肪细胞功能的重要机制,还将提供新的检测或治疗靶点,是脂肪代谢相关疾病研究中亟待开拓的重要科学问题。

发明内容

[0004] 本发明旨在提供与脂肪细胞分化功能相关的长非编码RNA slincRAD,并将slincRAD用于调控脂肪细胞的增殖和分化行为,并且建立slincRAD敲低的小鼠模型,用于脂肪代谢相关疾病药物的筛选等研究。

[0005] 在细胞和小鼠中敲低slincRAD的表达,导致脂肪细胞分化相关基因的表达出现下降,脂肪组织发育受到影响,体重减轻。

[0006] 本发明首先提供了长链非编码RNA slincRAD在制备促进脂肪细胞分化的制剂或药物中的应用,所述长链非编码RNA序列见SEQ ID No.300。

[0007] 其次,本发明提供了抑制长链非编码RNA slincRAD表达的抑制剂,包括小干扰核糖核酸(siRNA)和小发夹结构RNA(shRNA),序列见表2和表3。

[0008] 进一步地,本发明提供了作为长链非编码RNA slincRAD表达抑制剂的shRNA和

siRNA在制备抑制脂肪细胞分化药物中的应用。

[0009] 再次,本发明提供了检测长链非编码RNA slincRAD的寡聚核酸,选自如下组合:

[0010] 检测引物组合01:

[0011] 01正向引物:5' -ATCCATCTCCCCTACCCATC (SEQ ID NO:200)

[0012] 01反向引物:5' -TGCAGAGGACTCACAACCTGG (SEQ ID NO:201)

[0013] 检测引物组合08:

[0014] 08正向引物:5' -GGTGCAGTTTTGCACTGAGA (SEQ ID NO:202)

[0015] 08反向引物:5' -GATGGAGAGAAAGGAAGGGG (SEQ ID NO:203)

[0016] 检测引物组合16:

[0017] 16正向引物:5' -CCTAGTGCCTTTCTGCCTTG (SEQ ID NO:204)

[0018] 16反向引物:5' -TGGGGTGATTGTGTAGGGAT (SEQ ID NO:205)

[0019] 检测引物组合31:

[0020] 31正向引物:5' -CAAGTGGTTCCGGATTCTGT (SEQ ID NO:206)

[0021] 31反向引物:5' -CCGTGAAATGAAGTGGTGTG (SEQ ID NO:207)

[0022] 检测引物组合54:

[0023] 54正向引物:5' -GCATTTAATTGGTGCTGGCT (SEQ ID NO:208)

[0024] 54反向引物:5' -GACCCTTCTCCTAGCTGCCT (SEQ ID NO:209)

[0025] 进一步地,本发明提供了检测长链非编码RNA slincRAD表达水平的试剂在制备脂肪分化促进剂或抑制剂中的应用。

[0026] 第四方面,本发明提供了敲低长非编码RNA slincRAD的转基因小鼠模型,该小鼠模型的制备方法以及该小鼠模型在脂肪代谢相关疾病药物筛选中的应用。所述脂肪代谢相关疾病包括但不限于代谢综合症、肥胖症、高血糖、高血脂、糖尿病。

[0027] slincRAD可以促进小鼠3T3-L1细胞分化,此作用可能是通过PPAR γ 信号通路实现的。

[0028] 因此,slincRAD可用于促进脂肪细胞的分化,还可以用于制备或筛选制备治疗脂肪相关疾病,如肥胖症的药物。

[0029] 本发明的有益效果:

[0030] 本发明提供了一种与脂肪细胞分化相关的长非编码RNA slincRAD,该RNA通过与DNMT1蛋白结合,利用PPAR γ 等信号通路调节脂肪细胞的分化和脂肪组织的发育。利用靶向slincRAD的siRNA或shRNA,可以抑制slincRAD的表达,进而特异性地抑制脂肪的分化进程。敲低slincRAD的转基因小鼠表现出更好的血糖耐受性,对血脂代谢也有积极的作用。

附图说明

[0031] 图1为3T3-L1脂肪细胞的体外诱导分化过程。(A) 脂肪细胞分化过程的油红O染色结果。分别在脂肪细胞体外诱导分化的第0天、14天和21天取样,进行油红O染色,利用对脂肪滴的染色结果,判断脂肪细胞的分化情况。在诱导分化的第0天,油红O染色阳性细胞的比例为0%;诱导分化的第14天,油红O染色阳性细胞的比例为24.2%;诱导分化的第21天,油红O染色阳性细胞的比例为54.9%。(B) 脂肪细胞分化过程中PPAR γ 和CEBP α 的表达情况。利用实时荧光定量聚合酶链式反应(qRT-PCR),检测脂肪细胞分化过程中PPAR γ 和CEBP α 的表

达情况。以第0天各基因的表达水平为参照,计算诱导分化过程中基因的表达情况,表达值的表述方式为:平均值±标准差。

[0032] 图2为敲低slincRAD基因的表达能抑制脂肪细胞的体外诱导分化。(A) 油红O染色结果.在诱导分化前2天,对3T3-L1细胞进行第一次siRNA转染;在诱导分化处理的当天,进行第二次siRNA转染。在诱导分化的第九天,收获细胞,进行油红O染色,观察细胞内脂质的生成和积累情况。Control:未经诱导分化处理,且未转染siRNA的细胞。Mock:只经过诱导分化处理,未转染siRNA的细胞。NC-siRNA:经过诱导分化处理,且转染了一个序列无关的siRNA的细胞。siRNA1-siRNA17:经过诱导分化处理,转染了slincRAD特异性siRNA的细胞。(B) 油红O染色的定量分析结果。利用ImageJ软件(<http://imagej.nih.gov/ij/>),对油红O染色结果进行定量分析。为了消除背景染色,首先将Control细胞的染色值作为染色背景减去。然后以Mock的染色值为基准,对其他细胞的染色值进行归一化处理;随后再将得到的染色值,对细胞数目进行归一化处理,以反映siRNA处理对细胞分化的影响。利用t-tests进行实验结果的统计分析(*:以NC-siRNA为对照, $P<0.05$)。

[0033] 图3为slincRAD-shRNA对脂肪细胞分化的调节作用。(A) slincRAD的基因结构、转录本结构和shRNA靶点位置。(B) slincRAD-shRNA对靶基因的抑制效果。按照实施例二中的方案,对野生型、slincRADshRNA-8、slincRADshRNA-9 3T3-L1细胞进行激素诱导处理。处理6天后,收获细胞,提取总RNA,利用qRT-PCR检测slincRAD的表达水平。用一个序列无关的、靶向GFP蛋白基因的shRNA作为实验的对照组(CTL, control)。实验数据为三次生物学重复的平均值,数据表示方式为:平均值±s.e.m。(C) 对细胞脂质生成的抑制作用。激素诱导分化分离后的第7天,对培养细胞进行油红O染色,分析抑制slincRAD基因表达对细胞脂质的影响。上图:培养板的油红O染色;中图:培养板的局部染色图像;下图:用ImageJ软件对油红O染色的定量结果。对照组(CTL)为野生型3T3-L1细胞。

[0034] 图4为转基因小鼠构建过程。(A) 图示转基因小鼠构建的构成过程。(B) 第11窝转基因小鼠的基因型鉴定。

[0035] 图5为转基因小鼠的建系及鉴定。(A) 转基因小鼠的谱系图。将获得的两只基因型为shRNA8+/-的首代转基因小鼠(编号:13,15)和一只基因型为shRNA9+/-的首代转基因小鼠(编号:11),与野生型C57BL/6J雌性小鼠交配。利用编号为9号的首代转基因小鼠进行人工授精。总共获得20窝、143F1代小鼠,其中转基因小鼠81只。图中小鼠的标志方式如下,如9#(M3,F5)标示第9窝小鼠中有3只雄鼠和5只雌鼠。编号为1-6号的小鼠在出生前,即被处死,用于研究胚胎期的小鼠发育和基因表达等情况。(B) slincRAD基因的表达水平在转基因小鼠中被下调。利用qRT-PCR,对出生10天、15天、30天小鼠脏器中的基因表达水平进行了检测。在PCR中,以U6RNA作为检测对照。slincRAD基因的表达水平被表示为相对野生型基因水平的倍数关系。实验数据为三次生物学重复的平均值,数据表示方式:平均值±s.e.m。(C) 小鼠遗传模式图。本表表述的是每窝小鼠的遗传信息,如第9窝小鼠有3只雄性子鼠和5只雌性小鼠,3只雄性小鼠中有1只为转基因小鼠,5只雌性小鼠均为转基因小鼠。在发育阶段一栏中,ED15表示胚胎期第15天的小鼠;Day15表示出生后第15天的小鼠;7Mo表示出生后7个月的小鼠。

[0036] 图6表示敲低slincRAD影响小鼠的发育。(A) 出生后,转基因小鼠和野生型小鼠的体重对照(*,有显著性差异的值)。(B) 体重分布图(*,有显著性差异的值)。(C) 转基因小鼠

和野生型小鼠的身体形态图。

[0037] 图7表示敲低slincRAD基因表达影响了小鼠脂肪组织的发育。(A) 体脂和肌肉测量。利用小动物核磁仪,我们检测了1月龄和7月龄小鼠的身体体脂和肌肉含量(每组 $n \geq 4$)。白色柱:野生型小鼠;黑色柱,转基因小鼠。(B) 5月龄小鼠的主要脏器重量($n \geq 4$)。白色柱:野生型小鼠;黑色柱,转基因小鼠。(C) 脂肪组织的组织学切片观察。上图:白色脂肪组织的苏木精-伊红染色结果。白色柱:野生型小鼠;黑色柱,转基因小鼠。图上比例尺为 $50 \mu\text{m}$ 。下图:脂肪细胞的大小分布。空心圆:野生型小鼠;实心圆:基因敲除小鼠。数据表示方式:平均值 \pm S.E.M.,每组 $n=3$, $*p < 0.05$;*** $p < 0.001$ 。(D) 7月龄小鼠主要脏器的组织切片观察。图上比例尺为 $100 \mu\text{m}$ 。

[0038] 图8表示slincRAD对脂肪细胞分化关键因子的调控作用。利用qRT-PCR,我们在野生型和转基因小鼠的肝脏组织中,分析了脂肪细胞分化关键因子PPAR γ 和CD36、以及slincRAD的表达水平。以野生型小鼠基因表达水平为参照,计算转基因小鼠的表达水平(相对于野生型基因表达的倍数)。数据表示方式:平均值 \pm S.E.M.,每组 $n=10$ 。

[0039] 图9表示敲低slincRAD对小鼠血糖和血脂代谢的影响。(A) 7月龄野生型和转基因小鼠中,血糖、血浆总甘油三酯(TG)、总胆固醇(TC)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)含量的对比研究。空心柱:野生型小鼠;实心柱:转基因小鼠。数据表示方式:平均值 \pm S.E.M.,每组 $n=14$ 。 $*p < 0.05$;** $p < 0.01$;*** $p < 0.001$ 。(B) 糖耐受实验。空心圆圈:野生型小鼠;实心圆圈:转基因小鼠。数据表示方式:平均值 \pm S.E.M.,每组 $n=14$ 。(C) 胰岛素耐受性实验。空心圆圈:野生型小鼠;实心圆圈:转基因小鼠。数据表示方式:平均值 \pm S.E.M.,每组 $n \geq 3$ 。

[0040] 图10表示slincRAD对脂肪分化关键因子的影响。在脂肪细胞分化过程中,利用qRT-PCR,逐日检测分化关键因子的表达水平,绘制曲线图。蓝线:野生型细胞中的基因表达水平;红线,slincRAD敲低细胞株中的基因表达水平。内参为 β -actin。数据表示方式:平均值 \pm S.E.M.,每组 $n=3$ 。

[0041] 图11表示流式细胞仪检测野生型slincRAD细胞和slincRAD敲低型(shRNA8和shRNA9敲低)细胞分化过程中细胞周期的变化。

[0042] 图12表示Dnmt1基因的表达谱分析。利用qRT-PCR,分析了Dnmt1基因在脂肪细胞分化过程中的表达变化。内参为 β -actin。数据表示方式:平均值 \pm S.E.M.,每组 $n=3$ 生物学重复。

[0043] 图13表示RNA免疫共沉淀。利用抗DNMT1抗体和免疫共沉淀技术,获得与DNMT1发生相互作用的细胞RNA组分。随后利用qRT-PCR技术,检测免疫复合物中slincRAD基因转录本的含量。实验的阴性对照为抗IgG抗体捕获的免疫复合物。数据表示方式:平均值 \pm S.E.M.。

[0044] 图14是野生型和slincRAD敲低细胞中启动子甲基化水平的维恩图分析。

[0045] 图15是DEP基因的维恩图分析。

[0046] 图16是野生型3T3-L1细胞中,差异甲基化的增殖相关基因的DEP指数。

[0047] 图17是Heat-map分析。在脂肪细胞诱导分化的第(-2)天和第(+2)天,对比分析基因启动子甲基化水平的DEP指数。红色代表高甲基化水平的基因;绿色代表低甲基化基因,用Heatmap Illustrator绘制本图。

[0048] 图18是western杂交研究p21等蛋白的表达变化。被研究细胞系包括野生型3T3-L1

细胞 (WT)、slincRADshRNA-8 (sh8) 和slincRADshRNA-9 (sh9) slincRAD低表达细胞。研究时间点为脂肪细胞体外诱导分化的 (-2) 到 (+4) 天。

[0049] 图19是slincRAD作用模式图。

具体实施方式

[0050] 下面结合具体实施例及附图,进一步阐述本发明。应当理解,这些实施例仅用于说明本发明而不能用于限制本发明的范围。下列实施例中未注明具体条件的实验方法,通常按照常规条件,例如Sambrook等人,分子克隆:实验室手册 (New York: Cold Spring Harbor Laboratory Press, 1989) 中所述的条件,或按照制造厂商所建议的条件。

[0051] 实施例一:实验动物和材料

[0052] 试验用小鼠购自于北京维通利华实验动物技术有限公司提供,饲养在北京大学实验动物中心。所有实验方案和操作均得到北京大学实验动物伦理委员会的批准。

[0053] DNA寡核苷酸购自Invitrogen北京公司, RNA寡核苷酸购自广州市锐博生物科技有限公司。

[0054] 实施例二:3T3-L1脂肪细胞的体外诱导分化

[0055] 3T3-L1前脂肪细胞体外诱导分化是一个常用的脂肪细胞分化模型,在诱导剂(1-甲基-3-异丁基黄嘌呤 (IBMX)、胰岛素、地塞米松)的作用下,诱导下分化成成熟的脂肪细胞。为了研究细胞的分化进程,我们首先利用油红O染色,检测了细胞中脂肪滴的生成和积累情况,发现在诱导分化末期(第21天),54.9%的细胞呈现脂肪染色阳性。此外,我们还利用实时荧光定量聚合酶链式反应 (qRT-PCR),检测细胞分化关键因子PPAR γ 和CEBP α 的表达情况。发现这两个因子在细胞分化中的表达调控与文献报道一致,表明诱导分化过程是成功的。研究方案和实验结果具体如下:

[0056] 1、3T3-L1前脂肪细胞的培养和体外诱导分化:诱导分化时间点的定义:以加入诱导分化培养基,开始进行诱导分化的当天为诱导分化的第1天。诱导分化第1天的前一天为第0天。诱导分化第1天的后一天为第2天,并依此类推定义其他诱导分化时间节点。

[0057] 在含有10%胎牛血清的DMEM液体培养基中,常规培养3T3-L1小鼠前脂肪细胞,2至3天换液1次。在诱导分化的第1天,将常规培养基换成分化诱导培养基,进行体外诱导分化。诱导培养基是在常规培养基的基础上加入167nM人胰岛素 (Sigma)、0.5mmol/L 1-甲基-3-异丁基黄嘌呤 (Sigma) 和1 μ M地塞米松 (Sigma)。在诱导分化的第2天,将培养基换成仅含有167nM胰岛素的DMEM培养基。在诱导分化的第4天,将分化培养基换回到常规DMEM培养基,继续培养,直至分化过程结束。

[0058] 2、油红O染色:按常规方法,配置油红O试剂。在分化过程的关键时间节点:诱导分化前期(第0天),诱导分化中期(第14天)、以及诱导分化末期(第21天),取样进行油红O染色。

[0059] 实验步骤:1)对各个时间节点获得的培养细胞样本,先用经过冰浴的磷酸缓冲液 (PBS) 轻缓漂洗3次;2)用3.7%甲醛固定细胞2分钟;3)在室温条件下与油红O试剂孵育1小时,对细胞脂肪染色;4)去离子水漂洗3次;5)光学显微镜下观察并拍照;6)利用ImageJ软件 (<http://imagej.nih.gov/ij/>),以未进行诱导分化的细胞对对照,对油红O染色结果进行定量分析。

[0060] 油红O染色结果,如图1A所示。在诱导分化的第0天,油红O染色阳性细胞的比例为0%;诱导分化的第14天,油红O染色阳性细胞的比例为24.2%;诱导分化的第21天,油红O染色阳性细胞的比例为54.9%。成熟的脂肪细胞呈圆形,有大量脂滴聚集,油红O染色显现橘红色。

[0061] 3、PPAR γ 和CEBP α 的表达检测:利用qRT-PCR,分析PPAR γ 和CEBP α 在分化过程中的表达变化,内参基因为 β -actin。检测基因表达的引物序列信息见表1。实验结果如图1B所示,实验步骤具体如下:

[0062] 1) 总RNA提取:分别获得诱导分化第0天(诱导分化前期),第14天(诱导分化中期)、第21天(诱导分化末期)的细胞样本,利用Trizol试剂,提取细胞总RNA,并进行定量。

[0063] 2) RNA逆转录:使用天根生化科技公司的逆转录试剂盒(TIANScript M-MLV, cat: ER104-03)进行RNA样本的逆转录反应,具体按照试剂盒说明书的方法进行,步骤如下:取1微克总RNA样本,加入2 μ L (10 μ M) 6碱基随机逆转录引物,2 μ L dNTP (10mM),混匀后置70 $^{\circ}$ C水浴变性5分钟;冰上放置3分钟后取出,加入4 μ L 5 \times First-Strand Buffer,0.5 μ L RNase inhibitor (40U/ μ L),1 μ L M-MLV (200U/ μ L),总体积为20 μ L;混匀后短暂离心,置于Eppendorf PCR仪中进行逆转录反应,反应参数为25 $^{\circ}$ C,10分钟;42 $^{\circ}$ C,50分钟;95 $^{\circ}$ C,5分钟;随后置于4 $^{\circ}$ C保存。其中,RNase inhibitor为Promega公司的产品(cat#N211)。

[0064] 3) 实时荧光定量PCR:使用天根生化科技公司的HotMaster Taq DNA polymerase试剂(cat#:ET106-01-01),检测样本中基因的表达情况,实验步骤具体如下:取2 μ L逆转录产物,加入2.5 μ L 10 \times HotMaster Taq Buffer,0.5 μ L (10 μ M)上游引物,0.5 μ L (10 μ M)下游引物,1 μ L dNTP混合物(各2.5 μ M),1 μ L SYBR Green I (5 \times),0.2 μ L HotMaster Taq DNA polymerase (2.5U/ μ L),最后加入17.3 μ L去离子水,反应总体积为25 μ L。混匀后短暂离心,置于Eppendorf PCR仪中进行PCR扩增反应,反应参数为95 $^{\circ}$ C预变性2分钟,95 $^{\circ}$ C变性15秒,58 $^{\circ}$ C退火15秒,72 $^{\circ}$ C延伸30秒;循环次数为40个循环。每个反应设置3个重复。

[0065] 4) 数据分析:对同一样本,分别检测其中目标基因及内参基因(β -actin)的表达。以内参基因的表达量为基准,对目标基因的表达进行归一化处理。随后使用本领域通常使用的delta delta Ct法对目标基因的表达量进行定量分析。具体方法和步骤可以参见文献:Livak KJ and Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001Dec;25(4):402-408。

[0066] 表1、RT-PCR引物对

[0067]	β -actin	Forward primer: 5'-GAAGAGCTATGAGCTGCCTGA
		Reverse primer: 5'-CTCATCGTACTCCTGCTTGCT
[0067]	PPAR γ	Forward primer: 5'-AAGAGCTGACCCAATGGTTG
		Reverse primer: 5'-ACCCTTGCATCCTTCACAAG
[0067]	CEBP α	Forward primer: 5'-GCTTTTTGCACCTCCACCTA
		Reverse primer: 5'-CTCTGGGATGGATCGATTGT

[0068] 实施例三:敲低slincRAD对脂肪细胞体外诱导分化的抑制作用

[0069] 为了研究slincRAD基因的表达对脂肪细胞分化的影响,我们通过筛选,获得了6条

slincRAD基因特异的siRNAs,包括siRNA1、siRNA9、siRNA12、siRNA14、siRNA15和siRNA17(表2)。利用细胞转染试剂,我们将这些siRNA分别导入培养的3T3-L1细胞,敲低其中slincRAD基因的表达水平;随后利用油红O染色,鉴定细胞脂肪的生成是否受到影响,从而判断3T3-L1的脂肪细胞分化进程是否受到影响。我们发现,与未经siRNA处理的对照细胞和经scramble siRNA处理的对照细胞相比,某些基因特异的siRNA能显著抑制细胞脂质的生成和积累(图2);尤其是siRNA-17,利用该siRNA处理细胞能将细胞的脂质含量降低70%。除了研究细胞脂质生成以外,我们还利用实时荧光定量PCR,研究了敲低slincRAD对脂肪细胞分化关键因子PPAR γ 表达的影响。研究结果显示:利用siRNA(如siRNA-14)敲低slincRAD基因的表达,不仅影响了细胞脂质的生成,还能显著抑制细胞中PPAR γ 基因的表达(图2),这与其对细胞分化的抑制作用是一致的。实验步骤具体如下:

[0070] 1、3T3-L1细胞培养:在含有10%胎牛血清的DMEM液体培养基中,常规培养3T3-L1小鼠前脂肪细胞,2至3天换液1次。

[0071] 2、siRNA转染:利用BLOCK-iTTM RNAi Designer (Invitrogen) 程序,设计slincRAD基因特异的siRNA分子,具体序列如表2所示。

[0072] 转染前一天,将3T3-L1细胞接种于6孔培养板中,使细胞贴壁后的融合度达到60-70%。按照操作手册的要求,使用Invitrogen公司的LipofectamineTM RNAiMAX转染试剂进行细胞转染实验。对于6孔培养板的每个孔,将100pmol siRNA在400 μ L Opti-MEM (GIBCO) 细胞培养液中制备RNAiMAX/siRNA混合物,室温静置20分钟后,将RNAiMAX/siRNA混合物加入到6孔板中;转染4个小时后,加入正常细胞培养基进行培养。

[0073] 继续培养2天后,待细胞长至融合状态,加入含有分化诱导剂的DMEM培养基,开始诱导分化过程。并在当天进行第二次siRNA转染,将RNAiMAX/siRNA混合物直接加入到诱导分化培养基中,进行siRNA转染。

[0074] 3、体外诱导分化:3T3-L1体外诱导分化时间节点的定义:以加入诱导分化培养基,开始进行诱导分化的当天为诱导分化的第1天。诱导分化第1天的前一天为第0天。诱导分化第1天的后一天为第2天,并依此类推定义其他诱导分化时间节点。

[0075] 在含有10%胎牛血清的DMEM液体培养基中,常规培养3T3-L1小鼠前脂肪细胞,2至3天换液1次。在诱导分化的第1天,将常规培养基换成分化诱导培养基,进行体外诱导分化。诱导培养基是在常规培养基的基础上加入167nM人胰岛素(Sigma)、0.5mmol/L 1-甲基-3-异丁基黄嘌呤(Sigma)和1 μ M地塞米松(Sigma)。在诱导分化的第2天,将培养基换成仅含有167nM胰岛素的DMEM培养基。在诱导分化的第4天,将分化培养基换回到常规DMEM培养基,继续培养,直至分化过程结束。

[0076] 4、油红O染色:在脂肪细胞体外诱导分化的第9天,获得细胞样本,进行油红O染色分析。实验步骤具体见实施例二。实验结果见图2。

[0077] 表2、siRNA序列

siRNA	序列
siRNA1	正义链 (SEQ ID No 1) : 5'-CAACUAGGCUUCACAAAUAtt-3'
	反义链 (SEQ ID No 2) : 5'-UAUUUGUGAAGCCUAGUUGtt-3'
siRNA9	正义链 (SEQ ID No 3) : 5'-GCGUGGAUGUGGAGAAAGAtt-3'
	反义链 (SEQ ID No 4) : 5'-UCUUUCUCCACAUCCACGctt-3'
siRNA12	正义链 (SEQ ID No 5) : 5'-CCUAGCAGAAACUAAACUUt-3'
	反义链 (SEQ ID No 6) : 5'-AAGUUUAGUUUCUGCUAGGtt-3'
siRNA14	正义链 (SEQ ID No 7) : 5'-GGAAGAGGAUGACUAGGAAtt-3'
	反义链 (SEQ ID No 8) : 5'-UUCCUAGUCAUCCUCUUCctt-3'
siRNA15	正义链 (SEQ ID No 9) : 5'-GGAUUAGUGUGGCAGAUUAtt-3'
	反义链 (SEQ ID No 10) : 5'-UAAUCUGCCACACUAAUCCtt-3'
siRNA17	正义链 (SEQ ID No 11) : 5'-CCACUACCCGCCAUGAUUUtt-3'
	反义链 (SEQ ID No 12) : 5'-AAUCAUGGCGGGUAGUGGtt-3'

[0078] [0079] 实施例四:构建slincRAD shRNA转基因小鼠

[0080] 为了鉴定slincRAD基因的在体功能,需要在敲低小鼠体内slincRAD基因表达的情况下,研究其对脂肪细胞分化、细胞脂质生成、以及关键分化因子表达的影响。为此,我们利用靶向slincRAD的特异性shRNA,构建了slincRAD shRNA转基因小鼠。具体如下:

[0081] slincRAD特异性shRNA (slincRAD-shRNA) 的筛选。1) 设计slincRAD特异性shRNA。利用在线设计工具,我们针对slincRAD基因的序列,设计了不同的shRNA表达序列,通过筛选得到4条特异性的shRNA的表达序列 (shRNA-8、shRNA-9、shRNA-15、shRNA-17; 图3A; 序列见表3)。2) shRNA表达载体的构建。利用购置于Invitrogen公司的pSD31逆转录病毒载体,构建slincRAD特异性的shRNA表达载体。按照试剂盒说明书所描述的方案,我们首先合成双链的shRNA表达框,将其亚克隆到线性化的pSD31逆转录病毒载体中,通过测序鉴定,获得针对

slincRAD基因的shRNA表达载体。3) 细胞转染和体外诱导分化。利用Lipofectamine 2000细胞转染试剂,将shRNA表达载体导入培养的3T3-L1细胞。利用实施例一描述的体外诱导分化方案,对导入shRNA的细胞进行诱导分化。4) 活性shRNA的鉴定。在诱导分化的第6天,收获细胞。按照实施例一描述的方法,利用实时荧光定量PCR,检测slincRAD基因的表达水平,检测slincRAD基因表达的引物序列见表4。发现slincRAD-shRNA8和slincRAD-shRNA9能高效抑制细胞内源性slincRAD的表达。其中,slincRAD-shRNA8能将靶基因的表达水平降低至野生型细胞水平的1%,而slincRAD-shRNA9则能将靶基因的表达降低至野生型细胞水平的3%(图3B)。油红O染色发现,slincRAD-shRNA8和slincRAD-shRNA9在抑制目标基因的同时,还显著抑制了细胞脂质的生成(图3C)。

[0082] 表3、shRNA序列

[0083] shRNA8 (SEQ ID No 21) :

[0084] 5' GTGGAAAGGACGAAACACCCGGCCTATAACCAGTACAGTTAATCAAGAGTAACTGTACTGGTTATAGGCTTTTTTGGATCCCGAAT 3'

[0085] shRNA 9 (SEQ ID No 22) :

[0086] 5' GTGGAAAGGACGAAACACCCGGCACCAACCTCTTCCAATATCTCAAGAGGATATTGGAAGAGGTTGTGCTTTTTTGGATCCCGAAT 3'

[0087] shRNA 15 (SEQ ID No 23) :

[0088] 5' GTGGAAAGGACGAAACACCCGGGATTAGTGTGGCAGATTATCAAGAGTAATCTGCCACACTAATCCTTTTTGGATCCCGAAT 3'

[0089] shRNA 17 (SEQ ID No 24) :

[0090] 5' GTGGAAAGGACGAAACACCCGGGATTAGTGTGGCAGATTATCAAGAGTAATCTGCCACACTAATCCTTTTTGGATCCCGAAT 3'

[0091] 表4、slincRAD扩增引物序列

[0092] 01检测引物组合:

[0093] 01正向引物: 5' -ATCCATCTCCCCTACCCATC (SEQ ID NO:200)

[0094] 01反向引物: 5' -TGCAGAGGACTCACAACCTGG (SEQ ID NO:201)

[0095] 08检测引物组合:

[0096] 08正向引物: 5' -GGTGCAGTTTTGCACTGAGA (SEQ ID NO:202)

[0097] 08反向引物: 5' -GATGGAGAGAAAGGAAGGGG (SEQ ID NO:203)

[0098] 16检测引物组合:

[0099] 16正向引物: 5' -CCTAGTGCCTTTCTGCCTTG (SEQ ID NO:204)

[0100] 16反向引物: 5' -TGGGGTGATTGTGTAGGGAT (SEQ ID NO:205)

[0101] 31检测引物组合:

[0102] 31正向引物: 5' -CAAGTGGTTCCGGATTCTGT (SEQ ID NO:206)

[0103] 31反向引物: 5' -CCGTGAAATGAAGTGGTGTG (SEQ ID NO:207)

[0104] 54检测引物组合:

[0105] 54正向引物: 5' -GCATTTAATTGGTGTCTGGCT (SEQ ID NO:208)

[0106] 54反向引物: 5' -GACCCTTCTCCTAGCTGCCT (SEQ ID NO:209)

[0107] 构建转基因小鼠:获得分别编码slincRAD-shRNA8和slincRAD-shRNA9表达框的

DNA片段,该DNA片段长度为285个碱基,包含U6启动子、shRNA编码序列、以及一段6核苷酸的终止序列TTTTTT。利用显微注射将DNA片段导入C57BL/6小鼠受精卵的原核中,然后将受精卵移植到假孕的母鼠体内,使其发育成小鼠(图4A)。为了鉴定转基因小鼠,我们设计了两对独立的、能扩增shRNA表达框的引物对(表5)。通过扩增小鼠基因组中整合的shRNA表达框,我们分别鉴定了4只整合了slincRAD-shRNA8和slincRAD-shRNA9的雄性转基因小鼠——首代转基因小鼠(图4B,5A)。

[0108] 表5. shRNA表达框扩增引物对

引物名称	序列
shR-insert-F1	5'-ggcctatttcccatgattcct
[0109] shR-insert-R1	5'-gggtgtttcgtcctttccac
shR-insert-F2	5'-gagagggcctatttcccatgat
shR-insert-R2	5'-gggtgtttcgtcctttccaca

[0110] 转基因小鼠的建系:将转基因小鼠与野生型雌鼠进行交配,获得子代小鼠。提取子代小鼠尾部组织的基因组DNA,利用特异性引物对(表5),对其中整合的shRNA表达框进行PCR扩增,扩增信号阳性的即为整合了shRNA表达框的子代小鼠。这样共获得四个slincRAD-shRNA转基因小鼠系(图5A)。三个小鼠系的基因型为slincRAD-shRNA8+/-,因而被命名为slincRAD^{shRNA8}小鼠,一个小鼠系的基因型为slincRAD-shRNA9+/-,因而被命名为slincRAD^{shRNA9}。

[0111] 为了检测shRNA抑制目标基因表达的情况,我们在小鼠出生后的第10天、15天和30天,处死小鼠,获得小鼠组织,利用qRT-PCR,检测slincRAD在脏器中的表达水平(图5B)。我们发现,与对照组野生型小鼠相比,除了第十天的脑组织外,slincRAD在其他脏器中的表达量均出现显著降低,平均降低到野生型组织表达水平的60%及以下。

[0112] 为了得到足够量的转基因小鼠,用于后续研究,我们采用自然交配和人工授精的方法,进行转基因小鼠繁育。在人工授精繁育中,我们首先取出一只slincRAD^{shRNA8}小鼠的一侧精囊,分离已经成熟的精子,将其转入野生型假孕母鼠体内。这样,我们总共获得了143F₁代小鼠,其中81为slincRAD^{shRNA8}阳性小鼠,62只为野生型小鼠(图5C)。所获得子代小鼠中阳性小鼠和野生型小鼠的比例基本为1:1,符合孟德尔分离规律。这表明,敲低slincRAD的表达水平,对小鼠的生存能力并未产生严重的影响。为方便起见,slincRAD^{shRNA8}转基因小鼠也被称为slincRAD敲低小鼠、或KD小鼠。

[0113] 实施例五:敲低slincRAD表达对小鼠发育的影响

[0114] 为了研究敲低slincRAD对小鼠发育的影响,我们对野生型和转基因小鼠的身体发育状况进行了对比研究,时间段为胚胎期第15天至出生后7个月。在胚胎发育期,转基因小鼠与野生型小鼠在slincRAD表达水平上没有明显差异,在个体形态和出生体重上非常相似。出生以后,转基因小鼠的体重开始变得明显低于野生型小鼠,尽管保持了相同的饲养条件(图6A)。出生后5天,与野生型对照小鼠(n=9)相比,转基因小鼠(n=11)的体重要低~12%(p<0.05)。这种差异性一直保持到小鼠的成年期(图6B)。在形态上,转基因小鼠没有野生型小鼠的腹部隆起(图6C),这种现象可能是源于小鼠腹部脂肪的正常发育受到了影响。

[0115] 本实施例数据表明,敲低小鼠slincRAD基因的表达,未对小鼠胚胎期发育产生影响,但显著影响了转基因小鼠的出生后发育过程。尽管与对照小鼠相比,slincRAD基因的表达水平在胚胎期和出生后期均呈现显著降低。

[0116] 实施例六:敲低slincRAD基因表达对小鼠脂肪组织发育的影响

[0117] 在上述工作的基础上,我们推测slincRAD对小鼠发育的影响,可能是源于其干扰了脂肪组织的正常分化。为了验证这一设想,我们利用小动物核磁成像设备Nuclear magnetic resonance spectroscopy (EchoMR-700, MchoMRI, Houston TX),在清醒状态下,对小鼠的体脂、肌肉、以及水分含量进行了检测。具体操作按照设备生产厂家提供的方案进行,扫描间隔为0.5-3.2分钟。每只动物进行3次独立的测量。

[0118] 对1月龄小鼠的研究发现,转基因小鼠的体脂含量比野生型小鼠低12%,肌肉含量比野生型小鼠高9%。对7月龄小鼠的研究发现,转基因小鼠的体脂含量比野生型小鼠低22%,肌肉含量比野生型低6% (图7A)。进一步的,我们对小鼠主要脏器的重量进行了对比研究,发现无显著差异 (图7B)。

[0119] 为了分析敲低slincRAD对小鼠脂肪及其他组织发育的影响,我们制备了7月龄小鼠主要脏器的组织切片。首先获得转基因小鼠和野生型小鼠的脏器组织,将其浸润在4%的多聚甲醛溶液中,4℃条件下固定过夜;石蜡包埋,以5μm宽度连续切片;随后进行苏木精-伊红染色和显微镜观察。我们发现与野生型小鼠的正常组织相比,转基因小鼠的脂肪组织中出现着色较深的小岛状区域 (图7C)。高倍显微镜观察发现,这些区域由较小的脂肪细胞组成。在7月龄的转基因小鼠中,脂肪细胞的平均尺寸为 $19.5 \pm 4.8 \mu\text{m}$,而在野生型对照小鼠中,脂肪细胞的尺寸则为 $58 \pm 10 \mu\text{m}$ 。在9月龄转基因小鼠中,脂肪细胞的平均尺寸为 $21.4 \pm 4.6 \mu\text{m}$,在野生型小鼠中,脂肪细胞的尺寸为 $74.7 \pm 14 \mu\text{m}$ (图7D)。除脂肪组织外,其他脏器的组织结构均未见明显改变 (图7D)。

[0120] 实施例七:slincRAD的作用机制研究

[0121] 为了阐明slincRAD的作用机制,我们研究了其对PPAR γ 和CD36这两个脂肪细胞分化关键转录因子的调控作用。PPAR- γ 是一种细胞核受体,调节脂肪酸代谢的几乎所有方面,例如脂肪酸的运输、合成、储存、动员、活化和氧化。CD36是一种B类清道夫受体,能促进脂肪细胞分化和脂肪形成的。

[0122] 利用qRT-PCR,我们在小鼠出生后的第10天、15天和30天,分别检测了肝脏中PPAR γ 、CD36和slincRAD基因的表达水平 (图8)。在小鼠出生的第10天,转基因小鼠肝脏中PPAR γ 、CD36和slincRAD的表达水平比野生型小鼠降低了50%。但随着发育过程的继续,PPAR γ 和CD36的表达水平在第15恢复到野生型小鼠的水平,在第30天上升到高于野生型小鼠的水平,表现出一定的剂量补偿效应。这些数据一方面提示slincRAD是通过PPAR γ 信号通路发挥作用的,另一方面也解释了为什么slincRAD对小鼠发育的调节作用主要表现在胚胎发育的早期阶段。

[0123] 实施例八:敲低slincRAD对小鼠血糖、血脂代谢的影响

[0124] 白色脂肪组织是机体能量代谢中的一个重要环节,人体白色脂肪组织的过度累积会导致机体代谢异常。为了探讨slincRAD在能量代谢方面的作用,我们以9月龄野生型和转基因小鼠为研究对象,研究敲低slincRAD基因表达对小鼠血糖、血脂代谢的影响。

[0125] 血糖含量检测:从小鼠尾静脉采血,用罗氏公司的血糖检测仪ACCU-CHEK

Performa Glucometer (Roche, Denmark) 检测小鼠血糖含量,具体操作按血糖检测仪说明书进行。血脂含量检测:将小鼠禁食6小时,尾静脉采血,分离其中的血浆成分,用罗氏公司的分析仪(Cobas 4000 analyzer),检测其中甘油三酯、总胆固醇、LDL-C、HDL-C3的含量水平。

[0126] 如图9A所示,与野生型对照小鼠相比,转基因小鼠的血浆甘油三酯含量显著降低,HDL-c含量显著升高。血浆总胆固醇(TC)和LDL-c呈现上升趋势,但无显著性差异。

[0127] 此外,我们还进行了葡萄糖和胰岛素耐受性实验。开始实验前,连续三天测定实验小鼠的血糖基线水平。实验前将小鼠禁食过夜(大约16小时),随后按1.5g/kg体重的剂量向小鼠腹腔内注射D-葡萄糖,在注射后的第0、15、30、60、120和180分钟,进行尾静脉采血,用罗氏公司的血糖检测仪检测小鼠血糖含量,分析小鼠血糖含量的变化,绘制糖耐量曲线(图9B)。

[0128] 胰岛素耐受性实验前,将小鼠禁食6小时,随后按1IU/kg体重的剂量,腹腔内注射人胰岛素、在注射后的0、15、30、60和120分钟,进行尾静脉采血,监测小鼠血糖含量的变化,绘制胰岛素耐受性曲线(图9C)。

[0129] 分析发现,与野生型对照小鼠相比,转基因小鼠的禁食血糖水平显著降低(图9A)。在糖耐量实验中,转基因小鼠表现出的葡萄糖耐受性要显著好于野生型小鼠(图9B),如GTT曲线所示。但在胰岛素耐受性方面,转基因小鼠和野生型小鼠之间没有明显差异(图9C)。

[0130] 实施例九:敲低slincRAD对3T3-L1细胞分化的影响

[0131] 为了分析slincRAD在脂肪细胞分化中的作用,我们利用实施例四中建立的psd31逆转录病毒载体和常规嘌呤霉素筛选,构建了稳定转染slincRAD-shRNA8和slincRAD-shRNA9的细胞株,分别命名为slincRAD^{shRNA-8}、slincRAD^{shRNA-9}细胞株。此外,我们还将一个靶向绿色荧光蛋白、且与slincRAD序列无关的shRNA转入3T3-L1细胞,构建了一个用作阴性对照的稳转细胞株,命名为shGFP 3T3-L1细胞株。

[0132] 参照逆转录病毒载体的用户手册和常规技术方法,我们首先生成含有shRNA表达框的逆转录病毒,将收获的病毒感染细胞,对感染细胞进行嘌呤霉素筛选,建立shRNA稳定转染细胞株。实验步骤大致如下:在T25培养瓶中培养293T细胞,使细胞生长至几乎完全融合(sub-confluent)状态;利用Lipofectamine 2000转染试剂,将3.25 μ g shRNA慢病毒质粒、2.88 μ g pRSV质粒、1.44 μ g PRRE质粒和1.44 μ g pMD2G-VSVG质粒,共转培养细胞。转染6小时后更换培养基,72小时后收获病毒颗粒,并通过0.45 μ m过滤器过滤。随后,在含有8mg/mL polybrene的培养基中,将获得的病毒颗粒加入到6孔板中培养的3T3-L1细胞,使其感染细胞。利用含有4mg/mL嘌呤霉素的培养基进行筛选,筛选获得稳定转染shRNA的细胞株。

[0133] 利用实施例二建立的检测方法,对slincRAD^{shRNA-8}、slincRAD^{shRNA-9}以及野生型3T3-L1细胞进行了诱导分化。我们将加入诱导剂的当天命名为day (0)天,前一天命名为day (-1)天,后一天被命名为day (+1)天,并以此类推。

[0134] 在诱导分化的第4天day (+4),收获细胞,检测其中slincRAD基因的表达水平。以野生型细胞为参照,我们发现slincRAD^{shRNA-8}和slincRAD^{shRNA-9}细胞中slincRAD基因的表达水平降低到野生型的32%和55%。

[0135] 进一步的,我们利用Perkin Elmer公司的高内涵分析仪(Columbus Image Data Storage and Analysis System),对细胞的脂质含量进行了分析。所使用的脂质分析试剂盒为Life Technologies公司的Bodipy 493/503试剂盒,具体操作参考试剂盒和高内涵分

析仪的用户手册。实验方案大体如下：将处于不同分化阶段的3T3-L1细胞用4%多聚甲醛固定15分钟，室温下用0.5%Triton X-100打孔15分钟。PBS洗涤后，用1:1000的Bodipy 493/503溶液和1:10000的Hoechst 350/461缓冲液染色45分钟。

[0136] 使用Columbus Image Data Storage and Analysis System高内涵分析仪，在20倍物镜下进行细胞的观察和记录。用Hoechst 33342和Alexa 488通道检测Hoechst (核) 和Bodipy 493 (脂质) 的荧光强度，利用明场图像记录细胞的数量。用高内涵分析仪附带的软件系统，分析获得的荧光图像。

[0137] 我们发现，在slincRAD^{shRNA-8}和slincRAD^{shRNA-9}细胞中，细胞脂质的含量减少到野生型细胞脂质含量的27%和30%。

[0138] 实施例十：敲低slincRAD对细胞基因表达的影响

[0139] 为了阐明slincRAD的作用机制，我们对比研究了野生型和shRNA稳转细胞株 (slincRAD敲低细胞株) 的基因表达。在分化启动后的6天时间里，我们对脂肪细胞分化相关的细胞因子的表达变化进行了逐日分析，包括C/EBP α 、PPAR γ 、pre-adipocyte factor-1 (pref1)、CD36和Fabp4。C/EBP和PPAR γ 是脂肪细胞分化中最关键的转录因子，其他基因则在脂肪酸转运过程中发挥作用。

[0140] 3T3-L1脂肪细胞诱导分化过程中，在出现接触抑制后的day (-2) 天，slincRAD基因的表达水平即开始上调 (图10, 位于上方的一条线)。在随后的整个“接触抑制期”，slincRAD基因的表达水平持续上调，其表达峰值出现在day (0) 天，即加入分化诱导剂的当天。诱导分化开始后，slincRAD的表达水平逐步下降。与此形成鲜明对比的是，C/EBP α 和PPAR γ 的表达上调出现在诱导分化后的第day (+1) 天和day (+2) 天，随后pref1、CD36、Fabp4的表达水平才开始次第上调。

[0141] 以上数据表明，slincRAD基因的表达上调要显著早于其他细胞因子，提示该基因可能在分化的起始阶段发挥作用。

[0142] 除了野生型细胞以外，我们也研究了slincRAD低表达细胞株中基因的表达调控。发现敲低slincRAD基因的表达水平，能显著抑制脂肪分化相关因子的表达 (图10, 位于下方的一条线)，这与野生型细胞中活跃的表达调控形态形成了鲜明的对比。C/EBP α 和PPAR γ 的表达水平只有野生型细胞的1/4-1/2，pref1、Fabp4和CD36的表达也被显著抑制或迟滞。这些结果表明，敲低slincRAD影响了脂肪细胞分化、以及细胞脂质生成关键因子的表达，并最终导致细胞脂质合成的减少。

[0143] 实施例十一：敲低slincRAD对细胞周期的影响

[0144] 对细胞周期的调节是细胞分化调控的一个重要方面。为了研究敲低slincRAD对细胞周期的影响，我们对比研究了野生型3T3-L1细胞、slincRAD^{shRNA-8}和slincRAD^{shRNA-9}细胞的分化过程，重点关注细胞周期行为的改变。在诱导分化过程中，我们选择了三个时间节点，分别代表增殖期细胞day (-2)、生长抑制期细胞day (0)、和终末分化期细胞day (+2)。

[0145] 细胞周期检测系统：BD Immunocytometry Systems公司的流式细胞仪FACS Calibur system (San Jose, CA)；分析软件：Verity Software House公司的MODFIT软件包 (Topsham, ME)；使用相同的仪器设置完成所有的检测。上机分析前，将细胞悬浮于35mm培养皿中，70%乙醇4℃固定过夜；冰浴条件下，用propidium iodide染色 (BD Biosciences, San Jose, CA) 染色30分钟；随后上机分析，每个样品中至少计数10,000个细胞。

[0146] 在细胞增殖和分化阶段,野生型和slincRAD敲低细胞的细胞周期行为并无明显差异;两者之间的差异主要出现在生长抑制阶段。在细胞生长抑制阶段,31.8%的野生型细胞处于S-phase,而处于S-phases的slincRAD^{shRNA-8}细胞的数量则增加到42.1%,在slincRAD^{shRNA-9}细胞中S-phases细胞的数量进一步增加到51.1%。相应的,处于G2-phase的野生型细胞的比例为28%,在slincRAD^{shRNA-8}中这一比例下降到18%,而在slincRAD^{shRNA-9}中则仅为10%(图11)。这些数据表明,敲低slincRAD影响了细胞周期行为。此外我们还发现,在slincRAD基因的抑制水平和对细胞周期的影响效果之间,存在明显的剂量-效应关系。

[0147] 实施例十二:敲低slincRAD对细胞分化表观调控作用的影响

[0148] 作为长非编码RNA效应机制的一个重要方面,人们对脂肪细胞分化过程中的表观调控进行了较为系统的研究,发现甲基化酶DNMT1在其中发挥了重要的作用。

[0149] 在这些以及我们的工作基础上,我们推测DNMT1可能也参与了slincRAD作用的信号通路。为了验证这一假说,我们首先在脂肪细胞体外诱导分化过程中,研究了Dnmt1基因的表达变化。发现在诱导分化起始阶段的day(-1)和day(0)天,Dnmt1基因的表达水平较前期降低;在day(+1)天加入分化诱导剂后,该基因的表达水平突然上调至较高水平(图12)。这些结果表明与slincRAD基因类似,Dnmt1基因的表达水平在诱导分化早期是受到严格调控的。这种共调控关系提示我们,这两个基因在功能上可能也是相互联系的。

[0150] 为了研究slincRAD基因转录本与DNMT1之间可能存在相互作用,我们进行了RNA免疫共沉淀实验。研究方案基本参照Keene等人的论文(Keene JD, Komisarow JM, Friedersdorf MB. RIP-Chip: the isolation and identification of mRNAs, microRNAs and protein components of ribonucleoprotein complexes from cell extracts. Nat Protoc. 2006; 1(1): 302-7)。在诱导分化的day(+1)天,将 1×10^8 个3T3-L1细胞用1%甲醛进行交联。用含有1mM PMSF的磷酸盐缓冲盐(PBS)溶液洗涤细胞,加入裂解缓冲液,进行超声破碎,使细胞裂解并释放细胞核。为了去除非特异性结合,向每个样品中加入50 μ L蛋白G Dynabeads (Life Technologies),在4 $^{\circ}$ C条件下孵育1个小时。在除去Dynabeads以及与其结合的蛋白后,将剩余的裂解物与5 μ g抗DNMT1抗体(Abcam, 中国)进行孵育,4 $^{\circ}$ C条件下温育过夜。加入100 μ L蛋白G包被的磁珠,并与抗体-细胞裂解物在4 $^{\circ}$ C下温育3小时。彻底洗涤后,利用蛋白酶K降解蛋白质,使RNA组分释放到溶液中。沉淀RNA组分,用DNase I (NEB)酶处理降解其中的基因组DNA,将最终获得的RNA组分重悬浮于50 μ L无RNA酶的去离子水中。该实验的阴性对照为与抗IgG抗体(Santa Cruz)孵育的样本、和无抗体处理的样本。

[0151] 将150ng的RNA免疫共沉淀产物进行逆转录、qRT-PCR扩增,分析其中slincRAD基因转录本的含量。用于PCR扩增的引物对序列如下:

[0152] slincRAD-A forward: 5'-TCTGAATTGCCCATCTCTCC-3';

[0153] slincRAD-A reverse: 5'-CGTGCCTATGTTCCAATATCC-3';

[0154] slincRAD-B forward: 5'-GCCACAGCACTAGGGAAGAC-3';

[0155] slincRAD-B reverse: 5'-ACAGTCATGCGTGAAAGCAG-3';

[0156] slincRAD-C forward: 5'-TACCATGTGGTCCCATTTT-3';

[0157] slincRAD-C reverse: 5'-TGTGCCAAGTCTTCAGGTTG-3'.

[0158] 在3T3-L1脂肪细胞分化的Day(0)天,我们利用抗DNMT1抗体和RNA免疫共沉淀技术,捕获与DNMT1蛋白以及与其发生相互作用的RNA组分。利用qRT-PCR,我们发现与阴性对

对照组相比,slincRAD基因转录本在抗DNMT1抗体复合物中得到大量富集,说明slincRAD基因转录本与DNMT1蛋白之间具有物理性的相互作用(图13)。

[0159] slincRAD与DNMT1之间的物理相互作用提示我们,slincRAD基因转录本参与了脂肪细胞分化的表观调控过程。为了鉴定受slincRAD调控的下游信号分子,我们委托上海康成生物工程有限公司,利用基因启动子甲基化芯片(NimbleGen meCHIP,Arraystar Mouse RefSeq Promoter Microarray),对比研究了野生型和slincRAD敲低3T3-L1细胞中基因的启动子甲基化水平,以期发现slincRAD基因对下游因子启动子甲基化的影响。

[0160] 实验步骤大致如下:在诱导分化的day(-2)和day(+2)天,收获细胞,用DNeasy Blood&Tissue Kit(Qiagen,CA)提取细胞基因组DNA。取1 μ g基因组DNA,进行超声处理,用抗小鼠5-methylcytosine单克隆抗体(Diagenode)进行免疫共沉淀,获得含有5-methylcytosine的基因组片段。经标记和纯化后,与Arraystar Mouse RefSeq Promoter Microarray进行杂交,用Agilent Scanner G2505C扫描仪扫描杂交芯片,获得芯片杂交的结果。利用NimbleScan v2.5(Roche-NimbleGen)提供的算法分析芯片数据,采用paired t-test计算p值,将甲基化程度上调或下调的阈值设为倍数变化 ≥ 2.0 和p值 ≤ 0.05 。

[0161] 3T3-L1脂肪细胞体外诱导分化过程中,细胞在day(-2)天处于增殖状态,在day(+2)天则进入分化状态。因此,在这两个时间点分别收集细胞,对比分析基因的表达水平和启动子的甲基化水平,即可了解分化过程中基因表达的表观调控。我们首先对野生型细胞进行了分析,发现与增殖期细胞相比,分化期野生型细胞中的7509基因组位点的甲基化水平发生了改变,这些位点对应于2334个小鼠基因(peak score >2 ;p <0.05)。其中,582个基因启动子的甲基化水平在分化细胞中上调,584个基因启动子的甲基化水平在分化细胞中下调。进一步分析slincRAD敲低细胞时发现,与增殖期细胞相比,分化期细胞中941个基因的甲基化水平上调,469个基因的甲基化水平下调。

[0162] 为了形象地展示基因启动子的甲基化状态,我们对这些数据进行了维恩图(Venn diagram analyses)分析。在野生型和slincRAD敲低细胞中,我们发现增殖相关基因的表达受到了普遍的抑制,而分化相关的基因则普遍被诱导表达。与野生型细胞相比,slincRAD敲低细胞中被抑制的增殖相关基因的数量较少,而被诱导的分化相关基因的数量也少于野生型细胞(图14)。其中,9个增殖相关基因在野生型细胞中被特异性甲基化,而另外4个增殖相关基因在slincRAD敲低细胞中被特异性甲基化。对于分化相关基因而言,情况正好相反:20个分化相关基因在野生型细胞中被特异性甲基化,94个分化相关基因在slincRAD敲低细胞中被特异性甲基化。为了进一步分析每个甲基化位点的状态,我们对发生差异调节的基因进行differential enrichment peak(DEP Promoter)分析,在野生型细胞中发现550个DEP位点,在slincRAD敲低细胞中发现913个DEP位点,其中共有的DEP位点仅为49个。

[0163] 随后,我们进行了Gene ontology(GO)分析。GO分析将发生差异调节的基因分为18个组,包括蛋白质代谢组、脂质代谢组、增殖相关组等(图15)。考虑到敲低slincRAD对细胞周期的影响,我们参照以下标准,对增殖相关基因做了进一步分类。1)在野生型细胞分化中,基因启动子的甲基化水平呈现上升趋势;2)在slincRAD敲低细胞分化中,启动子甲基化水平上升的幅度较野生型细胞减小;3)基因启动子上有DNMT1结合位点。用前两个标准进行筛选,获得12个基因,其中包括细胞周期调节基因CDKN1A(p21)。已报道的研究工作表明,

CDKN1A基因与脂肪细胞的分化过程密切相关。分析野生型细胞数据时发现,与增殖期细胞相比,分化期细胞中p21基因启动子的甲基化水平提高了2.64倍(图16)。但这种情况在slincRAD敲低细胞中并未出现(图17)。此外,我们在p21基因的启动子区域鉴定了多个DNMT1结合位点,提示该基因可能也参与了slincRAD/DNMT1的表观调控通路。

[0164] 进一步的,利用western杂交,我们检测了p21蛋白、cyclin-A、cyclin-B和cyclin-dependent kinase 1 (CDK1、cdc2)的表达变化。按照常规的实验方案进行western杂交。具体的,在脂肪细胞体外诱导分化的day (-2) 至day (+4) 天,逐日收获细胞,裂解细胞,获得细胞总蛋白。在加入蛋白酶抑制剂(cocktail protease inhibitor,Roche)的情况下,用RIPA缓冲液(1%NP-40,0.5%脱氧胆酸盐,0.1%SDS,150 mM NaCl和50mM Tris[pH 8])处理细胞总蛋白。经超声处理后,用Pierce公司的bicinchoninic acid assays,测定蛋白样本浓度。然后将蛋白样品上样,进行SDS-PAGE电泳分离。杂交使用GE Healthcare公司的polyvinylidene difluoride膜,使用的一抗有Abcam公司的抗DNMT1抗体、Transgene公司的抗 β -actin抗体、以及上海CST (Univ-bio) 公司的抗p21抗体、抗cyclin-A抗体、抗cyclin-B1抗体和抗磷酸化cdc2抗体。二抗为CST公司的辣根过氧化物酶(HRP)缀合抗体、兔HRP抗体和小鼠HRP抗体。用BIORAD ChemiDoc XRS系统进行杂交印迹成像。

[0165] 我们发现与野生型细胞相比,slincRAD敲低细胞中的cyclin-A、cyclin-B蛋白的表达水平并未发生显著变化,而p21和磷酸化cdc2蛋白的水平则存在显著差异。在分化的day (0) 天,slincRAD敲低细胞中p21蛋白和磷酸化cdc2蛋白的表达量显著升高(图18)。

[0166] 实施例十三:slincRAD作用机制假说

[0167] 综合以上研究结果,我们提出长非编码RNA slincRAD通过slincRAD/DNMT1表观调控通路,调节脂肪细胞分化的作用机制,具体见图19。在细胞分化的早期阶段,slincRAD基因转录本通过与DNMT1蛋白因子之间的相互作用,改变下游因子(如p21)启动子的甲基化状态,调节它们的表达水平。对p21而言,下调该基因表达可进一步下调cdc2蛋白的磷酸化水平,从而激活cyclin-A/cdc2和cyclin-B/cdc2蛋白复合物,使细胞从活跃的增殖状态转变为“生长抑制”(growth arrest)状态。

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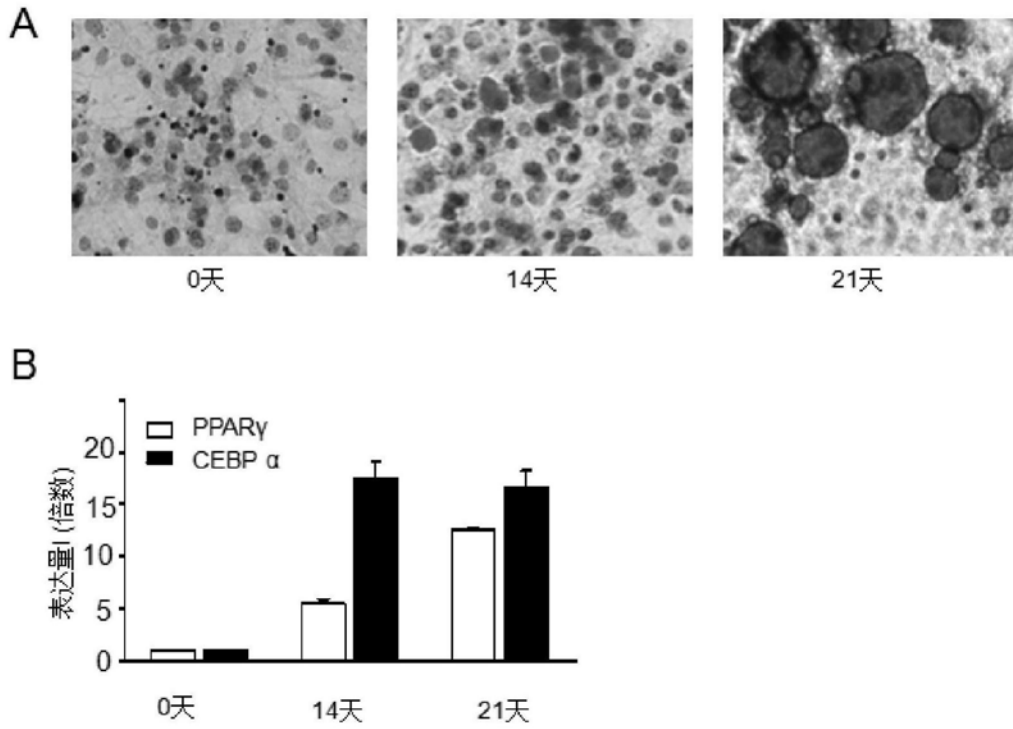


图1

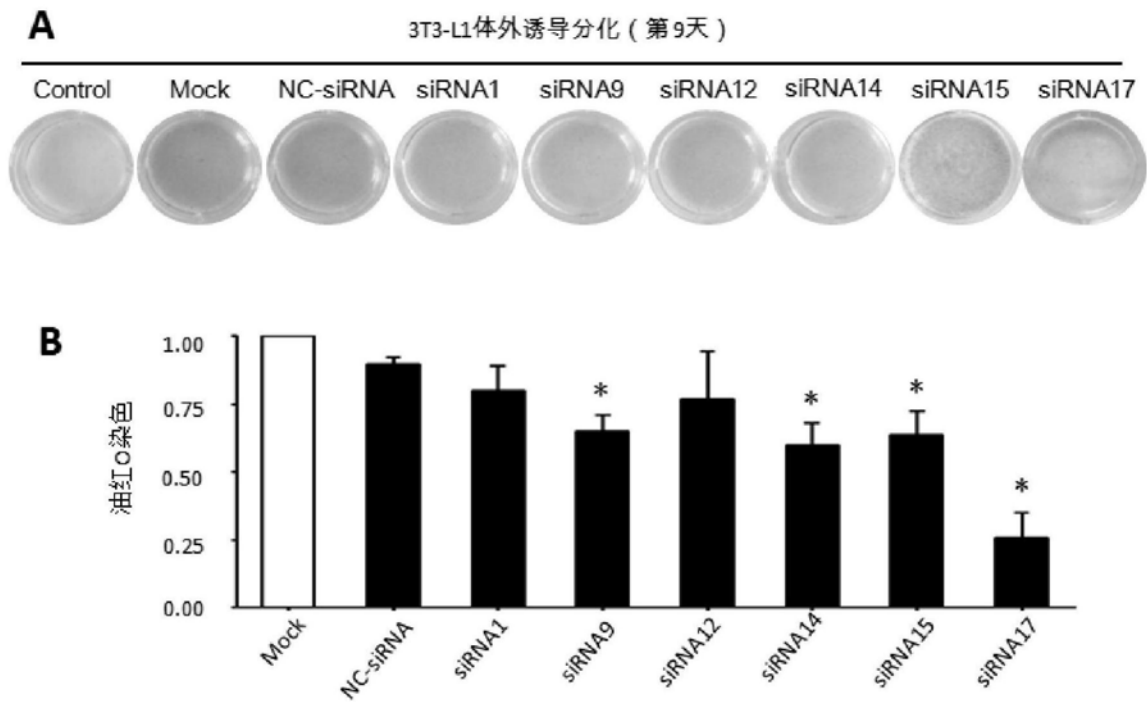
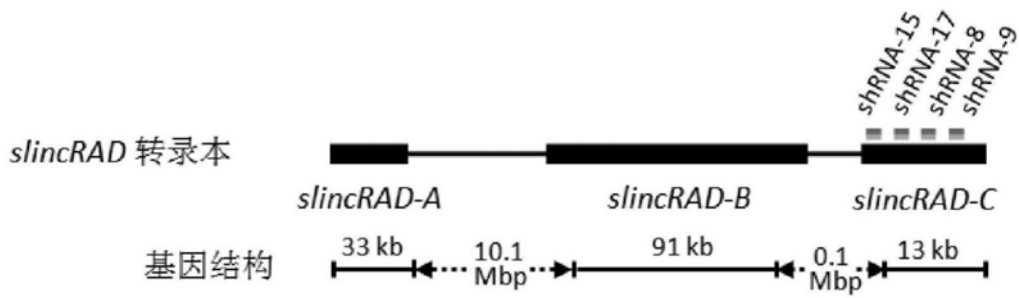
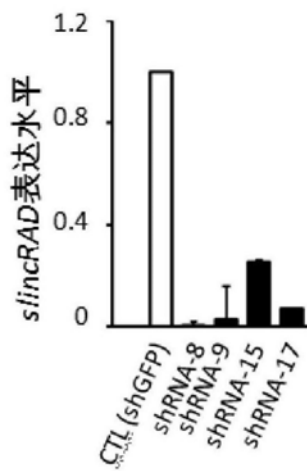


图2

A



B



C

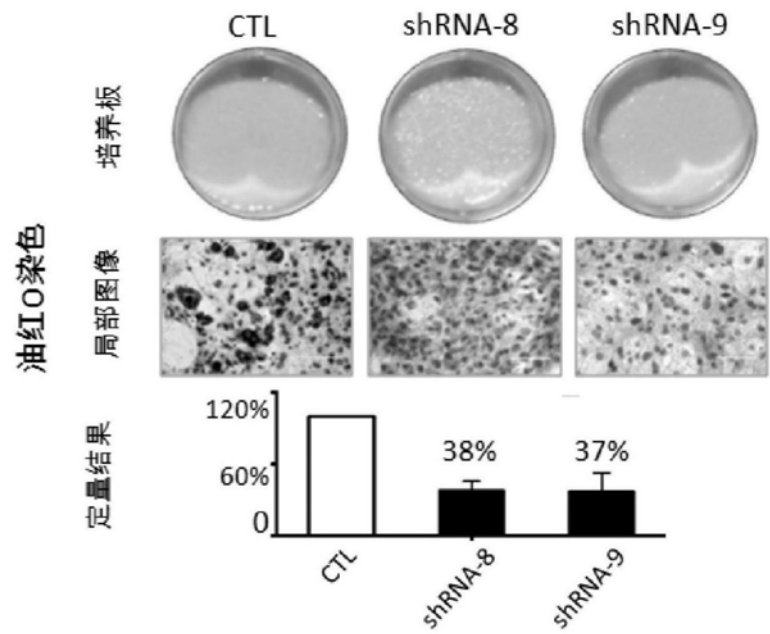
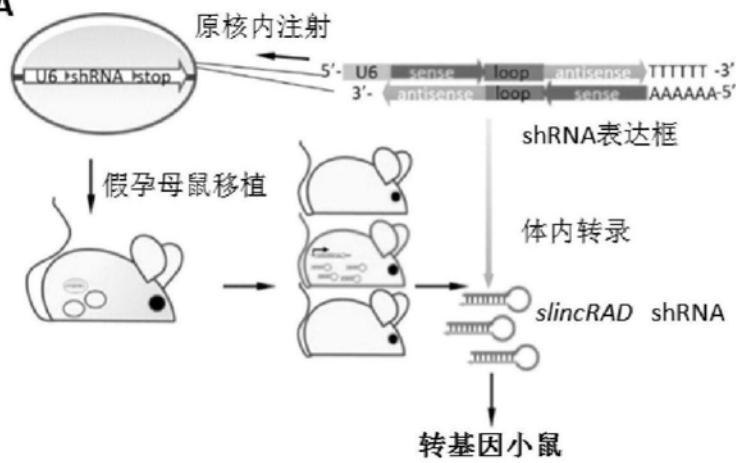


图3

A



B

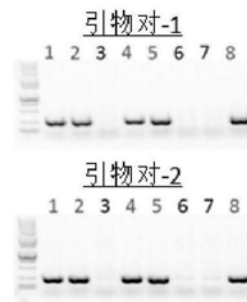


图4

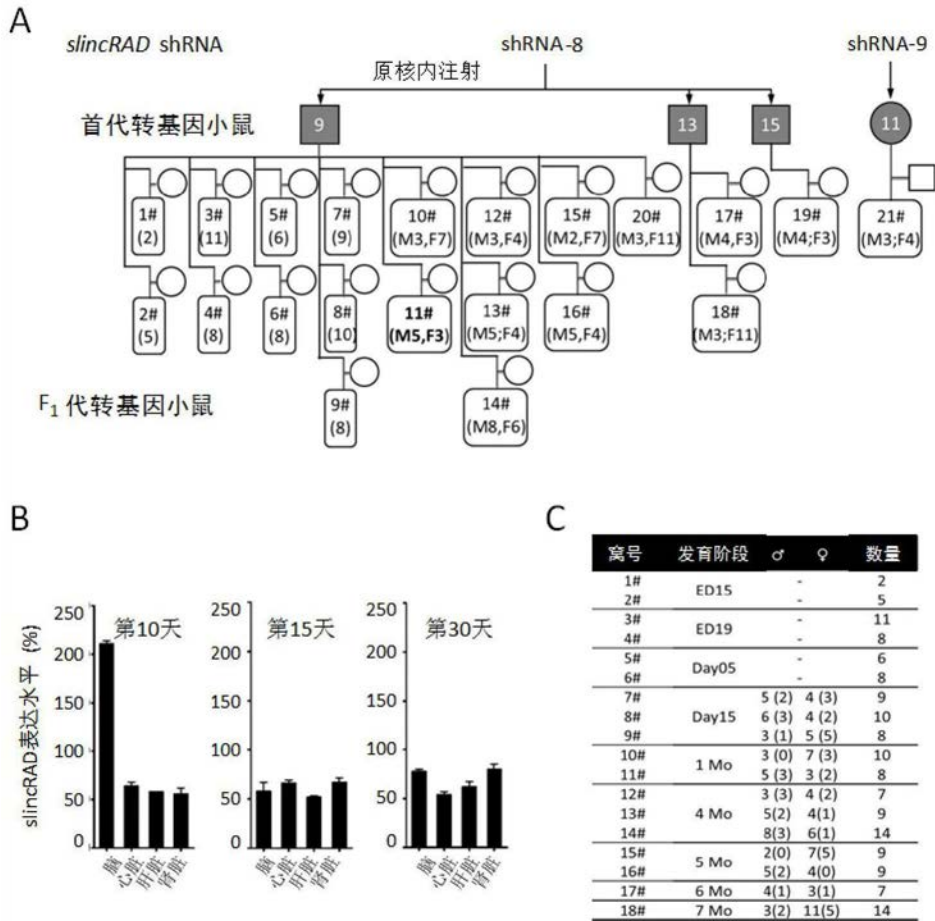


图5

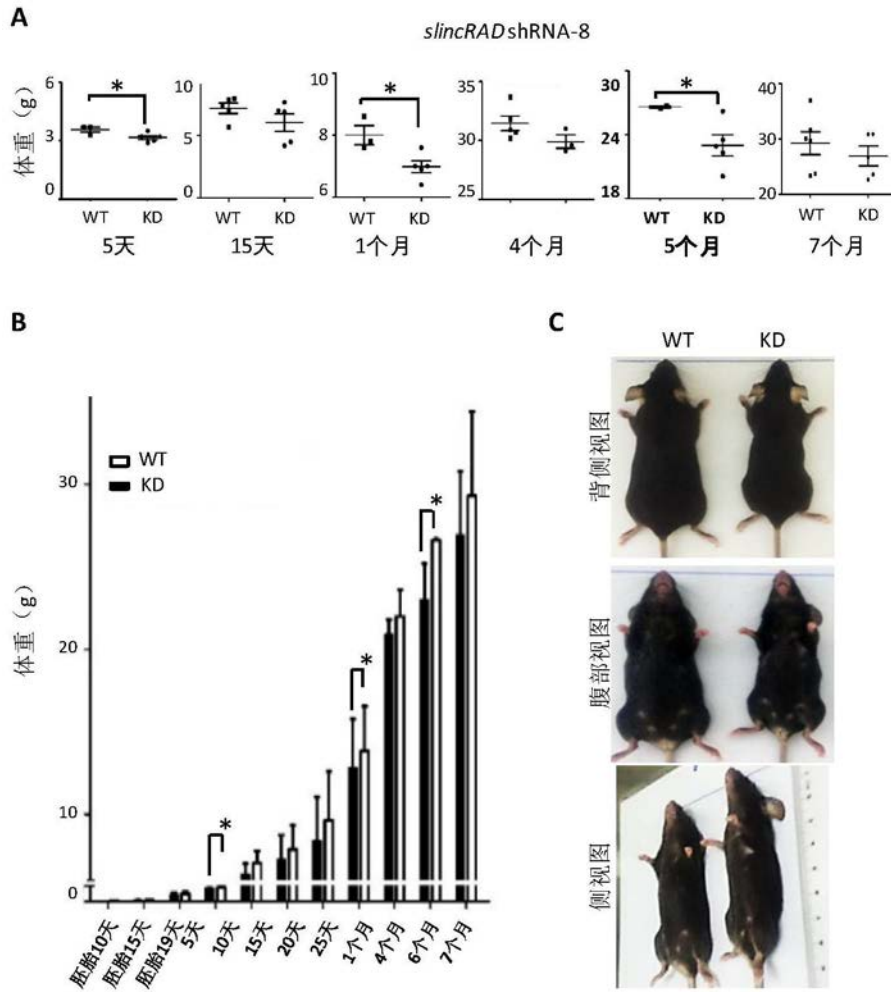


图6

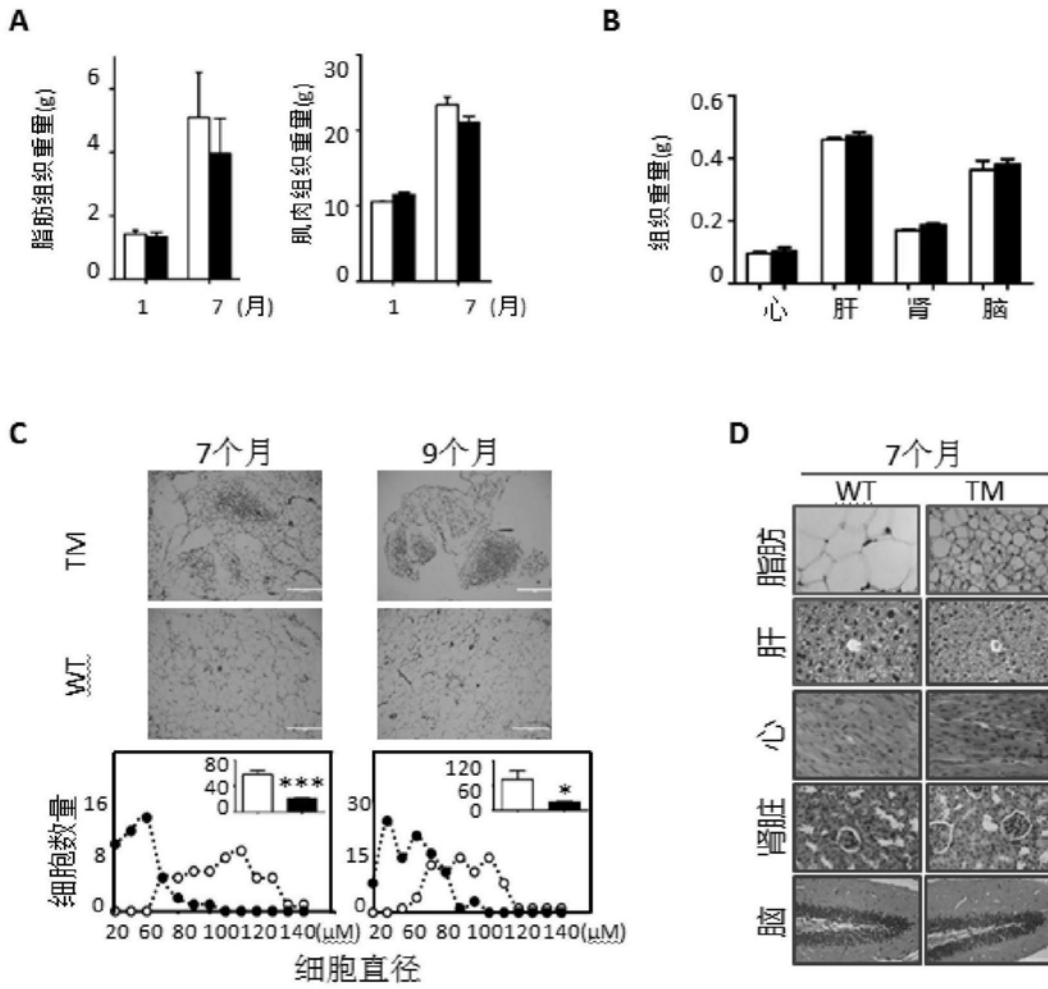


图7

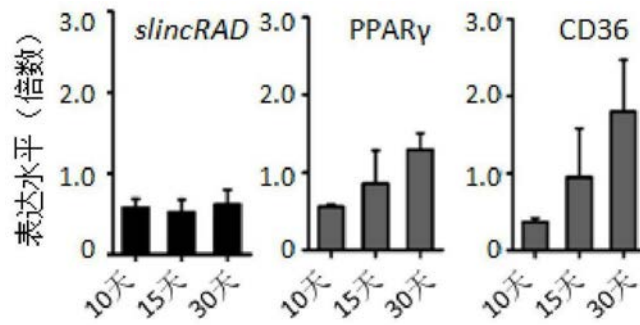


图8

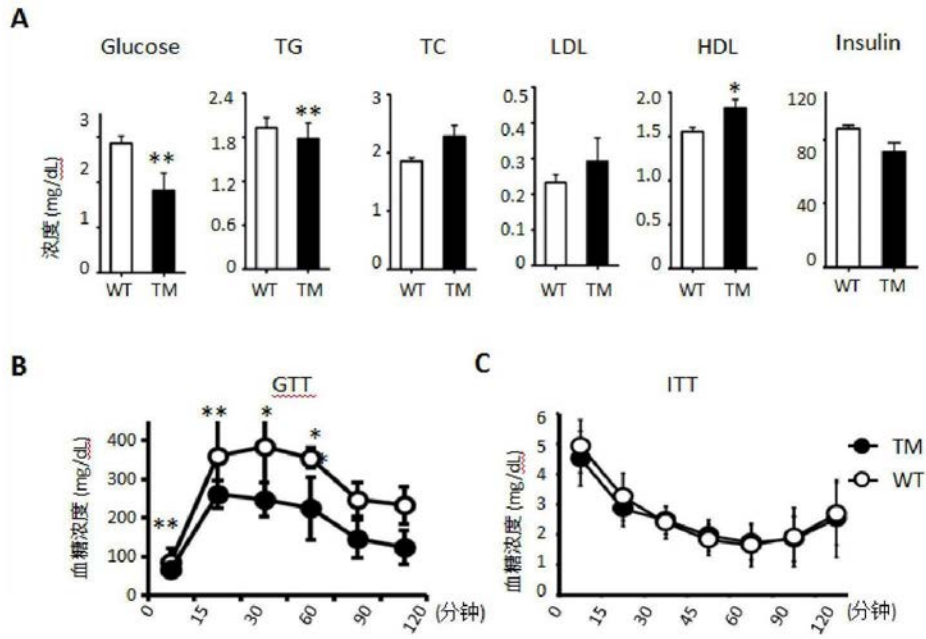


图9

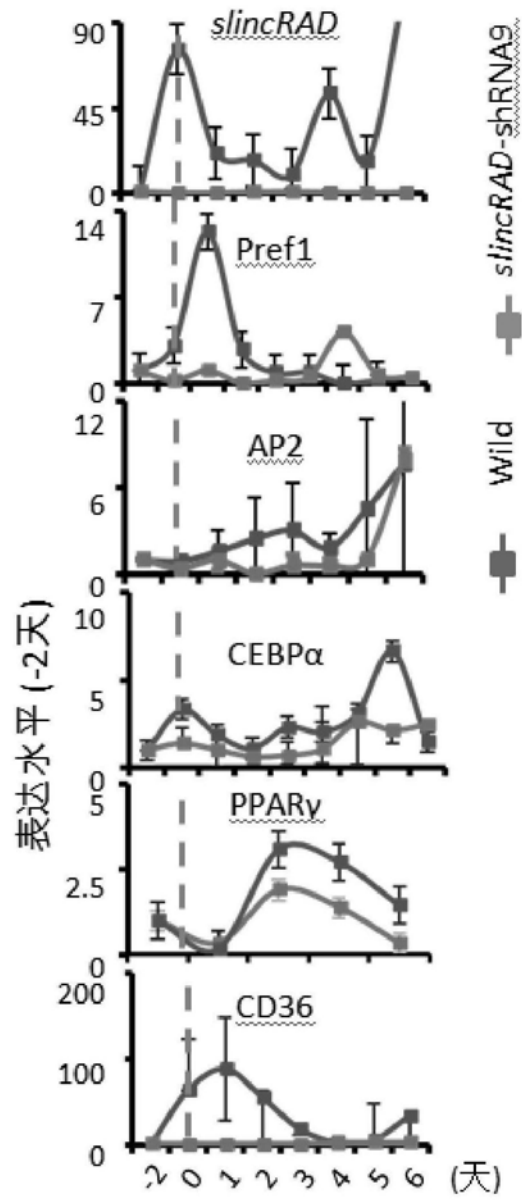


图10

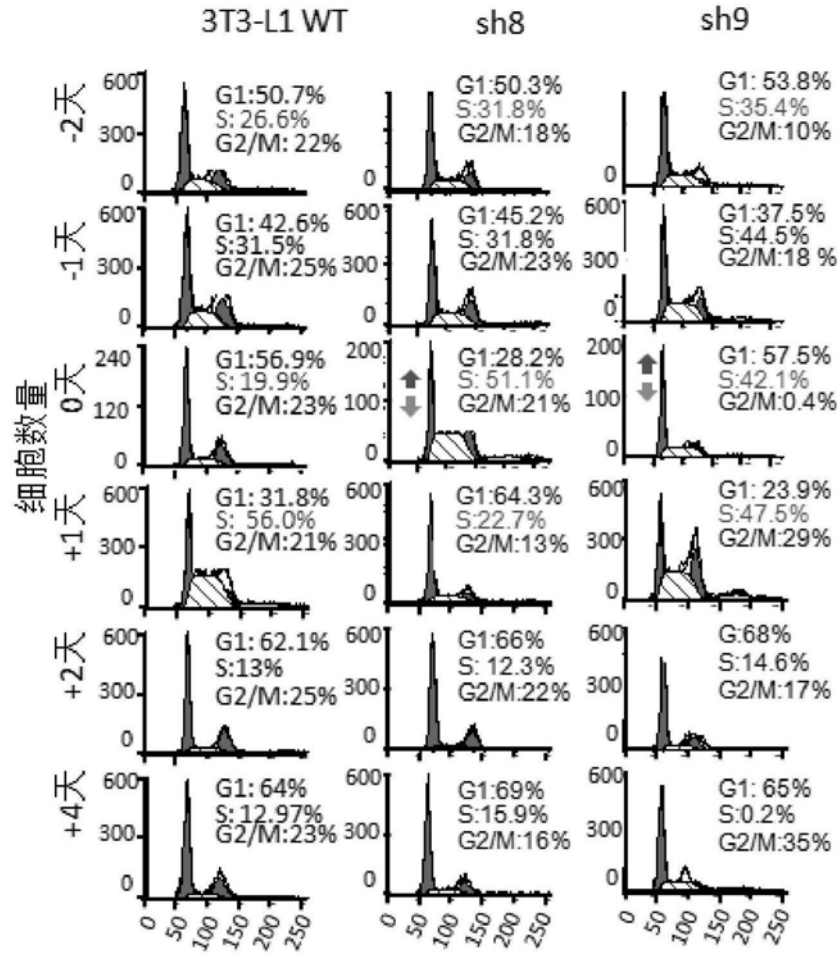


图11

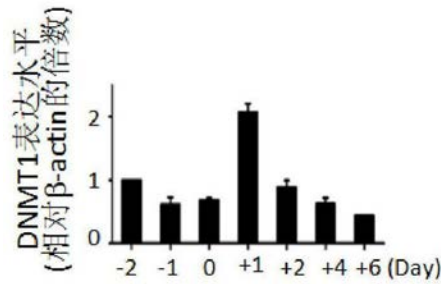


图12

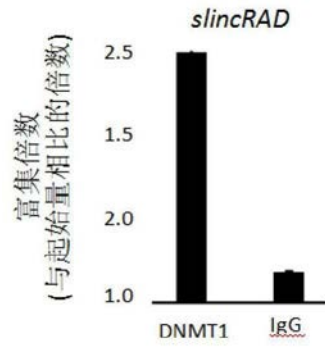


图13

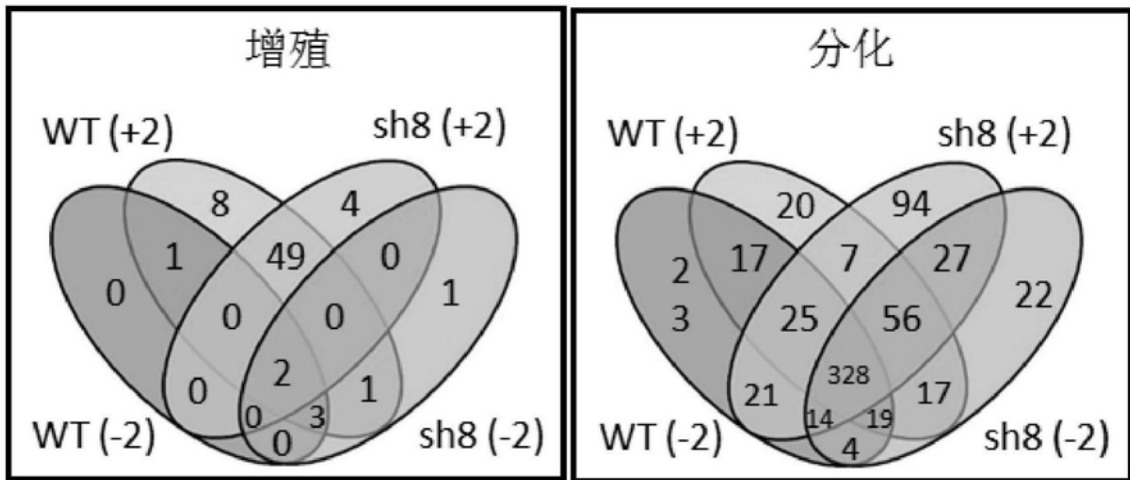


图14

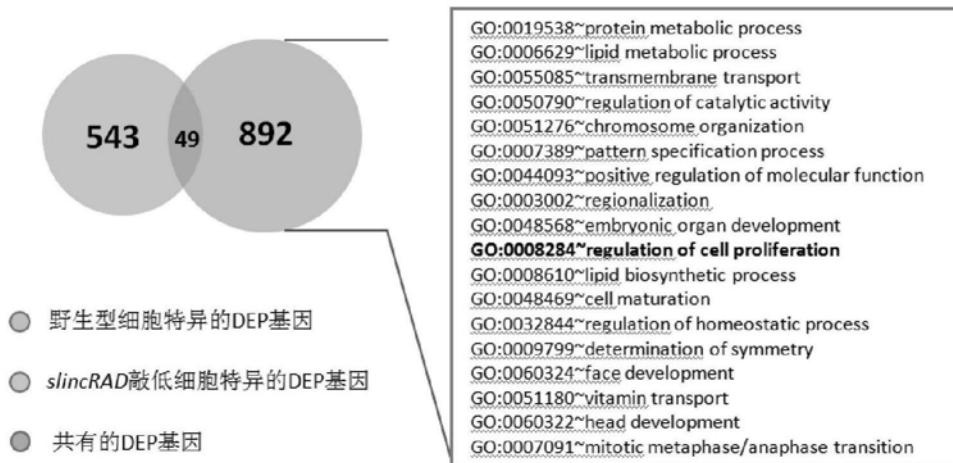


图15

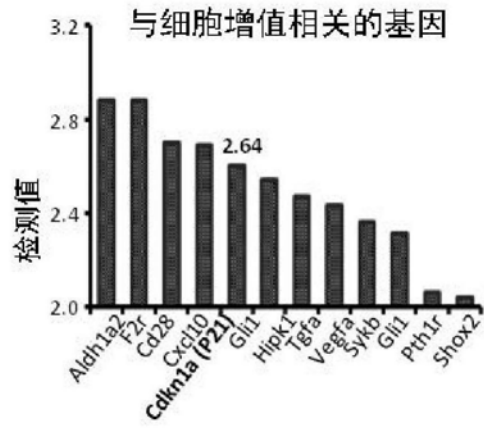


图16

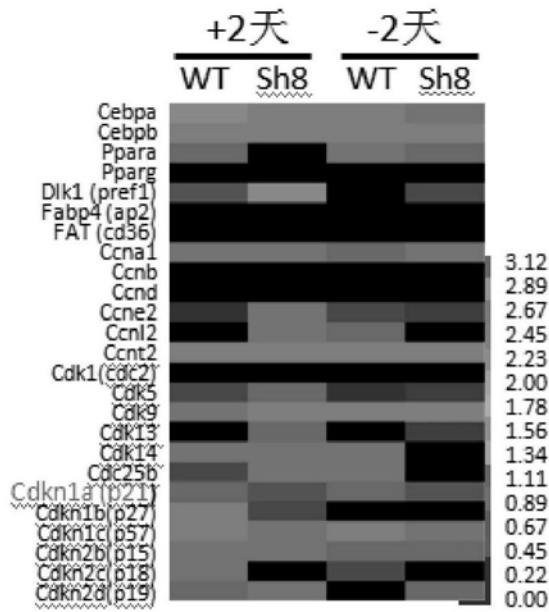


图17

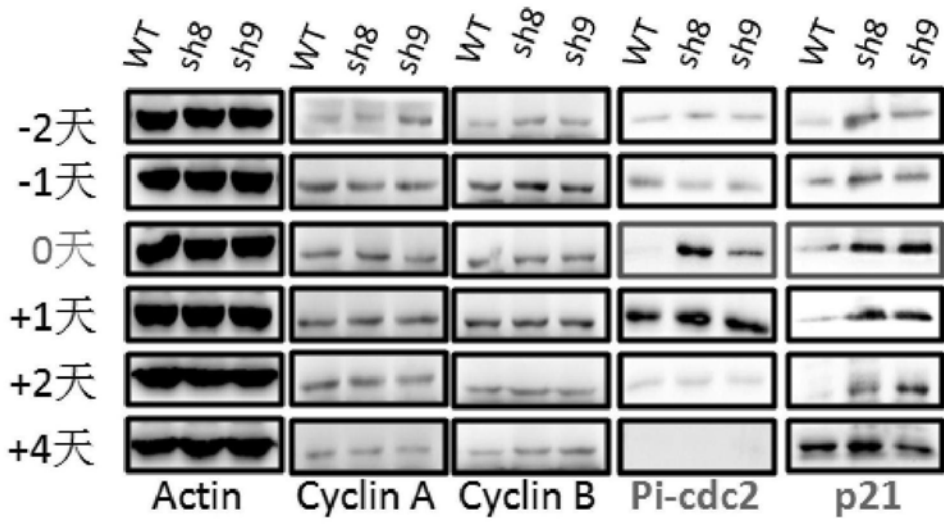


图18

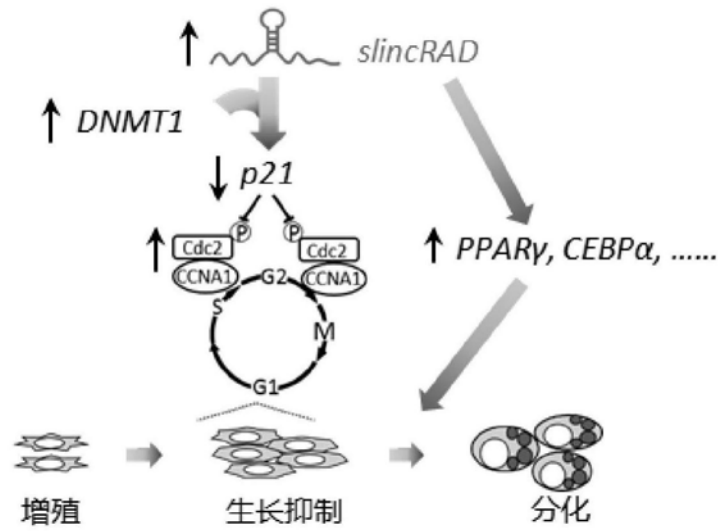


图19