SIRT3通过线粒体途径调控年龄相关疾病——从发病机制到治疗

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摘要 细胞中损伤线粒体出现堆积现象是年龄相关疾病的特征之一。当细胞受到氧化应激时, 作为一种NAD^+依赖性的去乙酰基酶——SIRT3可以通过调节线粒体功能与代谢来对抗外界刺激。SIRT3作用于线粒体的机制较复杂, 包括了能量的产生、抗氧化、线粒体动力学变化、维持膜电位以及线粒体自噬等。作为研究热点, SIRT3正被学者们从各个方面进行探索。然而, 目前现有关于SIRT3与年龄相关疾病的系统性总结。因此, 该文将从发病机制到治疗对SIRT3和年龄相关疾病作一综述。

关键词 SIRT3; 年龄相关疾病; 线粒体; 治疗

SIRT3 Regulates Age-Related Diseases via Mitochondrial Pathway: From Pathogenesis to Therapy

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Abstract One of the common features of age-related diseases is progressive accumulation of defective mitochondria. As a NAD^+-dependent protein deacetylase, SIRT3 regulates mitochondrial function and metabolism in response to oxdiative stress. The effects of SIRT3 on mitochondria are complicated, including energy production, antioxidation, mitochondrial dynamics, sustaining membrane potential and mitophagy, etc. SIRT3 has been explored from different aspects. However, there are still few summaries that systematacially illuminate how SIRT3 exerts its functions in protecting organism against age-related diseases. Thus, the aim of this review is to elucidate the relationship between SIRT3 and age-related diseases from pathogenesis to therapy.

Keywords SIRT3; age-related diseases; mitochondria; therapy

1 引言

“年龄相关疾病”是近年来提出的一种新的概念, 其与年龄相关性改变有关, 即随着年龄的增长, 衰老细胞内会出现端粒缩短、蛋白质内稳态失衡、基因不稳定以及线粒体功能紊乱等现象[1]。研究发现, 衰老动物组织中的线粒体会发生质量下降和功能退化, 即线粒体的失稳态[2-3]。功能紊乱的线粒体不仅无法维持其自身原有的功能与形态, 还会引起

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一系列细胞内病理改变, 从而导致一系列年龄相关疾病。

Sirtuins家族是一类烟酰胺腺嘌呤二核苷酸(NAD^+)依赖性的组蛋白去乙酰化酶, 在1979年首次由Rine等[4]在酵母内发现, 被命名为“沉默信息调控因子2(silence information regulator 2, SIR2)”。SIRT3(Sirtuin 3)作为Sirtuins家族的一员[5-6], 凭借其广泛的调控线粒体形态与功能的能力, 成为近几年来的研究热点。本文将从SIRT3在年龄相关疾病的发病机制中所起的作用到以SIRT3为靶点展开的一系列治疗作一综述。

2 线粒体

线粒体是真核生物所独有的细胞器, 也是除植物细胞叶绿体外, 真核细胞内唯一包含核外基因的细胞器。线粒体主要功能是传递电子和进行氧化磷酸化, 为机体提供生命活动所需的能量, 涉及氨基酸、核苷和脂质合成与细胞的离子运输等过程。

衰老的组织器官中会出现氧化应激的堆积, 例如, 在退变的椎间盘内可以发现晚期糖化终末产物的堆积[7]。衰老常伴随DNA的突变, 而线粒体DNA(mitochondrial DNA, mtDNA)的基因突变可以损伤线粒体活性氧(reactive oxygen species, ROS)清除功能, 导致ROS在线粒体内堆积, 使线粒体发生氧化损伤, 造成更多的mtDNA的突变。当异常的mtDNA达到一定数量时, 细胞内ROS的产生和消除失衡, 就会导致组织器官发生一系列改变[8]。

3 SIRT3

3.1 SIRT3促进机体能量生成

线粒体是细胞内的“能量工厂”。SIRT3可以通过发挥其去乙酰基酶的活性, 使线粒体呼吸链复合体亚基蛋白质去乙酰化, 以达到促进能量产生的作用[9-12]。*SIRT3*敲除小鼠的各种组织与正常小鼠相比, 其ATP产生量下降将近50%[9]。学者们还发现, 产能旺盛的组织具有更高的SIRT3表达量[9]。目前, 已经有多个研究报道, SIRT3是通过对ATP合酶内多种亚基进行去乙酰化而达到促进能量生成作用的。除了直接调控ATP合酶, SIRT3还可以使乙酰辅酶A合成酶2(一种乙酰辅酶合成的关键酶)和长链酯酰辅酶A脱氢酶(一种脂肪酸氧化的关键酶)发生去乙酰化并使之活化, 间接推动能量的产生[13]。

3.2 SIRT3提升线粒体生物合成能力

叉头转录因子家族中的FOXO3a(forkhead box O3a)调节了多种细胞活动过程, 其中包括了细胞生长、分化、生存、凋亡、应激、代谢、自噬以及长寿[14-16]。SIRT3激动剂FOXO3a可以通过提高细胞内抗氧化酶的活性, 以减少细胞内ROS的水平[17]。在氧化应激的刺激下, SIRT3可以作用于FOXO3a的K271和K290位点来完成去乙酰化, 实现对下游蛋白质的调节, 而K259位点却仍可处于乙酰化状态[18]。

过氧化物酶体增殖活化受体γ共激活因子-1α(peroxlsome proliferator-activated receptor-γ co-activator-1α, PGC-1α)可以调控线粒体蛋白质的合成, 具有提高细胞抗氧化应激的功能[19]。Tseng等[18]通过在人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVECs)过表达SIRT3以激活SIRT3-FOXO3a-PGC-1α通路, 并发现在双氧水的刺激下, SIRT3过表达组的线粒体质量显著优于对照组。另外, 线粒体转录因子A(mitochondrial transcription factor A, TFAM)是人类线粒体内高迁移率蛋白超家族的成员之一, 也是mtDNA合成和组装所必需的蛋白质[20-21]。研究表明, 在敲除*SIRT3*之后, TFAM表达下降, 并影响线粒体的合成功能[22]。PGC-1α与TFAM作为SIRT3的下游蛋白质, 参与了线粒体蛋白合成的调控, 两者的表达变化对线粒体合成功能具有重要意义。

3.3 SIRT3增强线粒体动力学变化

线粒体是一个具有高度动态性的细胞器, 即其始终处于分裂与融合的过程之中。SIRT3通过对下游FOXO3a进行去乙酰化, 再由FOXO3a调控一系列线粒体融合分裂的蛋白质, 可以增强线粒体的动力学变化, 以对抗应激。SIRT3-FOXO3a的激活不仅可以上调动力相关蛋白-1(dynamin-related protein-1, Drp-1)和线粒体分裂蛋白1(fission 1, Fis1), 还可使线粒体融合相关蛋白2(mitofusin 2, Mfn2)的表达增加[18]。Mfn2表达上调可以促进线粒体融合以促进损伤mtDNA的修复, 而Drp1和Fis1可以介导损伤线粒体从母线粒体中分离出来以便于损伤线粒体的清除[23-24]。视神经萎缩蛋白1(optic atrophy 1, OPA1)可起到维持线粒体嵴结构[25]和抗细胞凋亡的作用[26]。研究发现, *SIRT3*敲除的细胞在氧化应激的条件下, 细胞内OPA1的K926和931位点会发生高度乙酰化从而失去功能, 但将这两个位点进行去乙酰化后, 线粒体功能则明显恢复[27]。由此可

以得出, SIRT3通过调节一系列融合分裂蛋白质以加快线粒体动力学变化、及时中和病理性膜电位以及分离出损伤的线粒体, 从而维护线粒体的稳态。

3.4 SIRT3可以促进线粒体自噬发生

线粒体自噬(mitophagy)是一种选择性的自噬, 是细胞清除损伤线粒体的一种方式。目前, SIRT3对线粒体自噬的调控主要分为直接调控和间接调控。

SIRT3对线粒体自噬的直接调控主要表现在起始阶段, 即SIRT3的下游FOXO3a可以上调线粒体自噬关键调节蛋白Bnip3(Bcl2/E1B 19 kDa protein-interacting protein 3)、Nix(Bcl-2/E1B 19 kDa interacting protein 3-like)和LC3(microtubule-associated protein 1 light chain 3, MAP1LC3, LC3)水平[18,28-29]。定位在线粒体外膜的Bnip3和Nix以二聚体的形式连接在一起。Nix是通过介导线粒体与吞噬泡上的LC3相连接, 从而诱导线粒体自噬泡形成的[30]。研究表明, *SIRT3*敲除的糖尿病小鼠会出现线粒体自噬功能被抑制, 从而出现心肌肥大[29]。线粒体自噬需要线粒体分裂提供损伤的细小线粒体以作为吞噬对象, 即线粒体分裂是线粒体自噬发生的前提[31]。沉默或者突变*SIRT3*后可以使线粒体分裂相关蛋白Drp1和Fis1下调, 即抑制线粒体分裂[18]。所以, SIRT3也以通过增强线粒体分裂间接促进线粒体自噬。

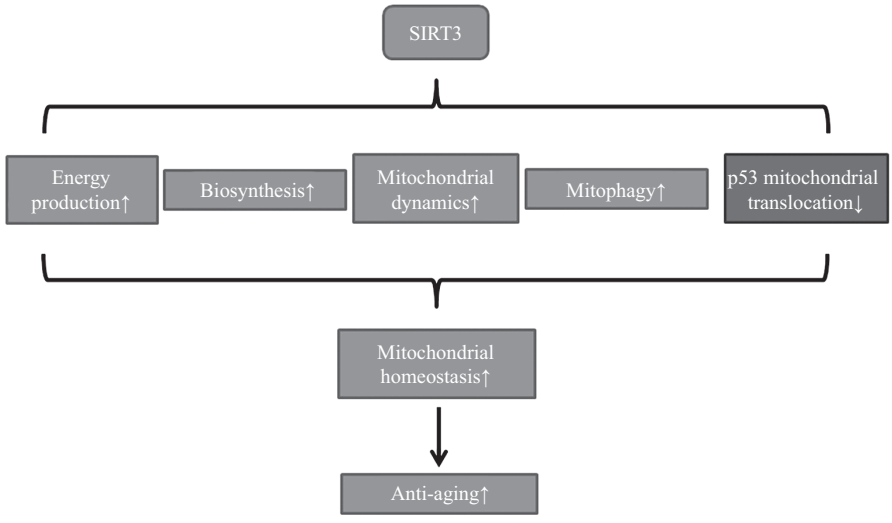
3.5 SIRT3能够阻止p53的线粒体转移以保护线粒体功能

作为一种抑癌基因, *p53*在正常细胞内的表达量很低。当细胞出现应激时, p53磷酸化形式表达上调, 引起一系列细胞内改变。例如, 衰老、细胞周期阻滞以及DNA损伤修复等。近年来, SIRT3与p53的关系开始引起人们的关注。其中, p53的线粒体转移与线粒体功能紊乱密切相关。利用肿瘤诱导剂12-O-十四烷酰佛波酯-13-乙酸酯(12-o-tetradecanoylophorbol-13-acetate, TPA)处理肝细胞10 min, p53开始在线粒体聚集并且与线粒体抗氧化酶SOD(superoxide dismutase)相结合(p53核转移发生在1.5 h左右), 导致细胞抗氧化应激能力下降以及线粒体膜电位的降低, 提示p53的线粒体移位可以引起线粒体功能紊乱[32]。此外, p53的线粒体转移还与SIRT3活性以及线粒体•O_2^-有关[33-34]。Coleman等[35]发现, *SIRT3*$^{-/-}$小鼠在经过辐射处理后, 与对照组相比, 其肝脏内p53的线粒体转移升高、线粒体膜电位下降, 并且在运用SOD类似物GC4401后, 以上现象都有所改善。由此可以推断, p53的线粒体转移可以导致线粒体功能紊乱, 并且主要体现在抗氧化功能上, 尤其是SOD的活性下降(图1)。

4 SIRT3与疾病中的关系

4.1 SIRT3在年龄相关疾病中的作用

4.1.1 SIRT3治疗帕金森病 帕金森病(Parkinson's disease, PD)在老年人神经退行性疾病发病率中排在第二位, 严重影响患者的生活质量与寿命。PD主要特点是中脑黑质多巴胺能神经元丢失以及路易氏



↑: 上调; ↓: 下调。

↑: upregulation; ↓: downregulation.

图1 SIRT3维持线粒体稳态的示意图

Fig.1 Schematic representation of the maintenance of mitochondrial homeostasis of SIRT3

体的出现。研究表明, PD与线粒体功能紊乱密切相关, 因为具有缺陷的线粒体无法为细胞提供足够的能量[36]。三羧酸循环是生命体三大营养物质代谢的最终途径。柠檬酸合酶作为三羧酸循环的关键酶之一, 会在MPP^+(一种PD细胞/动物造模药物)的作用下发生乙酰化。在SIRT3过表达后, 柠檬酸合酶可去乙酰化并且出现活性上升, 使ATP合成增加[37]。此外, Zhang等[38]通过敲除*SIRT3*, 再用鱼藤酮(一种呼吸链解偶联剂)刺激神经母细胞瘤SH-SY5Y细胞系, 发现*SIRT3*敲除细胞出现生存率下降、线粒体膜电位下降以及α-突触核蛋白聚集等现象。由此可见, SIRT3具有抗帕金森病的作用。

4.1.2 SIRT3治疗阿尔茨海默病 大量研究表明, 氧化应激不仅在阿尔茨海默病(Alzheimer disease, AD)的病理变化出现前增加, 还可以损伤神经元细胞的大分子物质[39]。此外, 还有学者发现, AD患者和AD小鼠组织内, SIRT3表达上升[40]。 这些都提示了SIRT3与AD存在相关性。SIRT3可以提高细胞对ROS的反应, 即一系列抗氧化应答机制。SIRT3在AD患者以及AD动物模型中的表达上调, 很可能是机体通过代偿性增加SIRT3含量来提高细胞的抗氧化能力。Weir等[41]通过慢病毒转染使原代神经元过表达SIRT3, 发现在氧化应激环境下, SIRT3过表达的神经元细胞的寿命长于野生型。此外, 载脂蛋白E4(apolipoprotein E4, APOE4)作为一种晚期AD的危险信号, 也被报道与SIRT3存在联系。尸检发现, *APOE4*基因携带者其大脑额叶中的SIRT3表达要低于非携带者[42]。*SIRT3*在AD患者体内究竟是上调还是下调, 各研究给出了不同的回答。但可以推测, SIRT3的表达可以在AD不同时期发生变化。一旦这个假设成立, 那么SIRT3便有望作为AD的一种分期诊断指标而应用于临床。

4.1.3 SIRT3抑制心肌肥大 线粒体功能紊乱在肥厚型心肌病、扩张型心肌病、冠心病、肺动脉高压和动脉粥样硬化早期的内皮细胞损伤中均起到一定的作用[43-45], 其中, 心肌肥大与氧化应激密切相关。SIRT3不仅可以通过FOXO3a来调节MnSOD(manganese-dependent superoxide dismutase), 还可以直接对MnSOD去乙酰化来提高细胞的抗氧化能力[46]。PI3K/Akt信号通路的激活是心肌肥大的发病机制之一[47]。SIRT3激活后可以上调LKB1(liver kinase B1)-AMPK(AMP-activated protein kinase)通路的表达, 并且进一步抑制ROS引起的Akt磷酸化, 从而抑制心肌肥大[48]。*SIRT3*敲除小鼠更容易患与年龄相关和大动脉紧缩性相关的左心室心肌肥大, 其主要原因是, SIRT3的缺失导致线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)过度激活[49]。目前, 已经有研究利用SIRT3激动剂Honokiol作用于心肌肥大小鼠, 发现上调SIRT3可以有效缓解甚至逆转心肌肥大的进程[50], 这说明了SIRT3是一种潜在的治疗应激导致的心肌肥大的靶蛋白。

4.1.4 SIRT3治疗冠心病 据统计, 35岁以上死亡的人群中有1/3因为冠心病而死亡[51], 所以研究冠心病对提高人类寿命具有重要意义。冠心病的主要病理变化是缺血再灌注损伤与心肌梗塞。

不断有文献提出, 缺血再灌注损伤与SIRT3有关。SIRT3的表达会在缺血再灌注之后出现下降[52], 并且SIRT3的下调会导致缺血再灌注损伤的进一步加重[53]。然而, 又有文献报道, *SIRT3*缺陷小鼠并不会在缺血再灌注后增加梗塞面积或者是损伤心脏功能[54]。因此, SIRT3与冠心病的关系还需要更多的研究进一步佐证。

低氧是心肌梗塞时常见的病理生理改变, 而低氧诱导因子(hypoxia inducible factors, HIFs)会在心肌缺血早期出现表达上调, 这提示, HIF-1α可能在心肌缺氧时发挥了一种代偿性的保护作用[55]。在心肌梗塞后, 予以外源性的HIF-1α可以减少梗塞面积以及改善血供[56]。目前, 尚未有研究证明SIRT3与HIF-1α在心肌缺血中的相互关系。但在其他系统, SIRT3可以通过HIF-1α抑制肿瘤细胞增殖[57]。这提示, SIRT3在冠心病中仍具有很大的研究空间。

由此可见, 研究SIRT3在冠心病中的作用对于缓解冠心病病理改变以及预防并发症具有重要的意义。

4.1.5 SIRT3预防骨质疏松 骨质疏松是哺乳动物衰老的特征之一, 是骨质内成骨细胞与破骨细胞活动不平衡的结果。

成骨细胞主要是由间充质干细胞分化而来。在间充质干细胞向破骨分化的过程中, 细胞内的线粒体和抗氧化酶起到了重要的作用。相比于间充质干细胞, 已经成骨分化的细胞表现出更多线粒体及呼吸相关酶、抗氧化酶等相关作用[58], 这提示了线粒体调节蛋白SIRT3与间充质干细胞的成骨分化有着

密切的联系。间充质干细胞除了可分化为成骨细胞外, 还可分化为脂肪细胞, 并且其脂肪细胞分化与ROS堆积密切相关[59]。研究表明, SIRT3过表达后可以通过激活SIRT3/PGC-1α/SOD2信号通路调节线粒体功能, 降低ROS的水平, 以促进干细胞的成骨分化[60]。

破骨细胞主要是由造血祖细胞分化而来。跨膜蛋白RANKL(receptor activator of NF-κB ligand)与造血祖细胞或者破骨细胞表面上的RANK(receptor activator of NF-κB)结合, 诱导了破骨细胞的分化和激活[61]。研究表明, RANKL和RANK的结合可导致SIRT3表达代偿性上调, SIRT3的激活可以抑制破骨细胞的分化。此外, *SIRT3*敲除小鼠可出现严重的骨质疏松, 并且SIRT3的抗骨质疏松功能与其下游PGC-1β密切相关[62]。

SIRT3作为调控线粒体形态功能的一个重要蛋白质, 可通过促进成骨分化以及抑制破骨分化两方面同时延缓骨质疏松的进程。因此, 以SIRT3为靶点, 可开发临床相关骨质疏松治疗药物。

4.1.6 SIRT3治疗糖尿病 SIRT3被认为与代谢性疾病紧密相关。1型和2型糖尿病小鼠骨骼肌SIRT3表达出现下降, 并且*SIRT3*敲除小鼠可出现胰岛素抵抗和摄糖能力下降[63]。晚期糖化终末产物(advanced glycation end products, AGES)是由非酶促性糖化反应对蛋白质进行转录后修饰生成的, 其表达量与糖尿病的时间与严重程度呈正相关。外源性AGES刺激血管内皮细胞, 会降低SIRT3水平, 并且过表达SIRT3后, 内皮细胞表现出更强的抗氧化和抗内皮细胞功能紊乱的能力[64]。

此外, 在糖尿病的富营养化内环境中, 大量的葡萄糖经细胞摄取后形成乙酰辅酶A。乙酰辅酶A可以使细胞内部分蛋白质的赖氨酸残基发生乙酰化, 导致这些蛋白质失去原本的功能。而SIRT3可以使这些被修饰的蛋白质脱去乙酰化, 恢复原本的生物活性, 以维持细胞的正常生理功能[65]。

4.1.7 SIRT3预防肿瘤 目前, SIRT3与人类肿瘤的相关性已被广泛研究。人们发现, SIRT3与恶性口腔鳞状上皮癌、乳腺癌、食管癌、肺癌、胃癌以及膀胱癌等有关[40]。细胞内的ROS可以使mtDNA发生突变, 导致抑癌基因的沉默或者原癌基因的过度激活, 引起肿瘤的发生。作为线粒体稳态调控的蛋白质, SIRT3可以通过清除细胞内ROS以抑制肿瘤的发生[66]。MnSOD是线粒体内一种重要的抗氧化酶, 其结构的K68位点会随着衰老而发生乙酰化, 导致自身抗氧化活性下降[67]。SIRT3可以结合MnSOD并且使之发生去乙酰化, 恢复其抗氧化酶活性。Kim等[68]发现, 在*SIRT3*敲除的小鼠胚胎成纤维细胞(mouseembryonic fibroblasts, MEFs)内过表达MnSOD后, 可以改善*SIRT3*敲除引起的线粒体功能的紊乱、氧化应激的增加以及抑制原癌基因的激活。

恶性肿瘤细胞存在一个共同特点, 即在O_2尚未缺乏的情况下, 肿瘤细胞也会将大量的葡萄糖通过糖酵解途径来进行能量代谢, 即瓦博格效应(Warburg effect)[69]。SIRT3可以降低肿瘤细胞内的糖酵解速度来缓解瓦博格效应, 从而起到抑癌的功能[11]。

4.2 SIRT3激动剂

随着对SIRT3的分子生物学功能的深入了解, 人们逐渐发现, SIRT3在多种药物治疗线粒体相关疾病中发挥重要作用。本文罗列出近年来发表的有关SIRT3激动剂治疗年龄相关疾病的案例, 为研究人员提供参考(表1)。

5 展望

随着人口老龄化的加剧, 人们关注的焦点开始转移到如何去延缓衰老。SIRT3作为一种衰老相关蛋白质, 这几年越来越被重视。SIRT3作为一种NAD^+依赖性的蛋白去乙酰基酶, 可以从多个方面来调控线粒体的功能与结构。目前已经围绕SIRT3展开了一系列广泛的研究, 包括SIRT3的生理学、病理学以及药理学研究等。在机体衰老进程中, SIRT3的下调将对细胞能量合成、mtDNA修复及ROS生成等过程产生影响, 从而导致一系列年龄相关疾病, 例如帕金森病、糖尿病、骨质疏松、心脏病及肿瘤等的发生。随着对SIRT3的分子生物学机制的了解逐渐深入, 人们发现许多的抗氧化药物与SIRT3相关。相信将来SIRT3可以作为一种对抗线粒体相关疾病的靶蛋白运用于临床, 对提高人们生活质量以及延长寿命具有重要意义。

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表1 关于不同药物治疗线粒体相关疾病的机制

Table 1 Mechanisms of drugs on age-related diseases via regulation of SIRT3

药物 Drugs	实验模型 Experiment Models	治疗效果 Efficacy	机制 Mechanisms	参考文献 References
Metformin	Rats	Signifcantly reduce blood glucose levels and improve glucose intolerance	Activate SIRT3-AMPK signaling pathway	[70]
Nitrite	Rats	Improve hyperglycemia and glucose intolerance and elevated the circulation levels of adiponectin	Activate SIRT3-AMPK signaling pathway	[70]
Resveratrol	Human fibroblasts	Attenuate oxidative stress in mitochondrial complex I deficiency	Activate estrogen receptor-ERRα-SIRT3-SOD2 signaling pathway	[71]
Polydatin	Rats and small intestine IEC-6 cells	Ameliorate injury to the small intestine induced by hemorrhagic shock	Activate SIRT3-SOD2 signaling pathway	[72]
Liraglutide	Mice	Ameliorate non-alcohol fatty liver disease	Enhance mitochondrial architecture and promoting autophagy through SIRT1/SIRT3-FOXO3a pathway	[73]
Green tea polyphenols	Rats	Reduce oxidative stress in kidney tissues	Activate SIRT3, PPARα	[74]
Melatonin	HepG2 cells	Ameliorate cadmium-induced hepatotoxicity	Activate SIRT3-SOD2-mROS-dependent autophagy	[75]
Celastrol	Rats	Attenuate oxidative stress in the skeletal muscle of diabetic rats	Regulate AMPK-PGC1α-SIRT3 signaling pathway	[76]

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