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长寿与衰老相关分子机制研究进展

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摘 要:长寿是一个复杂的特征,因遗传、环境等因素的差异而不同,理想情况下主要取决于衰老速率。相关分子机制多种多样,主要有生长激素(GH)和胰岛素样生长因子1(IGF-1)途径、Forkhead box O3 基因(*FOXO*3)、AMP 活化蛋白激酶(AMPK)、sirtuins 家族基因、载脂蛋白 E 基因(*APOE*)、端粒酶基因、mTOR 信号通路、抑癌基因 *p*53、慢性炎症转录因子 NF-κB、自噬-溶酶体信号通路、长链非编码 RNA(lncRNAs)、蛋氨酸亚砜还原酶系统(Msr)。同时,环境因素也影响着人类的寿命,例如饮食限制、运动、地理条件、环境压力等。本文从遗传和环境两方面综述影响人类寿命因素的最新研究进展。

关键词:长寿基因;衰老;遗传;寿命
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Recent advances in molecular mechanisms related to longevity and aging

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Abstract: Longevity is a complex trait that varies depending on genetic, environmental, and other factors, while it mainly depends on the rate of aging under ideal conditions. There are various molecular mechanisms involved, including growth hormone (GH) and insulin-like growth factor 1 (IGF-1) pathway, Forkhead box O3 gene (*FOXO*3), AMP-activated protein kinase (AMPK), sirtuins family gene, apolipoprotein. E gene (*APOE*), telomerase gene, mTOR signaling pathway, tumor suppressor gene *p*53, chronic inflammatory transcription factor NF-κB, autophagy-lysosomal signaling pathway, long noncoding RNAs (lncRNAs), and methionine sulfoxide reductase system (Msr). At the same time, environmental factors also affect the life expectancy of human beings, such as dietary restrictions, exercise, geographical conditions, environmental pressures, and so on. This paper reviews the latest research progress on factors affecting human life expectancy from the aspects of genetics and environment.

Keywords: Longevity genes; Aging; Inheritance; Life expectancy

据估计,受遗传因素影响的寿命变化约占25%[1]。在最理想的情况下,寿命的长短主要是由衰老速率决定的。衰老是由在组织、细胞、分子和遗传水平上发生的相互关联的过程控制的。本文综述了与长寿和衰老相关的遗传因素和环境因素的最新知识,主要涉及了生长激素(GH)/胰岛素样生长因子-1(IGF-1)途径、Forkhead box O3 基因(*FOXO*3)、AMP 活化蛋白激酶(AMPK)、脱乙酰化酶家族基因(*Sirtuins*)、载脂蛋白基因(*APOE*)、端粒延长、雷帕霉素靶蛋白信号通路(mTOR)、抑癌基因 *P*53、慢性炎症抑制转录因子 NF-κB、自噬-溶酶体信号通路、长链非编码 RNA(lncRNAs)、蛋氨酸亚砜还原酶系统(Msr)等遗传相关因素和饮食限制、运动、地理条件,抵抗力等环境相关因素。

遗传因素和环境因素共同影响体内内部环境的稳态,机体的基础功能和代谢等。这些因素极大的

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影响了与年龄相关的疾病(如:心血管疾病(CAD)和阿尔兹海默症(AD)等)的患病率,最终影响长寿和衰老[2]。本文通过查阅大量文献,总结出各因素与长寿和衰老之间的相互关联。

1 影响遗传的分子通路

1.1 生长激素和胰岛素/胰岛素样生长因子途径(GH/insulin/IGF-1)

影响长寿和衰老的第一个因素是生长激素(GH)和胰岛素/胰岛素样生长因子(Insulin/IGF-1)途径[3]。该途径是从酵母到哺乳动物(甚至包括人类),对长寿和衰老影响最大的途径之一[4-6]。生长激素(GH)和胰岛素/胰岛素样生长因子(Insulin/IGF-1)途径有许多多效性作用[7],该途径中已知一种基因是由 *FOXO*3 基因编码。生长激素的主要生理作用是生长刺激,激素受体复合物 GH/GHR 具有酪氨酸激酶活性,触发肝细胞 JAK/STAT 通路从而促进 IGF-1 表达。在血流中循环的 IGF-1 与周围组织细胞表面的受体 IGF-1R 相互作用,受体将信号转导到 IRS 蛋白,其进一步激活 mTOR 信号通路,在 mTOR 作用的情况下,激酶 S6K 被激活以增强细胞代谢和生长从而加速衰老[8]。有研究结果表明,抑制体内的 GH/insulin/IGF-1 途径后,延长了酵母、线虫、果蝇[9-10]和小鼠[11]等模式生物的寿命。在对人类群体中 GH/ insulin/IGF-1 途径抑制的研究中也有类似的观察结果。

1.2 Forkhead box O3 基因(*FOXO*3)

*FOXO*3 在模式生物中的过度表达与延长寿命有关[12]。当 *FOXO*3 在果蝇[13]和小鼠的脂肪组织过度表达时,可以使其寿命延长[14]。人类中 *FOXO*3 基因的多态性也与长寿相关[15]。

*FOXO*3 基因编码了一种胰岛素/IGF-1 途径的关键调节因子,但对基因表达的影响通常与胰岛素/IGF-1 相反[16]。*FOXO*3 对多种生理功能有调节作用,包括细胞增殖、凋亡和新陈代谢,影响细胞周期的进展,提高体外抗氧化应激反应的能力,进而增长人类寿命[17]。它通过与许多长寿基因共同作用来延长寿命,可以抑制雷帕霉素激酶(mTOR)途径[18],*FOXO*1 和 *FOXO*3 均抑制 mTOR 相关蛋白的活性,从而降低 mTOR 复合体 1(mTORC1)的活性;但与 *FOXO*1 不同的是,*FOXO*3 对 mTOR 复合体 2(mTORC2)的活动没有影响[19]。*FOXO*3 基因还能调节免疫系统[20],当机体进入老年后,免疫系统恶化,从而增加感染的风险,*FOXO*3 诱导人肾、肺、肠中抗菌肽的合成[21],它们作为先天免疫的效应分子有效抑制不同物种的微生物感染;控制细胞因子的产生,抑制慢性炎症转录因子 NF-κB 的激活,降低炎症的发病率[22];与抑癌基因 *P*53 协同作用[23],抑制肿瘤生长[24],P53 蛋白促进 *FOXO*3 的表达[25]。

1.3 AMP 活化蛋白激酶(AMPK)

另一个有利于长寿和调节代谢的蛋白质是 AMP 活化蛋白激酶(AMPK)。AMPK 是一种营养和能量传感器,它是通过细胞能量匮乏、线粒体呼吸中断或缺氧引起的 AMP ∶ ATP 比值升高来调节代谢的[26]。当细胞的 AMP ∶ ATP 比值上升时,它会激活葡萄糖和脂质氧化的分解代谢途径,并抑制合成代谢途径[27]。它还可能影响动物和人类的寿命和健康[28],有研究表明,过度表达的 AMPK 延长了线虫的寿命[29];用 AMPK 激活剂:phenformin(苯乙双胍) 和 metformin(二甲双胍)(两种均为降血糖药)处理后的小鼠和蠕虫的寿命得以延长[30-31]。

1.4 脱乙酰化酶家族基因(*Sirtuins*)

Sirtuins 是烟酰胺腺嘌呤二核苷酸 NAD+-依赖性酶家族,具有脱乙酰化酶和 ADP-核糖转移酶活性[32]。研究发现,sirtuins 的过度表达延长了酵母、蠕虫和果蝇的寿命[33]。这个酶家族中与长寿最有关联的成员是 *SIRT*1 及其在无脊椎动物和酵母中的同源物 Sir2。*SIRT* 1 的脱乙酰化酶活性随着 NAD+ ∶ NADH 比率的升高和氧化应激反应增强而增强[34]。Sir2 在细胞分裂期间促进了受损蛋白(如已被碳化的蛋白质)的分离来保证细胞分裂的正常进行[35]。最近一项研究表明 Sir2 通过在衰老过程中维持基因沉默来延长寿命[36]。哺乳动物 *SIRT*1 是与年龄相关疾病相关的生理过程的关键调节因子,如:肥胖症、神经退行性疾病和肿瘤[37-39],它也参与细胞凋亡[40]和各种应激反应[41]。*SIRT*1 在小鼠全身或大脑中的适度过表达延缓了衰老[42-43],而 *SIRT*1 发生突变的小鼠在某些组织中有加速老化的迹象[44]。其他 sirtuin 家族基因也能延长动物的寿命,*SIRT*6 刺激各种 DNA 修复蛋白在应激反应中的活性[45]。

1.5 载脂蛋白基因(*APOE*)

载脂蛋白基因(*APOE*)编码了一种主要的胆固醇载体[46],有助于调节胆固醇和脂质代谢,以及帮助细胞修复[47-48]。*APOE* 是脂质代谢的关键,整个脂质代谢包括脂质合成、吸收、储存和利用,胰岛素促进肝脏甘油三酯的合成,并在供养时将甘油三酯储存在白色脂肪组织中,而在其他组织中,当营养不充足时,胰高血糖素和肾上腺素则会刺激脂肪组织中的脂类分解和脂肪酸氧化[49]。

APOE 是与长寿相关研究最多的基因之一,其

基因位点与人类家族寿命显著相关,有三个常见的等位基因 ε2、ε3 和 ε4[50],分别对低密度脂蛋白(LDL)具有不同亲和力。ε4 等位基因亲和力最低,会增加总胆固醇水平[51],与长寿呈负相关[52],并且有研究者发现携带 ε4 等位基因会增加患心血管疾病(CAD)(高达 40%)和阿尔兹海默症(AD)的风险[52-63]。而 ε2 等位基因与低密度脂蛋白(LDL)的结合亲和力较高,总胆固醇水平较低[64],与长寿呈正相关[65]。有研究者通过对美国和丹麦两地长寿家庭的实验调查也获得了类似的结果,观察到长寿家庭中 ε4 等位基因的频率降低,ε2 等位基因的频率增加[66]。

1.6　端粒酶基因

端粒是位于真核染色体末端的特殊结构,其主要功能是细胞在 DNA 断裂时可通过端粒感知线性染色体末端。在脊椎动物中,端粒由 TTAGG 的串联重复序列组成,这些重复序列与特定蛋白质一起形成帽状结构,从而抑制 DNA 损伤反应(DDR)的激活[67]。然而,随着每个细胞分裂周期,端粒逐渐缩短,最终导致一个或多个端粒功能失调,并因此启动永久 DDR。因此,端粒缩短被认为是一种有丝分裂时钟,用来测量细胞分裂的次数[68-69]。

端粒酶是一种包含逆转录酶催化亚基(TERT)和相关 RNA 成分(TERC)的多蛋白复合物[70]。它合成高度重复的端粒 DNA,成熟体细胞的每一次分裂都会缩短端粒 DNA[71]。端粒酶将端粒 DNA 重复添加到染色体末端,来抵消细胞周期导致的端粒缩短[72]。端粒酶或端粒相关蛋白(Shelterin)突变的动物模型有助于揭示端粒在癌症和衰老中的作用[73-82]。通过实验得知,成年小鼠激活端粒酶后在不增加肿瘤发生机率的情况下延长其寿命[83]。端粒酶也参与细胞内信号通路的调控,如 mTOR 信号通路[84],慢性炎症转录因子调控(NF-κB)[85],以及线粒体功能机制对氧化应激的反应。

1.7　雷帕霉素靶蛋白信号通路(*mTOR*)

雷帕霉素靶蛋白(mTOR)是一种丝氨酸-苏氨酸蛋白激酶,它是环境营养和能量的传感器,是细胞和有机体寿命的重要调节器。mTOR 信号通路实际上是一个复杂的、不断进化的营养感应途径,在控制脂质合成,特别是脂肪生成方面具有重要作用,越来越多的研究指出其是影响寿命的关键调节因子。

研究表明,与 insulin/IGF-1 途径紧密相连共同影响人类寿命的 mTOR 通路是由两种 mTOR 复合物,即 mTORC1 和 mTORC2 介导,调节细胞生长、增殖、发育、自噬,先天和适应性免疫反应以及寿命[49]。*mTORC*1 控制翻译调节(激活翻译起始因子 *eIF-4E* 并抑制翻译抑制剂 4E-BP)、核糖体生成(S6)、抑制自噬作用(抑制 ULK1),糖酵解(HIF-1)、血管生成(VEGF)和脂肪酸生成(SREBP1)[86]。这种蛋白质复合物由溶酶体表面的氨基酸和蛋白质 Rheb 直接活化。因此,根据营养浓度,Mtorc1 对细胞的新陈代谢进行靶向调控[87]。mTORC2 复合物有助于肌动蛋白细胞骨架重塑,与 AKT-PKC-SGK 复合物协同抑制氧化应激反应转录因子 *FOXO*1 和*FOXO*3,并激活慢性炎症转录因子 *NF-κB*,从而降低了抗应激反应能力,诱导炎症、肿瘤形成和细胞衰老[88],最终缩短寿命。

一直以来,由于 mTOR 信号通路在高营养条件下,通过激活核糖体亚单位 S6 激酶和抑制 4E BP(一种翻译抑制剂)使 mTOR 翻译增多,寿命缩短;低营养条件下活性下降,翻译水平也下降,寿命延长。许多研究者都提出将通过各种方法抑制 mTOR 相关通路[89],降低 mTOR 调控信号作为一种主要的分子机制来延缓从酵母到哺乳动物等生物体的衰老[90]。并且在许多模式生物中,mTOR 通路成为通过饮食营养限制来延长寿命的主要候选途径[91]。如:通过抑制核糖体亚单位 S6 激酶活性延长了酵母、蠕虫、果蝇和小鼠的寿命[92-96],并通过人为激活 4E BP 的过表达,抑制转录翻译,来增加寿命[97]。

1.8　抑癌基因 *P53*

抑癌基因 *P*53 用于碱基和核苷酸切除修复和错配修复基因的表达,激活 *P*53 基因对于细胞的各种反应是至关重要的:细胞周期阻滞,DNA 修复,端粒 DNA 损伤修复和细胞凋亡。*P*53 的一个重要功能是抑制肿瘤的生长。超过一半的人类肿瘤与 *P*53 基因的异常表达有关[98]。更重要的是,在小鼠体内敲除 *P*53 基因后表现出早衰、器官萎缩、骨质疏松症和抗应激反应能力差等症状[99]。

1.9　慢性炎症转录因子 NF-κB

组织中的慢性炎症是衰老的原因之一。慢性炎症是由与转录因子 NF-κB 活性相关的信号通路触发的[100]。该蛋白参与了免疫形成、细胞因子和生长因子的调节以及胚胎发生[101]。NF-κB 的激活诱导炎症相关抗菌基因的表达,并激活抗氧化酶的基因,如超氧化物歧化酶[102]。NF-κB 的活性随着年龄的增长而增加,并导致慢性炎症和年龄相关的疾病。抑制 NF-κB 的活性后延长了果蝇和小鼠的生命[103-104]。在用抗炎药物、乙酰水杨酸和布洛芬处理后的线虫和果蝇中观察到寿命延长[105-106]。在小鼠中,抑制 NF-κB 可防止皮肤衰老,促使细胞增殖,并延缓细胞衰老[107]。

1.10 自噬-溶酶体信号通路

自噬-溶酶体信号通路通过自噬清除有毒的、易聚集的蛋白质来维持线虫[108]、果蝇[109]和老鼠[110]等模式生物甚至人类细胞的正常功能从而达到延长寿命的作用。例如最近在小鼠身上进行了两项研究,其中一项研究表明,激活自噬-溶酶体信号通路可以改善老年小鼠静脉神经干细胞的功能[111],而另一项研究表明,通过破坏 beclin 1-BCL2 复合物来增加自噬功能,可以改善小鼠的健康状况,从而延长寿命[112]。同样,通过对 171 名百岁老人及其子女和子女配偶的外周血白细胞转录组进行 RNA 测序分析,发现百岁老人的自噬-溶酶体活性与普通老人相比显著增强,并且增强的自噬-溶酶体活性可以部分地传递给后代,表现为自噬编码基因和 beclin 1 血清(BECN1)水平较高[113],该研究认为,百岁老人存在特有的显著差异表达的基因,这些基因来自与长寿相关的途径,如生长激素和胰岛素/胰岛素样生长因子途径、mTOR 通路和 *P*53[114-116],且其中有几个基因位于通路的节点上,并始终具有诱导自噬的可能性。例如,*IGF*1*R* 和 *IRS*1 基因的表达降低可通过降低胰岛素/IGF-1 信号激活自噬功能[117],而 *DDIT*4 基因的高表达可通过抑制 mTOR 信号通路促进自噬[118]。这些发现说明自噬-溶酶体信号通路对长寿和延缓衰老具有积极意义。

1.11 长链非编码 RNA(lncRNAs)

长链非编码 RNA 是一类调节性非编码 RNA,其转录长度>200 个核苷酸[119]。它们通常在基因转录中作为信号、诱饵、向导,以染色质重组、转录调节和转录后修饰等不同模式影响基因表达[120],从而影响寿命长短和机体衰老。从调控的角度来看,lncRNAs 可以调节不同阶段的基因表达和信号通路[121-123],它们比其他非编码 RNA 或编码基因更具有特异性和复杂性。虽然已经通过全基因组分析鉴定出了大量的 lncRNAs 和转录谱,但其中只有一小部分功能明确。合适的已知基因重叠、组织特异性高、疾病状态差异表达大的 lncRNAs 可作为未来探索功能的候选基因。此外,还可以通过高通量方法深入研究 lncRNAs 调控的基因位点或基因[124]。

1.12 蛋氨酸亚砜还原酶系统(Msr)

蛋氨酸亚砜还原酶(Msr)是一种特殊的抗氧化剂,可以减少蛋白质的蛋氨酸亚砜,同时作为一般的细胞抗氧化剂清除自由基对生物氧化应激起保护作用[125-126]。已经证明对这种抗氧化系统的修饰会影响几种模式生物的寿命。在人体中,蛋白质的蛋氨酸氧化和蛋氨酸亚砜还原酶系统的缺陷与年龄相关的疾病有关,包括癌症和神经退行性疾病。生物氧化应激的特点是细胞和组织中自由基和活性氧含量的升高,细胞的抗氧化能力的降低[127-129]。

细胞和组织中的活性氧可以直接氧化氨基酸,蛋氨酸表面暴露的硫原子很容易氧化成蛋氨酸亚砜,这些产生的蛋氨酸亚砜是翻译后修饰的,可以被蛋氨酸亚砜还原酶逆转录[130]。此外,在哺乳动物中,Msr 的表达水平随着年龄的增长而降低[131],这已在 Msr 表达通常较高的大鼠器官(肝脏、肾脏、大脑)中得到了证实[132]。这表明可能 Msr 系统在长寿和与年龄相关的疾病中有一定作用[131,133-137]。因此,蛋氨酸亚砜的产生被认为是生物衰老的标志物[138]。

蛋氨酸侧链中的硫通过氧化反应会生成 S 或 R 亚砜非对映体[139]。利用蛋氨酸亚砜还原酶 A(MsrA)对蛋白质中的 S 亚硫氨酸亚砜进行分解并降低游离蛋氨酸-s-亚砜的含量,从而促进细胞自由基清除,多项研究报道白藜芦醇可以增加 MsrA 的表达[140-141],通过 Sirt1-FOXO3 通路促进该表达[142],从而延衰老。

2 环境因素对长寿与衰老的影响

2.1 饮食限制

饮食限制是指通过控制食物的合理摄入从而达到营养均衡[143]。AMPK、mTOR 等营养和能量传感器可以通过对营养浓度高低的反应来延长寿命,从酵母到灵长类动物中已经得到证实[143]。饮食限制最初被认为只是通过降低营养代谢导致细胞损伤随时间累积的速率来延长寿命。然而,最近一项针对果蝇的实验表明,饮食限制导致死亡率迅速下降,这表明饮食限制以一种特殊的方式延缓了衰老[144]。对饮食限制的长寿反应受到涉及雷帕霉素靶蛋白(mTOR)[145-147]、AMP 激酶(AMPK)[148]、脱乙酰化酶(Sirtuins)[149-150]和胰岛素/胰岛素样生长因子(IGF-1)[151-153]等途径的积极调节。

2.2 运动

适宜的运动可以强身健体,增强抵抗力,延缓衰老。年龄与体内自由基含量密切相关,人体内的自由基含量与年龄呈正相关。适度的运动能增加体内自由基清除酶的含量并提高其活性,运动通过自由基清除酶清除自由基以延缓衰老[154]。最近还有研究表明运动与长寿相关,在 APOEε4 携带者中,缺乏运动会增加患阿尔兹海默症(AD)的风险[155]。相比,运动较多的 ε4 等位基因携带者在大约 20 年后对患阿尔兹海默症具有更强的抵抗作用。

2.3　地理条件

据调查,在日本和瑞典等低死亡率国家,女性年龄到 100 岁的可能性从 2 千万分之一上升到 50 分之一[156];后续研究表明,这一概率增加到大约 1/2[157]。在美国,大约每 5 000 人中就有 1 人是百岁以上的老人[154],预计这一概率在美国和其他发达国家将显著增加,人口老龄化超过 115 岁[158]。据报道,1996 年死于法国的 Jeanne Calment 年龄为 122 岁[159],2013 年死于日本的 Jiroemon Kimura 年龄为 116 岁[160]。在日本冲绳,人体内的脱氢表雄酮(肾上腺分泌的一种内源性激素,寿命延长的标志)水平下降得更慢[161]。在哥斯达黎加、伊卡利亚岛、希腊等地也有较多的长寿个体出现。这表明不同的地理存在特定的环境因素可能对长寿有一定影响。

2.4　环境压力

越来越多的证据表明,环境压力会造成机体形成抵抗力,充分反应或抵抗各种压力因素,抵抗力在延长寿命方面起着关键作用。虽然具体的机制尚不明确,而且可能只存在于特定的组织或系统中,但许多领域的研究范例表明,环境压力造成的的抵抗力对衰老后的健康有着积极影响。尽管对人类的研究中很少涉及促进抵抗力的干预措施,但动物研究表明,运动(与饮食限制相比)可以更有效地提高抵抗力,抵御各种类型的压力。

3　讨　论

通过对遗传和环境这两种影响长寿的因素研究可知,在遗传上,GH/insulin/IGF-1 途径的作用是促进生长;mTOR 信号通路通过营养浓度高低影响寿命,当营养浓度高时,寿命缩短;营养浓度低时,寿命延长;GH/insulin/IGF-1 途径与 mTOR 信号通路协同作用。AMPK 与 mTOR 一样是营养传感器,其过表达延长寿命。脱乙酰化酶(Sirtuins)家族中的 SIRT1 及其同源物 Sir2 的活性随着 NAD+ : NADH 比率的升高而升高,从而使寿命增长。APOE 调节胆固醇和脂质运输,它的不同等位基因对 LDL 亲和力不同从而对寿命有着不同的影响,ε2 等位基因亲和力较高,延长寿命,ε4 等位基因亲和力较低,寿命缩短。端粒酶是包含 TERT 和 TERC 的复合物,端粒酶活性增强使端粒延长,从而延长寿命。*FOXO3* 基因通过抑制 mTOR 信号通路、慢性炎症转录因子 NF-κB 活性与促进抑癌基因 *P*53 表达以减少癌症发病率来延长寿命。自噬-溶酶体信号通路和长链非编码 RNA 通过调控基因表达促进生长激素和胰岛素/胰岛素样生长因子途径和抑癌基因 *P*53、抑制 mTOR 通路来延长寿命,延缓衰老。蛋氨酸亚砜还原酶系统(Msr)通过增强抗氧化能力,清除自由基并且促进 Sirt1-FOXO3 通路的表达延缓衰老,从而达到长寿的目的。

在环境上,适量的营养摄入能够有效的延长寿命,并且饮食限制受 AMPK 和 mTOR 等营养传感器的调节。运动对于衰老有正反两面作用,适宜的运动可以增强抵抗力和免疫力,延缓衰老;运动过量则会导致身体受损,不正确的运动方式更有可能会加速衰老。不同的地理环境对长寿也有着一定影响,日本、瑞典、美国等地出现长寿老人的概率较高并且仍在不断增加。较强的抵抗力对长寿和延缓衰老也有许多积极影响。

图 1　影响长寿与衰老的各种因素

Fig.1　Factors affecting longevity and aging

4　结　论

长寿是由遗传和环境共同影响的。*Forkhead box O3* 基因、AMP 活化蛋白激酶(AMPK)、脱乙酰化酶家族基因(*Sirtuins*)、端粒酶基因、抑癌基因 *P*53、自噬-溶酶体信号通路、长链非编码 RNA(lncRNAs)、蛋氨酸亚砜还原酶系统(Msr)与寿命延长呈正相关。生长激素和胰岛素/胰岛素样生长因子途径、雷帕霉素靶蛋白信号通路和慢性炎症转录因子 NF-κB 与寿命延长呈负相关。载脂蛋白基因(APOE)根据其等位基因的不同与寿命的相关性也不同。环境因素与上述遗传因素可能存在复杂的相互作用,仍待深入探索。

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