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长寿人群健康老龄发生机制研究进展

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摘 要:随着全球人口老龄化进程的加剧,衰老带来的系统性功能衰退,以及衰老相关疾病的高发对个人健康、社会公共卫生体系及经济可持续发展带来了前所未有的挑战。长寿人群作为成功延缓甚至规避重大增龄相关疾病的独特群体,为研究人类健康老龄提供了理想的自然模型,也是近年来国内外研究的焦点。本文从遗传基础、表达调控及环境生活方式等多个维度系统概述了当前针对长寿人群健康老龄机制的重要研究进展。在解析遗传蓝图对机体系统稳态维系方面,本文以*FOXO3A*、*APOE*等重要基因(突变)为例介绍了其如何通过重塑能量网络、优化脂质代谢谱系及构建免疫韧性来防御分子损伤,并探讨了遗传缓冲与环境筛选在长寿性别差异中的作用;其次,针对基因表达调控在机体健康老龄过程中的作用,本文概述了长寿个体如何通过维持年轻化的DNA甲基化景观和利用非编码RNA网络进行转录调控,以及增强蛋白质稳态与长寿的关联;而在剖析环境-机体互作这一外源性重塑力量时,本文重点关注并介绍了肠道微生态作为代谢与免疫共生引擎的关键角色,其与长寿间的因果关联,以及生活方式干预(如热量限制、运动与心理韧性)的保护效应。深入理解以上多维度的保护因子及其作用机制,不仅是解码人类长寿奥秘的关键,也为未来开发新型抗衰老策略提供了重要的理论依据。未来,以此为基础的转化研究有望推动从“长寿分子发现”向“长寿医学干预”的跨越,从而全面提升人类健康寿命,加速迈向高质量的健康老龄化社会。

关键词:长寿;健康老龄;百岁老人;保护因子;长寿机制
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Research progress on the biological mechanisms of healthy aging in long-lived individuals

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Abstract: With the acceleration of global population aging, the rising prevalence of age-related diseases presents unprecedented challenges to individual health, public health systems, and sustainable economic development. Long-lived

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individuals serve as ideal natural models for researching healthy aging, since they have successfully delayed or even avoided the onset of major age-related diseases. This unique longevity phenotype is not attributed to a single factor but reflects the cumulative protective contributions of multidimensional factors, including genetic endowment, epigenetic modifications, and environmental lifestyles. This article provides a comprehensive review of recent advances in understanding the mechanisms of healthy aging derived from longevity cohort studies. Firstly, we explore the foundational role of the genetic blueprint in maintaining systemic homeostasis. We discuss how important longevity loci, such as *FOXO3A*, *APOE* and *IL-6*, defend against molecular damage by reshaping energy networks, optimizing lipid metabolic profiles, and building immune resilience, while also exploring the roles of genetic buffering and environmental selection in sex differences in longevity. Then, we review current findings regarding gene expression regulation in healthy aging, noting that long-lived individuals exhibit younger DNA methylation landscapes and utilize non-coding RNA networks for transcriptional regulation, and mention the association between enhanced proteostasis and longevity. Finally, we discuss the exogenous influences of environment-organism interactions on the maintenance of healthy aging. We specifically focus on the role of the gut microbiota in supporting metabolism and immunity within longevity cohorts, as well as its causal relationship with longevity, while also summarizing the combined benefits of lifestyle interventions, such as caloric restriction, physical exercise, and psychological resilience. Deeply understanding these multidimensional protective mechanisms is the key to decoding the mysteries of human longevity and provides a theoretical basis for developing novel anti-aging strategies. Future translational research based on these mechanisms is expected to drive the transition from ″longevity molecule discovery″ to ″longevity medical interventions″, ultimately extending human healthspan and facilitating a transition toward a high-quality healthy aging society.

Key words: longevity; healthy aging; centenarians; protective factors; longevity mechanisms

自20世纪以来,抗生素的普及、疫苗技术的革新以及公共卫生体系的完善等因素,推动全球人均预期寿命实现了历史性飞跃[1]。然而,随着人口老龄化的加速,衰老相关疾病(如恶性肿瘤、心血管疾病、神经退行性疾病和糖尿病等)已成为威胁人类健康和社会发展的主要负担[2]。目前,全球65岁以上人口中约80%罹患至少一种慢性疾病,50%同时遭受两种以上共病困扰[3]。而衰老及其伴随的系统性功能衰退,被公认为是此类疾病的首要风险因子。因此,深入探索健康老龄(healthy aging)的生物学机制,寻找延缓衰老、压缩疾病周期的有效策略,不仅是生命科学前沿的重大挑战,更是维系人类社会健康、可持续发展的必然选择。

在健康老龄研究领域,长寿老人以其独特的抵抗衰老特征和遗传优势,成为健康老龄和人类长寿研究的关键自然模型[4]。长寿人群通常被定义为年龄达到90岁及以上的个体,包括九旬老人、百岁老人(100~109岁)及超级百岁老人(110岁及以上)。在同一出生队列中,仅有1%~10%的人能够活到90岁以上,而百岁老人更为稀少,仅占总人群的1/10 000~1/5 000[5]。长寿人群还有一个显著的性别差异特征,女性在百岁老人中占比高达80%左右,性别比(男:女)约为1:4[6,7]。且依托中国规模宏大的百岁老人资源,如中国老年健康影响因素跟踪调查(Chinese Longitudinal Healthy Longevity Survey,CLHLS)[6]、海南百岁老人队列(China Hainan Centenarian Cohort Study,CHCCS)[7]及广西巴马长寿队列[8]等,我国学者开展的大规模遗传学研究揭示了长寿的遗传保护机制,为解析长寿遗传优势提供了独特的视角。在表型优势方面,长寿老人显著地延缓甚至规避了多种重大增龄相关疾病的发生,实现了“压缩发病期”的理想健康老龄模式。因此,与普通老年人相比,长寿老人一生中的住院率明显较低、住院时间 明显较短[9,10];其增龄相关疾病的发病率较低,例如肿瘤患病率在60~80岁人群中为25%~42%,而在90岁以上人群中降至16%,百岁老人更低至0%~4%[11]。这些证据表明,长寿老人掌握了延迟疾病发生的生物学策略。

不同长寿老人在应对衰老相关疾病时表现出明显的异质性,被概括为规避者、延后者和幸存者三种类型[12]。这种表型上的多样性提示,长寿很可能并非由单一路径达成,其背后必然涉及复杂的、由遗传与环境共同决定的生物学基础。其中,遗传因素在决定个体长寿潜能中扮演了非常重要的作用。早期基于双生子研究的数据估计,遗传对人类寿命的贡献率约为20%~30%[13,14];对于长寿家系,遗传因素的贡献度更为突出[15],甚至最新研究表明长寿遗传贡献率能够达到50%[16]。长寿的家族聚集性研究进一步证实了这一点:百岁老人的父母寿命达到90岁以上的几率比普通人高出7倍,其兄弟姐妹活到百

岁的可能性则高出8~17倍[17,18]。不仅如此，百岁老人的后代患衰老性疾病（如心血管病、糖尿病或癌症）的风险显著低于普通人群[19]。这些一致的流行病学证据共同指向一点：长寿个体及其家系极可能携带了某些重要的长寿保护性遗传或非遗传因子。因此，对长寿人群的研究具有难以替代的双重价值：它既是阐明长寿分子机制与调控规律的理论基石，也是驱动公共卫生策略优化、精准医疗干预及抗衰老药物研发的实践源泉。本文旨在系统综述基于长寿人群的健康老龄机制研究进展，重点探讨遗传蓝图支撑的系统稳态，基因表达的表观遗传和非编码RNA的多元调控，以及环境-机体互作的外源重塑等多维度保护机制（图1），以期深入解析驱动健康老龄的系统韧性网络，并为后续因果机制验证及精准抗衰老干预策略的开发提供理论参考。

1　遗传蓝图：长寿人群的系统稳态与抗逆防御机制

1.1　能量网络重塑：营养感应与细胞应激耐受的遗传调控

长寿的遗传基础首先体现在对机体代谢与应激反应通路的精妙调控上，这确保了个体能够高效管理能量并有效应对内外环境压力。

胰岛素/类胰岛素样生长因子-1（insulin/insulin-like growth factor 1，insulin/IGF-1）信号通路与营养感应：能量代谢与长寿过程密切相关，而insulin/IGF-1信号通路是其中跨物种高度保守的长寿调控枢纽[20,21]。在酵母、线虫、果蝇和小鼠等多种模式生

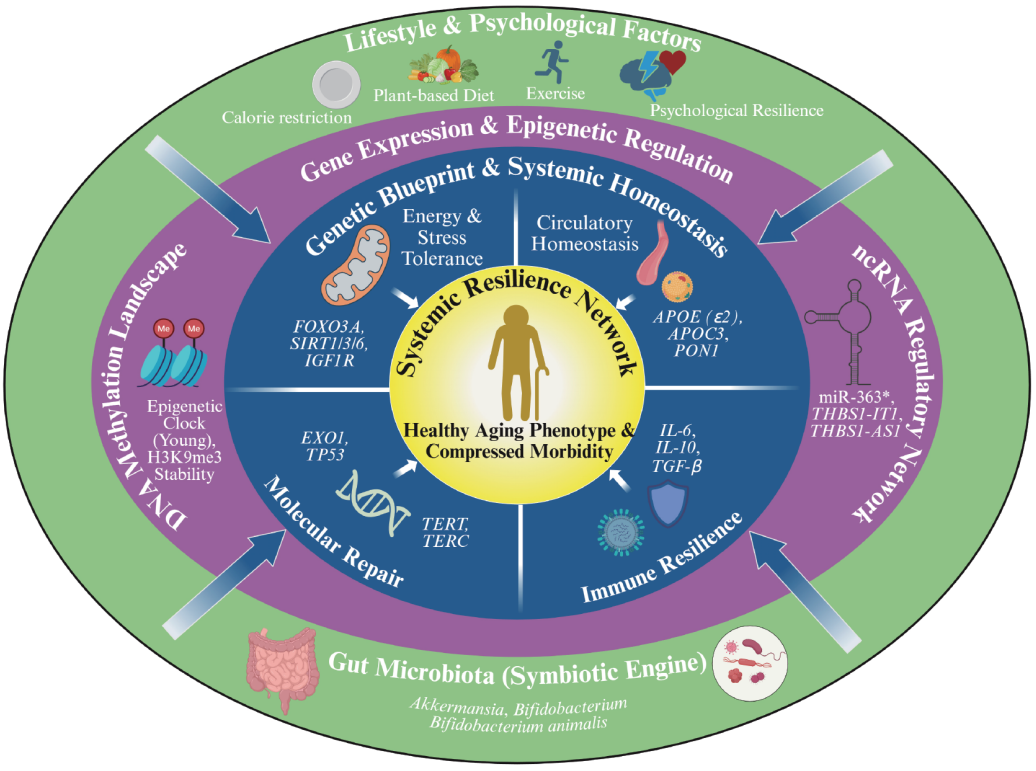

图1　长寿人群健康老龄的多维保护机制与系统韧性网络

该向心圆模型展示了外部环境与生活方式（外环，绿色）通过表观遗传调控层（中环，紫色），与机体遗传背景发生交互并调节各项系统稳态过程（内环，蓝色），最终汇聚形成系统韧性并实现健康老龄表型（核心，金色）。粗箭头指从环境到核心的多维驱动方向。

Figure 1　Multidimensional protective mechanisms and systemic resilience network of healthy aging in longevity populations

This concentric model illustrates how external environmental and lifestyle factors (Outer ring, green) interact with the host genetic background and modulate various systemic homeostatic processes (Inner ring, blue) via epigenetic regulation (Middle ring, purple), ultimately converging to build systemic resilience and achieve a healthy aging phenotype (Core, gold). Thick arrows indicate this multidimensional inward driving direction.

物中，降低insulin/IGF-1信号通路活性均能显著延长寿命[22]。这一规律同样适用于人类：高水平的生长激素（GH）和IGF-1与更高的癌症风险及全因死亡率相关，而低循环IGF-1水平则是长寿个体的普遍特征[23-25]。遗传学证据进一步证实，*IGF1R*基因中与低IGF-1水平相关的功能性突变在长寿人群中显著富集[20]。而作为insulin/IGF-1信号通路的关键下游转录因子，*FOXO3A*（forkhead box O3）基因的多态性（特别是rs2802292 G等位基因）是迄今为止在多个人群中重复性最强的长寿关联位点之一[26-28]。当insulin/IGF-1信号通路信号减弱时，FOXO3A被激活，通过上调抗氧化、DNA修复、自噬及细胞凋亡等一系列下游靶基因，系统性地增强细胞的应激抵抗能力，从而在延长寿命中发挥重要作用。在中国人群中，FOXO3A变异（如rs2802292）的长寿效应已得到广泛验证，并被证实与更优的胰岛素敏感性及糖代谢特征相关，提示其对中国饮食模式具有潜在适应性[29,30]。此外，GWAS分析显示，四条通路与汉族人群长寿高度相关，其中淀粉与蔗糖代谢通路为中国长寿人群长寿位点特异性富集的通路，进一步暗示了长寿遗传机制在环境适应上的新机制[31]。

作为长寿调控的中枢，FOXO3A通过调控庞大的下游基因网络维持细胞稳态，而解析其中直接驱动跨物种长寿效应的关键效应分子一直是该领域的研究热点。2024年的最新跨物种研究取得重要进展，确立了*OSER1*为FOXO3A的直接靶点与关键效应因子[32]。*OSER1*在进化上高度保守，FOXO3A通过直接结合*OSER1*启动子区域激活其转录，从而提升细胞清除活性氧的能力并维持线粒体结构完整性；在人类长寿队列中，*OSER1*的特定遗传多态性已被证实与90岁以上长寿表型显著相关。以上研究完善了从FOXO3A转录调控到OSER1效应执行的分子防御闭环。

Sirtuin家族与能量代谢：去乙酰化酶（Sirtuins）是一类关键的、依赖于NAD^+的能量感应蛋白，在衰老调控中扮演重要的角色[33]。与insulin/IGF-1信号通路相似，Sirtuins的延寿效应也在从酵母到果蝇的多种模式生物中得到证实[34,35]。在人类中，多个Sirtuin家族成员的遗传变异与长寿相关。例如，*SIRT1*（silent information regulator 1）在百岁老人的细胞中呈现高表达，可能有助于延缓神经退行性病变[36]；*SIRT3*（silent information regulator 3）的特定基因型及增强子变异与老年男性的生存优势相关[37,38]；而*SIRT6*（silent information regulator 6）高表达及其功能增强型稀有突变则通过强化基因组稳定性及优化肝脏代谢稳态来促进长寿。

1.2 循环稳态维持：脂质代谢与血管稳态的遗传优化

维持循环系统的生理稳态是实现健康长寿的先决条件，其基石在于机体通过遗传调控对血液微环境进行精细的质量控制。长寿人群的全基因组关联研究（genome-wide association study，GWAS）发现，脂质代谢通路是与人类寿命关联最显著的功能模块之一[39]，这反映了长寿个体在遗传水平上对循环系统代谢负担的有效规避。

其中，载脂蛋白E（apolipoprotein E，*APOE*）基因的多态性构成了这一稳态维护网络的代表性节点。在长寿人群中，显著增加心血管损伤、神经退行性疾病及全因死亡风险的*APOE ε4*等位基因频率极低；相反，具有显著保护效应的*ε2*等位基因显著富集[40-43]。从系统稳态的角度看，*APOE*的遗传变异不仅直接影响个体寿命，还通过优化脂蛋白颗粒的清除效率和调节炎症反应，维持循环环境的长期稳定。此外，长寿个体还通过其他载脂蛋白及抗氧化相关基因的协同作用来增强循环系统的韧性。例如，载脂蛋白*APOC3*（apolipoprotein C3）基因变异以及独特的脂蛋白表型遗传特征，均被证实与卓越的长寿潜力相关[44-46]；同时，与高密度脂蛋白功能紧密相关、能有效抵御脂质过氧化损伤的*PON1*（paraoxonase 1）基因，其特定多态性在长寿人群中亦展现出显著的保护效应[47,48]。在脂质代谢与解毒领域，中国学者的研究揭示了显著的长寿遗传背景种群异质性。以抗氧化酶基因*PON1*为例，在西方人群中常被视为风险因子的192R等位基因，在中国巴马长寿老人中反而呈现显著富集趋势，且与高水平的HDL-C相关。这为基因-环境交互筛选长寿基因提供了重要的中国人群证据[49]。这些遗传优化的脂质代谢谱系共同构建了一道循环防御屏障，确保了长寿个体在极端增龄过程中，其循环系统仍能保持出色的代谢稳态。

此外，最初在百岁老人群体中发现的*BPIFB4*长寿变异体（*LAV-BPIFB4*）[50]被证实是维持循环系统血管稳态的关键遗传因子。自该变异体在长寿GWAS研究中被鉴定后，近期的机制研究进一步揭示了其核心作用：它不仅能通过激活eNOS通路改善

血管内皮舒张功能,最新的研究更证实其能通过减少CD38$^+$促炎巨噬细胞并抑制NAD$^+$水平下降,从而重塑免疫表型并对抗血管衰老与微环境炎症,最终维持长寿个体优越的循环系统稳态[51,52]。

1.3 免疫韧性的维持:“炎症性衰老”的遗传抑制

长寿的另一大遗传策略在于维持一个能够精准响应、不过度反应的免疫系统,其重点是有效抑制随年龄增长而加剧的慢性低度炎症(炎症性衰老),从而在机体内部建立一个稳健的免疫与炎症平衡。炎症性衰老是多种老年病的潜在驱动因素[53,54],而长寿个体在遗传上普遍倾向于维持一种更具稳健性的免疫稳态。这种平衡体现在对促炎和抗炎信号的精细调控上。一方面,长寿与抑制过度的促炎反应相关。例如,在促炎细胞因子白细胞介素-6(interleukin-6,*IL-6*)基因启动子中,与低表达水平相关的−174 C等位基因在长寿人群中频率更高[55,56];同样,与促炎细胞因子干扰素-γ(interferon-gamma,*IFN-γ*)低表达相关的+874A等位基因,也被视为一种促进长寿的抗炎标志。另一方面,长寿也与增强有效的抗炎能力相关。例如,在具有代表性的抗炎细胞因子白细胞介素-10(interleukin-10,*IL-10*)基因中,与高表达水平相关的−1082 GG基因型在百岁老人中更为富集[57];同时,百岁老人血浆中的另一种抗炎因子转化生长因子β(transforming growth factor-beta,TGF-β)的含量也显著高于年轻个体[58]。此外,参与先天免疫防御的*TLR-4*(Toll-like receptor 4)基因变异也与长寿关联[59]。这种“抑促炎、扬抗炎”的遗传倾向,使得长寿个体能够更好地控制慢性炎症,从而规避其带来的有害后果。

1.4 分子损伤修复:基因组与线粒体的双重完整性维护

长寿的实现还依赖于机体维护自身稳定的强大能力,尤其是在基因组和线粒体层面,这套维护系统共同抵抗随年龄增长而累积的分子损伤[60,61]。

DNA修复与基因组稳定性:基因组不稳定性是衰老的重要驱动力之一,而长寿个体普遍展现出超强的DNA修复能力。研究表明,百岁老人的基因组和细胞损伤水平显著低于年轻对照[62-64]。在分子层面,DNA错配修复通路中的重要组分核酸外切酶1(exonuclease 1,*EXO1*)基因,其启动子区域的功能性变异已被证实与女性长寿显著相关[65]。同样,作为基因组守护者的肿瘤蛋白p53(tumor protein p53,*TP53*)基因,其特定多态性(密码子72 Pro/Pro)虽然可能增加癌症风险,却能显著提升个体生存率,表明在衰老过程中DNA修复与细胞凋亡之间存在促进长寿的精妙平衡[66]。

端粒维持机制:端粒作为染色体的保护性帽子,其长度的维持是延缓细胞复制性衰老的关键[67,68]。研究证实,与同龄对照组相比,百岁老人及其后代均保留了更长的端粒[69]。这种优势的遗传基础指向了维持端粒长度的主要功能酶——端粒酶。研究发现,端粒酶逆转录酶(telomerase reverse transcriptase,*TERT*)和端粒酶RNA组分(telomerase RNA component,*TERC*)基因变异在长寿人群中显著富集。这些功能性变异通过优化端粒酶活性,赋予了个体卓越的端粒稳态维持能力,从而有效延缓细胞衰老并促进健康长寿[70]。

线粒体功能与氧化应激防御:线粒体作为细胞的能量工厂,其功能完整性对健康老龄至关重要[71]。长寿与特定的线粒体DNA(mitochondrial DNA,mtDNA) 遗传背景密切相关,例如在欧洲人群中富集的mtDNA单倍群J以及在多个长寿队列中发现的C150T变异,可能通过轻微降低氧化磷酸化效率来减少活性氧的产生,从而降低氧化损伤[72-75]。

1.5 长寿的性别差异机制:遗传缓冲与环境筛选

长寿性别差异的形成是遗传缓冲机制与环境筛选压力共同作用的结果。首先,在核基因组层面,女性拥有的两条X染色体提供了关键的遗传保护。男性处于X染色体半合子状态(hemizygosity),缺乏同源染色体备份,导致其X染色体上的隐性有害突变往往直接表达;相比之下,女性细胞能够通过X染色体随机失活(random XCI)机制建立遗传嵌合体状态,从而有效代偿潜在的有害突变[76]。这一不设防X染色体假说(unguarded X hypothesis)已在小鼠研究中得到证实:拥有XX染色体的个体在寿命上显著优于XY个体,且该效应独立于性腺激素[77]。其次,环境与生活方式的交互亦扮演关键角色。覆盖近17万人的全国性大规模前瞻性队列研究(China National Hypertension Survey)表明,环境因素特别是长期吸烟,是导致中国男性死亡风险显著增加的关键推手,并显著加剧了男女之间的死亡率差异[78]。这种遗传-环境的双重筛选效应可能解释了长寿人群中独特的健康性别差异:女性虽然凭借遗传缓冲优势在数量上占据主导,但往往伴随着较长

的带病生存期;而百岁男性由于经历了缺乏X染色体保护和高风险生活方式的严苛筛选,能存活至今的个体通常具备了更优越的系统韧性(systemic resilience),从而在晚年展现出比同龄女性更佳的生理机能与认知状态。

2 多维表达调控:从表观遗传到蛋白质稳态

在遗传密码之上,表观遗传调控作为连接遗传倾向与环境因素的重要纽带,在决定健康老龄与长寿中扮演着重要的角色。例如,基因相同的双胞胎在基因组甲基化模式上随年龄增长会表现出显著差异,这些差异会影响基因表达和寿命[79]。

2.1 表观遗传调控:DNA甲基化景观与"生物学年轻态"的印记维持

DNA甲基化作为研究最深入的表观遗传修饰之一,其模式会随年龄发生显著变化。在普通人群中,衰老通常伴随全基因组范围的DNA甲基化水平下降,特别是在Alu等重复元件区域[80-83]。然而,长寿个体及其后代展现出对这种表观遗传漂移的强大抵抗力,其DNA甲基化水平的下降显著延迟[84]。基于DNA甲基化模式构建的表观遗传时钟同样表明,百岁老人及其后代的生物学年龄(biological age)远比其按照年代顺序的年龄(chronological age)年轻[85-88]。更深层次的研究揭示,长寿人群不仅维持了整体的甲基化稳定,更形成了独特的甲基化特征。在此方面,中国科学家取得了重要研究进展:他们针对中国百岁老人的甲基化组学研究发现,长寿个体在异染色质区域(H3K9me3)特异性地维持了高甲基化水平;这种独特的表观修饰模式不仅维持了异染色质的结构稳定,更有效抑制了逆转录转座子(如 LINE-1)的转录跳跃,从而极大降低了基因组的不稳定性与突变负荷[89]。

2.2 转录后调控:非编码RNA对长寿的精细干预

除了DNA甲基化,非编码RNA(non-coding RNAs,ncRNAs)——包括微小RNA(microRNAs,miRNAs)和长非编码RNA(long non-coding RNAs,lncRNAs)——也作为另一类重要的表观遗传调控因子参与调控长寿过程。研究发现,一些非编码RNA的表达模式在长寿人群中呈现出独特的保护性特征。例如,通常随年龄增长而表达下调的miR-363*,在百岁老人的B细胞中却能维持在较高水平,并可能通过靶向*PTEN*(phosphatase and tensin homolog)、*BCL2*(B-cell lymphoma 2)、*AKT1*(AKT serine/threonine kinase 1)、*IGFBP5*(insulin-like growth factor binding protein 5)等长寿通路基因发挥作用[90]。同样,研究人员也识别出了一系列在百岁老人中特异性高表达的lncRNAs,如THBS1-IT1与THBS1-AS1,功能性实验证实它们能够通过抑制p16、p21等靶点来有效延缓细胞衰老[91]。这些发现表明,特定的非编码RNA通过其抗衰老作用,构成了潜在的新型内源性长寿保护因子。

2.3 翻译后调控:蛋白质稳态与认知韧性的重塑

基因组与表观遗传决定了长寿的潜能。最新的GWAS分析证实,认知健康的百岁老人具备显著的阿尔茨海默病(Alzheimer's disease,AD)遗传保护特征,其多基因风险评分不到AD患者的1/5,且这种保护效应集中富集在内体-溶酶体系统与免疫系统关键基因(如*GRN*、*TMEM106B*等)上,构成了对抗神经退行性疾病的第一道遗传防线[92]。然而,遗传保护仅是基础,蛋白质稳态的维持才是长寿个体实现健康老龄的执行终端。针对百岁老人脑组织的深度蛋白质组学解析进一步揭示,极端长寿个体在蛋白质质量控制方面存在独特的超常稳态机制。不同于普通衰老过程中常见的蛋白质稳态崩溃,认知功能完好的百岁老人显示出先天免疫与泛素-蛋白酶体系统的协同持续激活特征。最新的研究指出,这种机制通过上调蛋白酶体核心组分及免疫蛋白酶体激活因子,高效清除氧化受损蛋白,并特异性地建立针对可溶性Tau蛋白的分子防线,从而在源头上阻断了病理蛋白向神经纤维缠结转化的进程[93]。这种高效的异常蛋白清除机制解释了为何部分百岁老人虽然存在Aβ斑块,却能免于神经元死亡和认知崩溃。

其次,翻译后调控在维持神经元连接中发挥决定性作用,长寿个体的蛋白质稳态还涉及突触蛋白质组的动态重塑与周转效率。基于大规模人脑队列的蛋白质组学证据表明,认知韧性的实现高度依赖于突触蛋白丰度的整体保留以及线粒体生物能量代谢的协同增强[94],即可能通过在翻译后水平上维持突触后致密区蛋白的高表达,并同步上调线粒体氧化磷酸化复合物,构建能量与结构的双重稳态,从而有效缓冲神经退行性病理的冲击。这种针对突触蛋白的翻译后质量控制能力在对抗衰老过程中尤为重要。2026年的最新研究揭示,普通衰老的病理特征

本质上是一场突触蛋白的周转危机,即伴随衰老进程,神经元产生的大量难降解突触蛋白因缺乏正确的翻译后降解标签,在小胶质细胞溶酶体中异常堆积,最终引发了胶质细胞的代谢衰竭与免疫稳态崩溃[95]。综上所述,长寿个体之所以能保持认知韧性,其可能机制在于拥有更高效的翻译后周转动力学,既通过线粒体供能维持了功能性突触蛋白的丰度,又有效避免了老化突触蛋白在微环境中的病理性蓄积。

3 环境-机体互作:驱动长寿表型的外源性重塑力量

除遗传背景外,外部环境因素尤其是环境与生活方式的交互作用,同样是决定个体长寿潜能能否实现的重要因素。研究估计,饮食、运动、健康习惯及心理社会因素等非遗传因素对人类寿命变异的贡献率可达50%[96]。因此,系统探讨与长寿相关的非遗传因素,对于理解健康老龄的全貌至关重要。

3.1 肠道微生态:驱动代谢稳态与免疫防御的共生引擎

肠道微生物群作为宿主与外部环境之间敏感和高度可塑的交互界面,在维持机体稳态以及调控衰老与长寿过程中发挥重要的内在调节作用。在普通衰老过程中,肠道微生物群通常表现为多样性下降和潜在致病菌增加[97,98]。然而,百岁老人展现出一种独特的、更具韧性的肠道微生物生态系统。研究发现,长寿老人的肠道微生物群不仅能够抵御共生菌群——瘤胃球菌科(*Ruminococcaceae*)的丰度衰减,更通过富集一系列具有健康益处的次优势分类群,如阿克曼氏菌属(*Akkermansia*)、双歧杆菌属(*Bifidobacterium*)以及克里斯滕森菌科(*Christensenellaceae*),从而构建出一种新型的动态健康稳态[99,100]。例如,在中国的百岁老人队列中,也发现了与长寿相关的特定菌种(如*Bacteroides fragilis*、*Parabacteroides merdae*等)的富集[101]。

值得注意的是,为了突破传统横断面研究中因果关系不明的局限,最新的孟德尔随机化(Mendelian randomization,MR)研究利用遗传变异作为工具变量,为解析菌群与长寿的因果架构提供了关键证据。大规模MR分析证实,*Alistipes*(阿里斯替普菌属)[102]与*Coriobacteriaceae*(红蜡菌科)[103]的丰度增加不仅仅是长寿的伴随现象,还与长寿及健康老龄存在显著的正向因果关联。同样重要的是,双向MR分析进一步揭示了长寿宿主对菌群的主动筛选效应:携带长寿相关遗传变异的个体,其肠道微环境倾向于特异性富集*Prevotella*(普雷沃氏菌属)并降低*Bacteroides*(拟杆菌属)的丰度[103]。这一基于双向因果推断的证据链提示:肠道微生态与长寿之间存在显著的双向因果关系——有益菌群的改变既是驱动健康老龄的潜在原因,亦是宿主长寿遗传背景主动筛选的结果。

更重要的是,一系列功能性研究证实了肠道微生物在调控寿命中的因果作用。益生菌补充剂的研究表明,特定菌株能够延长模式动物的寿命。例如,摄入 费氏丙酸杆菌(*Propionibacterium freudenreichii*) 或加氏乳杆菌(*Lactobacillus gasseri*)SBT2055能够通过激活先天免疫系统或调节应激反应途径,显著延长秀丽隐杆线虫(*Caenorhabditis elegans*)的平均寿命[104,105]。而在哺乳动物模型中,源自长寿村百岁老人的动物双歧杆菌(*Bifidobacterium animalis*)RH所分泌的胞外多糖(exopolysaccharide,EPS)展现出显著的抗氧化活性[106];此外,动物双歧杆菌乳亚种(*B. animalis* subsp. *lactis*)LKM512还能通过上调肠道内多胺的产生来抑制结肠衰老,从而有效促进小鼠的长寿[107]。粪便微生物群移植(fecal microbiota transplantation,FMT)为肠道菌群调控长寿提供了直接证据:研究发现,将年轻供体的菌群移植至非洲青鳉鱼(*Nothobranchius furzeri*)可使其中位寿命显著延长[108];而将长寿老人的菌群移植至小鼠体内,则能有效改善其肠道屏障功能并降低全身炎症水平[109]。其中,代表性益生菌如阿克曼菌(*Akkermansia muciniphila*),其移植不仅能延长早衰小鼠的寿命,还能通过改善肠道屏障、抑制炎症和产生有益代谢物(如短链脂肪酸)来系统性地延缓衰老[110]。这些发现共同揭示,靶向肠道微生物群可能成为一种极具前景的新型抗衰老疗法。

3.2 生活方式干预:热量限制、运动与心理韧性的协同效应

在由遗传背景与肠道微生物群共同构建的生理基础之上,个体的行为与生活方式作为高度可塑的调控变量,是塑造其健康轨迹并驱动长寿潜能最终转化为长寿表型的重要主动因素。

长寿的膳食模式:对全球长寿人群的观察表明,其饮食模式普遍具有两大普遍特征,即适度的能量

摄入和以植物性食物为主的膳食结构。热量限制(calorie restriction,CR)作为一种在果蝇[111]及小鼠[112,113]等多种模式生物中被反复验证的延寿策略,其健康获益在人类研究中也得到了初步证实[114-117]。研究发现,百岁老人的生理表型(如较低的体温、胰岛素水平及氧化应激标志物)与CR志愿者的表型相似,提示长期适度的热量摄入是其实现健康长寿的机制之一[100,114,115]。与此同时,这些长寿人群的膳食结构高度一致,普遍富含谷物、蔬菜、水果和豆类,并严格限制红肉摄入[118]。这种高质量的植物性饮食模式(plant-based dietary patterns,PBD)已被多项大规模前瞻性队列研究证实,与2型糖尿病(type 2 diabetes,T2D)[119,120]、冠心病(coronary heart disease,CHD)[121]、帕金森病(Parkinson's disease,PD)等神经退行性疾病[122]、衰弱症[123]及全因死亡率[124]的风险显著降低直接相关。

规律的体育锻炼:积极的身体活动是长寿人群的另一个共同特征[118]。规律锻炼的益处已在动物模型和大规模人群研究中得到证实。早期前瞻性研究指出,保持充足的身体活动能将全因死亡率和心血管疾病死亡率降低约30%[125,126]。2019年,英国生物样本库(UK Biobank)超过30万人的分析显示,高水平的身体活动还与预期寿命延长显著相关[127]。此外,这种健康获益还呈现出明确的剂量-反应关系。大规模汇总队列分析表明,即使是极低水平(每周10~59 min)的闲暇时间体育锻炼也能产生明显的生存获益;而随着运动强度的增加和时程的延长,其对死亡风险的降低作用更加显著,高强度运动最高可使预期寿命增加4.5年以上[128,129]。

健康习惯与心理韧性:除了饮食和运动,一系列积极的健康习惯与心理特质在驱动长寿潜能实现中亦发挥重要作用。大规模纵向研究显示,不吸烟、维持健康的体重指数(body mass index,BMI)、规律运动、适度饮酒以及高质量膳食这五项因素,能够使个体的预期寿命显著延长12~14年[130]。尤其是吸烟,作为加速衰老及增加中青年死亡风险的明确因素[131],在长寿人群中极为罕见[132];针对中国重庆[133]与海南[134]百岁老人的调查均证实,极低的吸烟率是该群体共同的生活习惯特征。此外,长寿与积极的心理状态及特定的人格特质密切相关。针对东京[135]、美国佐治亚州[136]及长寿家庭[137]的队列分析表明,百岁老人通常在五大人格模型中表现出更高的责任心、外向性与开放性,以及更低的神经质(即更强的情绪稳定性)。这些心理特质通过促进更健康的行为选择和更有效的压力管理,共同构成了维持健康老龄的内在保护性机制。

然而,流行病学证据也揭示了一个长寿悖论:部分百岁老人并未严格遵循健康生活方式指南,却依然实现了健康长寿。例如,针对阿什肯纳兹犹太百岁老人的研究显示,其在吸烟、饮酒及体力活动等方面并未表现出比普通人群更健康的行为模式[138]:具体而言,该人群的每日饮酒率与普通受访者相当,甚至有高达59.6%的百岁男性拥有吸烟史。这一现象提示,长寿并非单一环境因素的产物,而是基因-环境交互作用的结果。这类具有不良习惯的长寿者可能受益于特殊的基因缓冲机制,即其携带的保护性遗传变异赋予了机体对环境毒素或代谢压力的超常耐受性,从而抵消了不良表观暴露的负面效应。例如,研究发现,CETP蛋白的I405V变异与长寿显著相关,其作用机制在于该变异能诱导产生直径更大的HDL和LDL颗粒,这种特殊的脂蛋白表型与较低的高血压及心血管疾病风险相关[45];研究还证实,*FOXO3A*的长寿相关等位基因能显著降低冠心病等年龄相关疾病的患病风险并促进极长寿表型,具有强大的应激防御与损伤修复能力[26]。因此,这些拥有不良生活方式却依然长寿的个体诠释了基因与环境的动态交互机制:在面对吸烟或饮酒等环境压力时,有利的遗传背景发挥了关键的缓冲与保护作用,使机体得以规避或显著减轻不良生活习惯带来的病理损伤。

4 总结与展望

长寿人群研究已经清晰地表明,人类的健康老龄并非源于单一遗传位点或孤立分子通路的独立驱动,而是遗传蓝图、表观重塑、蛋白稳态、代谢稳态、免疫韧性、肠道微生态与生活方式等多维因素,通过多层次、多时序的交互作用,共同构成了驱动健康老龄的多维保护机制与系统韧性网络。尽管当前大量基于横断面关联的研究已经提示了值得关注的代表性通路(如*FOXO3A/APO*E变异、SIRT/NAD^+轴、端粒稳态及特征性微生物群落),但该领域的主流研究仍多停留在相关性描述阶段,这些因子驱动长寿的因果关系及体内功能机制尚未被系统性阐明。为此,未来研究的重点目标在于打破相关性研究的局

限,从“关联发现—因果验证—临床转化”的完整链条出发,把握由群体关联到分子机制、由动物模型到临床应用的转化路径。

4.1 方法突破:构建从时序关联到功能因果的证据链

要解码长寿的深层机制,必须超越单一时间点的快照式研究,构建一套融合“纵向多组学追踪”与“遗传因果推断”的严密逻辑体系。一方面,未来的队列建设应重点从横断面采样转向高质量的纵向时序追踪,结合甲基化时钟等量化工具,捕捉代谢物或蛋白水平改变先于健康状况演变的“时间优先性”。在此基础上,为突破观察性研究中环境混杂因素的瓶颈制约,MR分析已成为筛选长寿驱动因子的金标准。近期的MR研究已成功剔除饮食与药物的干扰,确立了一批具有明确因果属性的靶点:例如,*Alistipes*[102]与*Coriobacteriaceae*[103]丰度的增加被证实与长寿存在显著的正向因果关联。这类基于遗传工具变量的发现,有力地将这些生物标志物从伴随性结果提升为潜在的驱动性原因和干预靶点。

然而,统计学层面的因果推断仍需生物学功能的最终确证,即必须完成从候选靶点到功能实体的跨尺度验证闭环。针对MR或多组学锁定的关键分子,未来的核心任务是开展严格的功能获得性实验。这要求研究者利用CRISPR/Cas9基因编辑或AAV介导的组织特异性转导技术,在模式生物中复刻长寿特征以观察抗衰老表型。该领域的典范性工作包括:将*LAV-BPIFB4*长寿变异体导入老年小鼠体内,其成功逆转心血管衰老的实验结果直接证实了该基因的因果驱动力[50];同样,利用无菌小鼠进行的粪菌移植实验也确证了百岁老人特征菌群对宿主免疫稳态的主动重塑作用。综上所述,只有将研究范式从寻找相关性升级为确证因果性,才能真正筛选出那些能够支撑临床转化的核心长寿靶点。

4.2 理论深化:从静态平衡到系统韧性——构建长寿的动态适应模型

尽管目前长寿生物学领域尚未形成一个统一公认的理论范式来解释人类极端长寿的所有特征,但随着多组学证据的积累,以及基于前文梳理的遗传、分子及环境证据,我们尝试在此提出一个整合性的系统适应性稳态框架,旨在为理解长寿的生物学本质提供一个新的理论视角。针对百岁老人的表型特征,我们提出长寿的本质并非简单的无损伤,而是内稳态空间在全生命周期中的延缓坍缩与动态扩展。这一过程通过遗传界限与环境互作的双重机制,共同塑造了机体卓越的系统韧性。

首先,遗传蓝图决定了内稳态空间容忍压力的物理边界。长寿个体的遗传背景(如*FOXO3A*/*APOE*变异)并非仅仅是为了规避特定疾病,更本质的是设定了更高的生理储备阈值。这种高阈值赋予了机体更广阔的缓冲空间,使其在面临等量的衰老压力(如Aβ沉积或炎症负荷)时,仍能将生理参数维持在功能崩溃的临界点之上。这解释了为何百岁老人即使携带病理特征,仍能实现带病生存且保留认知功能——其核心优势在于其内稳态空间未随年龄增长而过早坍缩。其次,高效的稳态调控决定了压力累积的速率。如果在遗传上设定了更大的空间容量,那么蛋白质稳态网络(如异常蛋白清除)与肠道微生态(提供额外的代谢支持)则构成了高效的泄压阀。它们通过持续清除累积的分子熵增,显著降低了衰老压力填满该空间的速率,从而在时间维度上拉长了健康寿命。最后,长寿并非静止的平衡,而是压力驱动下的动态重塑。系统韧性的核心在于其适应性。长寿机体在面对持续的内部噪音与外部压力时,并未表现为被动的损耗,而是展现出一种反脆弱式的重塑能力:适度的衰老压力反而激活了更灵敏的应激感应网络(如DNA损伤修复与抗氧化防御的超量恢复),使得稳态能力在压力作用下得以重新塑造与加强。

综上所述,系统韧性模型为理解长寿提供了一个统一的理论框架——即通过最大化遗传赋予的空间容量与优化环境互作下的泄压效率,并在动态压力中不断重塑适应性,长寿个体最终成功抵抗了内稳态空间的坍缩,维持了高度有序的生命系统。

4.3 转化路径:设计分层化的长寿医学干预策略

基础研究的最终归宿是提升全人类的健康寿命。基于长寿人群发现的确证性靶点,未来的干预策略不应局限于传统的药物开发,而应转向长寿仿生(longevity biomimicry)——即通过医学手段复刻百岁老人天然携带的保护性机制,并依据其可转移性与可干预性实施分层转化。

第一,遗传与分子优势的功能性复刻。长寿个体的遗传变异虽然是先天固定的,但其下游的保护功能是可转移的。针对已确证的长寿相关变异体,基因疗法与小分子模拟物展现出了巨大的转

化潜力。例如，已在动物模型中证实，导入*LAV-BPIFB4*变异体可显著逆转心血管衰老并改善内皮功能，确立了该变异体作为“可转移长寿药物”的开发前景[50]。此外，基于长寿脑部蛋白质组学研究发现的蛋白酶体激活因子及突触韧性蛋白，开发特异性的激动剂以模拟长寿脑的认知韧性，将为神经退行性疾病的防治提供源于长寿人群的创新方案。这类针对特定分子靶点的医疗级干预，需遵循严格的药物研发流程，重点服务于高风险或老年病群体。

第二，微生态与代谢优势的生态移植。相较于遗传操作，肠道微生态具有更高的可干预性与可塑性。基于MR研究确证的长寿特征菌群（如*Alistipes*和*Coriobacteriaceae*）具备很高的移植价值潜力。未来的干预策略应致力于开发下一代精准益生菌、工程菌或后生元制剂，旨在将长寿个体的代谢与免疫优势移植给普通人群，重建以抗炎和代谢稳态为特征的肠道微环境。由于此类干预安全性高、可及性强，应确立为第一层级的非侵入性手段，用于广泛的健康促进。

第三，系统韧性的生活方式重塑。长寿研究揭示的表观遗传可塑性表明，通过环境干预重塑系统稳态是完全可行的。未来的公共卫生策略应推广模拟长寿人群生活方式的干预方案（如模拟热量限制的饮食模式、增强心理韧性的认知训练），通过表观遗传重编程激活内源性修复机制（如FOXO3A网络），实现低成本、广覆盖的衰老干预。

此外，保障这一转化路径的高效与可靠，还须并行推进数据共享与方法学标准化，并扩大队列的种群多样性，以确保研究结论的普适性。与此同时，长寿研究不仅是生物学问题，更伴随重要的伦理与社会考量，科研与临床推广应同步开展伦理评估，关注资源分配与代际公平。综上所述，通过构建多组学纵向队列、实施严格的因果推断并开展跨维度的功能验证，长寿研究正经历从描述性现象向功能性机制的根本跨越。同时，基于长寿仿生的转化视角，我们不仅能从长寿人群的自然实验中汲取生物学智慧，更能以此为蓝图，将具有明确因果效应的保护性特征转化为可转移、可干预的抗衰老策略。这种从天然生存优势向普适性医学干预的成功跨越，将最终催生出真正能有效延缓衰老、提升全人类健康寿命的系统性方案。

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