衰老与疾病及饮食中主要营养素的抗衰老作用

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摘　要:目的 概述衰老与疾病的关系及饮食中主要营养素的抗衰老作用研究进展。**方法** 结合大量文献,探讨了衰老的本质,引起疾病的原因,阐释饮食主要营养抗衰老机制。**结果** 衰老本质上是细胞随时间微观损伤积累产生衰老细胞(SC),伴有衰老相关分泌表型(SASP)细胞特异性表达增加,引起全身性慢性炎症及其免疫系统功能下降,是不同年龄相关人类疾病共同潜在病因,也增大了老年人患癌症和糖尿病以及COVID-19大流行等严重疾病的频率和易感性。衰老与年龄不呈正相关,科学的饮食营养能延缓衰老。**结论** 在控制碳水化合物摄入量的前提下,复合碳水化合物与其代谢中间产物,可通过调节细胞衰老、蛋白质平衡和炎症来抗衰老。植物蛋白及蛋白质和高碳水化合物类饮食以低于1∶10的比例,在衰老过程中有利健康和延长寿命。脂肪酸,特别是富含ω-3-多不饱和脂肪酸(PUFA)在改善与年龄相关疾病,显示有益作用。饮食中维生素如D、E、B2,合适的矿物质如Mg、Zn、Fe等,植物多酚类化合物及益生菌均有抗衰老,促进健康长寿的作用。

关键词:衰老; 衰老细胞; 疾病; 营养
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Aging and Disease and the Anti-aging Effects of Major Nutrients in Diet

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Abstract: Objective The relationship between aging and diseases and the research progress on the anti-aging effects of major nutrients in diet were reviewed. **Methods** Based on extensive literature, this study explored the essence of aging, investigated the causes of diseases, and elucidated the mechanisms of anti-aging effects of major nutrients in diet. **Results** Aging is essentially the accumulation of microscopic cell damage over time, resulting in the formation of senescent cells (SC). This process is accompanied by an increase in the expression of senescence-associated secretory phenotype (SASP) in cells, leading to systemic chronic inflammation and a decline in immune system function. Aging is a common underlying factor for various age-related human diseases, and it also increases the frequency and susceptibility of serious diseases such as cancer, diabetes, and the COVID-19 pandemic in the elderly. Aging is not positively correlated with age, and scientific dietary nutrition can delay aging. **Conclusion** Under the premise of controlling carbohydrate intake, complex carbohydrates and their metabolic intermediates can act as anti-aging agents by regulating cell aging, protein balance, and inflammation. A diet with a ratio of plant proteins and proteins to high carbohydrates of less than 1∶10 is beneficial to health and longevity during the aging process. Fatty acids, especially those rich in ω-3 polyunsaturated fatty acids (PUFAs), have been shown to be beneficial in ameliorating age-related diseases. Vitamins such as D, E, and B2, appropriate minerals such as Mg, Zn, and Fe, plant polyphenolic compounds, and probiotics in the diet all have anti-aging effects and promote health and longevity.

Keywords: aging; senescent cells; disease; nutrition

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1 引 言

人体健康、衰老和疾病是若干遗传、非遗传和环境因素动态相互作用和调节的结果。年轻健康个体调节复杂系统从而协调地工作,通过感知饮食营养的可用性和反应,调节细胞分裂和再生,阻止异物和感染因子,有效识别并清除机体有毒有害物质,保持神经反应的记忆和速度,维持细胞和组织的功能稳态。

在衰老和疾病期间,机体调节系统失去控制,任何预防或治疗方法都试图恢复“健康”的内稳状态[1]。衰老与疾病密切联系,衰老被认为是不同年龄相关人类疾病包括关节炎、糖尿病、神经退行性疾病、肌少症、癌症和心血管疾病共同潜在病因[2-3]。衰老也显著提高了老年人患癌症和糖尿病以及 COVID-19 大流行等严重疾病的频率和易感性[4-5]。

随年龄增长,衰老是不可避免的,它与生长和发育不同,因其随机和多面性,衰老不是程序化过程[6],与年龄不呈正相关[7],它与细胞、组织或器官老化有关。可通过非遗传因素如锻炼、生活方式和饮食营养等动态调节,营养被认为是最有效的调控因素[8]。

2 衰老与疾病及相互关系

衰老过程的可观察宏观表型,本质上是细胞随时间微观损伤积累的结果[9]。细胞是机体的基石,机体衰老是由身体的大多数细胞、组织或器官逐渐老化引起的。细胞衰老最早是 1961 年由 Hayfick 和 Moorhead 在成纤维细胞中发现的[10]。经多年的观察,现已有确凿证据说明细胞衰老是“衰老的标志”[11]。这些细胞被称为衰老细胞(SC),其特征是端粒缩短、肥大、染色质结构改变、DNA 损伤和活性氧(ROS)积累,激活细胞周期抑制通路(p53, p16Ink4a 和 p21CIP1)与衰老相关 β-半乳糖苷酶活性,抗凋亡细胞死亡,形成衰老相关的异色灶[12-13]。此外,SC 还伴有被称为衰老相关分泌表型(SASP)的慢性促炎行为,包括促炎细胞因子和生长因子的细胞特异性表达增加[14]。

在生命周期中,SC 的发展是一个复杂的过程,细胞受到各种内外应激源的进攻,机体应激反应失调与 SC 的发展间存在正相关[15]。随着 SC 在组织和器官中积累,SASP 的长期存在,通过旁分泌效应影响附近的健康细胞,导致促炎症和促肿瘤环境,引起系列与年龄相关疾病[14]。

同时,机体免疫系统伴随衰老过程,其免疫器官、免疫细胞老化及细胞因子活性降低,免疫功能减弱。人体免疫系统对抵御病原体入侵非常重要,也是组织修复和再生以及识别和清除受损宿主细胞包括 SC 必不可少的[16-17]。SC 是机体衰老的关键驱动因素,衰老的免疫细胞是 SC 中最危险的细胞。SC 有免疫原性,年轻健康个体免疫系统能有效识别并清除 SC,减少机体积累[18]。随年龄增长,免疫系统逐步重塑,阻碍免疫监视和吞噬潜能,导致 SC 识别和清除障碍。衰老个体积累的 SC 分泌更多的 SASP,帮助衰老细胞对抗免疫系统的清除,促进免疫功能的生理性下降及其全身性慢性炎症,导致人体疾病包括关节炎、糖尿病、神经退行性疾病、癌症及病毒如 COVID-19 感染,延缓伤口愈合,降低对某些类型疫苗产生抗体反应的能力。如此循环,SC 会越来越多,加速器官衰老,从而促进全身衰老。这也是衰老个体抵御病原体入侵能力差、疾病易感性强的原因。

研究观察到,小鼠造血细胞中的 DNA 损伤和衰老,驱动细胞衰老的系统性效应[19]。SC 规避免疫系统清除时,似于癌细胞[20]。探索细胞衰老与免疫系统的相互关联,已成热点的研究领域。

3 饮食主要营养素及其抗衰老作用

人体需要的营养除水外,主要有碳水化合物、蛋白质、脂肪、维生素、矿物质、益生菌以及植物化学物质如多酚、胡萝卜素等。饮食中主要营养通过对衰老相关因子及信号通路的调节,以预防疾病与抗衰老。

3.1 碳水化合物

碳水化合物是细胞能量的主要来源,在细胞结构和信号传递中的作用已为人所知。碳水化合物摄入与肥胖和糖尿病等慢性疾病有关,其代谢在衰老过程中具有重要意义[21]。在模型生物中,已被证明富含葡萄糖和果糖的饮食可以加速衰老,而减少碳水化合物的摄入通常可降低糖尿病等疾病的严重程度[22]。然而,复合碳水化合物或其衍生物(杂多聚糖)与其代谢中间物,可以抑制细胞衰老,促进健康老龄化。

从草药黄芪中提取的杂多聚糖,能抑制细胞衰老的发展,通过 mTOR 途径促进细胞自噬,在体外和体内缓解肝细胞的衰老[23]。黄芪多糖可以减少葡萄糖诱导的大鼠主动脉内皮细胞过早衰老和炎症小体激活[24]。D-半乳糖诱导的衰老小鼠模型,用黑果龙葵杂多糖,可调节 AMPK/SIRT1/NF-κB 信号通路和肠道菌群,改善小鼠的炎症和抗衰老[25]。研究发现,当归多糖在造血细胞和内皮祖细胞中,有抗细胞衰老和抗氧化特性。在该模型中,也观察到当归多糖有体内抑制细胞衰老和改善脑衰老作用[26-27]。蘑菇中分离的多糖 TLH-3 能在体外缓解过早衰小鼠的细胞衰老,并改善体内衰老标志物和 SASP[28]。药用植物枸杞中提取的多糖,可抑制氧化应激诱导的人晶状体上皮细胞衰老和凋亡[29]。海洋硫酸多糖 Fucoidan 缓解内皮细胞的衰老,

改善其生存、增殖和功能,这与增强体内新生血管的潜力有关[30]。C57BL/6J 小鼠每日服用红参浆果中提取的多糖,通过 Treg 和 NK 细胞增殖,改善免疫衰老和炎症衰老指标,减弱胸腺退化[31]。

在模型生物中,代谢复合碳水化合物中间产物通过调节营养信号通路,延长寿命。秀丽隐杆线虫用海藻糖处理,通过降低胰岛素/胰岛素生长因子-1 通路和抵消压力源,抑制线虫衰老[32]。秀丽线虫通过放大线粒体丙酮酸代谢,提高对氧化应激的耐受性[33],或经三羧酸循环代谢物如苹果酸和富马酸,调节转录因子 DAF-16/FOXO 与组蛋白去乙酰化酶 SIR-2.1 和增加 NAD+和 FAD 辅因子的数量,提高抗氧化能力,延长寿命[34]。补充如 N-聚糖和 N-乙酰氨基葡萄糖,通过(内质网)ER-相关的蛋白质降解、蛋白酶活性和自噬减少蛋白质的聚集,抗线虫衰老[35]。在衰老的酿酒酵母细胞中,海藻糖的积累引发了抗衰老反应,增加乙醇产量[36]。壳寡糖已被用于治疗与年龄相关的疾病的临床前研究[37]。

总之,复合碳水化合物和其代谢的中间产物可以通过调节细胞衰老、蛋白质平衡和炎症来抗衰老。然而,必须控制碳水化合物摄入量,高碳水化合物饮食与死亡风险增加有关[38]。

3.2　蛋白质和氨基酸

蛋白质和氨基酸是细胞的主要结构和功能成分,也是人类饮食的重要组成部分。人们已经尝试确定饮食中适当的碳水化合物与蛋白质的比例,促进健康衰老。

证据表明,低蛋白质(来自蛋白质的热量<10%)和高碳水化合物类饮食,通常以低于 1∶10 的比例,在衰老过程中有利健康和延长寿命[39]。即使是短期的低蛋白高碳水化合物饮食,也能改善小鼠的胰岛素、葡萄糖、脂类和稳态模型评估(HOMA)水平等代谢健康指标。令人惊讶的是,尽管总能量摄入量增加,但这与严格的卡路里饮食限制效果相似[40]。若老年人摄入高蛋白饮食(20%以上的热量来自蛋白质)全因死亡率提高 75%,癌症风险增加 400%。表明在衰老过程中高蛋白摄入的有害影响[41]。

此外,蛋白质代谢受损似乎与细胞衰老和生物体寿命密切相关。一项比较不同物种间纤维细胞蛋白质组学特征研究得出:长寿动物高度丰富的细胞蛋白质,通常有较低的周转率,最终产生较低的氧化应激和高效的能量管理[42],限制蛋白质合成可以在细胞和机体水平抑制细胞衰老[43]。在 SC 中,细胞蛋白质合成、折叠和降解(蛋白质内稳态)之间的平衡被破坏,维持蛋白质内稳态被认为是调节衰老的关键应对机制[44]。蛋白质消耗、细胞代谢和能量稳态密切相关,它们可以影响动物与人体的寿命。食用富含蛋白质的饮食,可加速小鼠的组织衰老和 SASP 发展,从而促进衰老。在健康中年人中,富含蛋白质饮食与血浆 NAD+水平降低和炎症有关,表明缺乏蛋白质的饮食,可能通过改善细胞能量消耗和 SIRTs 等酶表达,延长寿命[45]。

特别是支链氨基酸(BCAA)代谢与调节衰老有关[46]。补充 BCAA 可改善鼠软骨的生物合成,缓解 ROS 诱导应激,延长衰老小鼠寿命[47]。在诱导衰老肝癌细胞中补充 BCAA,能增强肿瘤抑制[48]。中年受试者中更高循环 BCAA 水平与较长的端粒长度呈正相关,抑制全身细胞衰老[49]。然而,关于膳食蛋白质和特定氨基酸对细胞和机体衰老影响的研究较少。

除了蛋白质摄入的数量外,饮食中蛋白质的来源(动物或植物)似乎也强烈影响细胞衰老与人体寿命[50]。

3.3　脂肪酸

脂肪酸是细胞必需的结构和信号分子,它们在生长、发育与衰老等方面发挥重要作用[51]。特别是 ω-3-多不饱和脂肪酸(PUFAs)在改善与年龄相关疾病,包括炎症、骨质减少、Ⅱ型糖尿病,并赋予血管舒张特性,显示有益作用[52]。SC 表现出细胞脂质积累增加,脂质代谢紊乱[53]。脂质组成在 SC 中发生全局变化,导致细胞膜重构,加速 SASP 的发展[54]。

食物中含较高海洋 ω-3 PUFAs 水平,可降低过早死亡风险[55]。富含 ω-3 脂肪酸的鱼油具有免疫调节和抗免疫衰老活性。食用鱼油可以加速免疫细胞的吞噬活性,增加 CD4+和 CD8+淋巴细胞,减少炎症细胞因子,增加老年人的肌肉力量[56]。罗格列酮诱导衰老 C57BL/6 小鼠补充鱼油,能改善骨质减少,提高衰老小鼠骨密度,增加抗炎细胞因子,减少促炎细胞因子[52]。衰老小鼠饲喂富含 ω-3 脂肪酸的鱼油,可减轻从心室肥厚到心脏重构的各种心脏功能障碍[57]。此外,脂类有调节复制和应激诱导的细胞衰老作用[58]。脂肪酸合酶在小鼠肝星状细胞和人原代成纤维细胞衰老程序的发展和启动,有重要作用[59]。

在肾移植受试者中摄入海洋 ω-3 PUFAs,可降低细胞衰老和 SASP 损伤的风险,促进机体恢复。食用 ω-3 脂肪酸可以通过保持人体免疫细胞的端粒长度,减少其复制性衰老[60]。中年受试者持续 4 个月补充 ω-3 脂肪酸,端粒酶活性得以维持,同时减轻压力和炎症标记[61]。D-半乳糖诱导的衰老小鼠,消耗 ω-3 PUFA 能减少细胞 DNA 损伤,保护肝脏和睾丸,抑制端粒缩短[62]。

猪补充 9 周亚麻籽油,发现能抵制与年龄相关的

TRF-1 表达,这可能与 PUFAs 促进端粒长度有关[63]。在应激诱导的衰老血管内皮细胞中补充 EPA 和 DHA,观察到:能通过抑制 DNA 损伤和增强细胞抗氧化潜能,衰减细胞衰老及其生物标志物。

3.4 维生素和矿物质

某些维生素也有调节细胞衰老方面的重要作用。特别是,维生素 D 似乎对细胞衰老有多方面影响。研究发现,维生素 D 缺乏和细胞衰老相关,它们影响实验动物肥胖的发病机制。维生素 D 补充剂可通过调节 pAMPK α/SIRT1/FOXO3a 复合物活性,上调 IL-10 和 FOXO3a 表达,抑制阿霉素诱导的人内皮细胞衰老[64],其结果很大程度上归因于维生素 D 调节细胞周期和增殖的能力。相对较高的维生素 D 也与提高细胞端粒长度有关。

较高 25-羟基维生素 D 的受试者,其全血细胞端粒明显较长[65]。对老年人独立研究也报告了血清 25-羟基维生素 D 与端粒平均长度呈正相关,与 Hb1Ac 水平监测的 II 型糖尿病指征呈负相关,表明维生素 D 与细胞衰老和年龄相关疾病间存在相关性[66]。

维生素 E 也具有抗细胞衰老特性,这可能是由于其强大的抗氧化活性。维生素 E 通过细胞周期抑制剂作用,抑制人内皮细胞和纤维母细胞的细胞衰老进程[67]。维生素 E 摄入不足,引起人类白细胞端粒长度较短,提示适当摄入维生素 E 可以减缓细胞衰老。维生素 B2 能促进线粒体能量稳态,是一种衰老抑制剂。因此,饮食中核黄素也可抗衰老[68]。

除了维生素,某些矿物质如 Mg、Zn、Fe 等也与细胞衰老有关。培养的成纤维细胞中长期缺乏 Mg 会加速衰老过程,其特征是细胞周期抑制剂和 SA-β- gal 活性的表达增加,以及端粒长度缩短。膳食中补充 Mg 可以增强线粒体功能,防止组织中的氧化应激,延长小鼠寿命[69]。Zn 通过调节免疫系统以及抑制全身细胞应激参与调节衰老[70]。Zn 缺乏或在 SC 中代谢受损,可能导致 SC 的积累和血管病理。此外,Zn 代谢受损也与端粒缩短和炎症增加有关,而 Zn 的积累与血管平滑肌细胞中 ROS 增加和衰老诱导有关[71]。补充 Zn 可以逆转免疫衰老如增加 naïvet 细胞亚群,改善免疫细胞功能,增加胸腺生成,减弱炎症老化,并在衰老过程中调节 Th1/Th2 免疫稳态。

Fe 也与衰老和健康相关。特别是,通过螯合阻断 Fe 离子的可用性,被认为是几种膳食天然分子(如 EGCG、黄连素和姜黄素)延长寿命的重要机制[72]。尽管缺 Fe 性贫血常在老年人中观察到,但随着年龄的增长,铁在 SC 中迅速积累,抑制铁诱导的细胞死亡,有助 SC 成活[73],从而增加与年龄有关的疾病。

3.5 多元酚

多酚是一类植物分子,被认为是健康饮食的重要组成部分。据报道,多酚参与调节细胞信号通路如 NRF2、NF-κB、mTOR、Sir tuins 以及自噬、免疫调节、细胞增殖和凋亡等关键过程[74],具有细胞保护和促进健康作用。研究表明,长期食用膳食多酚能减轻许多与年龄相关的疾病如癌症、心血管疾病、肌肉萎缩、神经退行性疾病、关节炎等疾病[75]。

在博莱霉素诱导的成纤维 SC 中,饮食中黄酮类多酚芹菜素和山奈酚,经 IRAK1/IκBα 信号通路抑制 NF-κB 活性,有抗 SASP 作用[76]。从柠檬、葡萄等水果中分离出的富含多酚的成分具有抑制细胞衰老的特性[77]。中年小鼠摄入多酚丁香松脂醇可通过增加 CD3+T 细胞总数和 naïve T 细胞数量来减少免疫衰老标记物,增强年轻对照小鼠抗流感疫苗接种的体液免疫,并减弱炎症衰老[78]。

多酚可能有选择性诱导 SC 细胞凋亡,以减轻随年龄增长组织中的 SC 积累[79]。槲皮素是第一种被鉴定出具有解毒活性的天然分子,在临床研究中,达沙替尼和槲皮素的结合在减少 SC,显示出令人鼓舞的结果,从而改善器官功能和延长寿命[80]。

3.6 益生菌

益生菌通过定殖在宿主内,调节对宿主有益的活性微生物菌群组成。益生菌被认为有助于维持肠道生态平衡,改善免疫反应和稳态。肠道细菌与营养成分相互作用,介导生物转化改变宿主分子的生理效应[81]。益生菌重塑健康的肠道菌群,促进维生素等营养产生与吸收,调节饮食营养对健康的影响[82]。

因年龄、饮食习惯或疾病,肠道菌群结构失调,成分发生变化。已被证明,补充特定的益生菌可以改善肠道菌群失调,缓解机体衰老,如免疫衰老、神经退行性变和慢性疾病。不良肠道菌群结构加强细胞衰老和伴随体内更多 SASP,从而增强衰老和疾病表型[83]。在前脂肪细胞中,益生菌发酵乳杆菌的分泌代谢物,通过改善细胞和代谢应激,抑制应激引起的衰老和 SASP 发展[84]。在老年小鼠中食用益生菌可以防止肠道衰老和炎症衰老,延长机体寿命[85]。消耗益生菌干酪乳杆菌 CRL431,不仅改善了免疫衰老的细胞和功能标记物,而且还恢复了胸腺髓质的年龄相关损伤[86]。

此外,膳食营养(包括植物多酚、胡萝卜素、维生素、微量元素)的抗细胞衰老效应,与调节体内肠道菌群组成有紧密联系[87]。饮食中主要营养素调节影响衰老相关因子如表 1 所示。

表 1 膳食主要营养素对影响衰老相关因子的调节

Table 1 Regulation of main dietary nutrients on factors related to aging

膳食主要营养素	影响衰老相关因子
复合碳水化合物及代谢中间产物	↓ SC、↓炎症、↑TREG 和 NK 细胞增殖、↑NAD/NADH 比率、调节肠道菌群
蛋白质/碳水化合物(>20%)	↑ SASP、↑炎症、↓蛋白质内稳态、↓血浆 NAD+水平
蛋白质蛋白质/碳水化合物(<10%)	↓ SC、↓炎症、↓ROS、↑蛋白质内稳态、↑血浆 NAD+水平、↑端粒长度、↑SIRTS 等表达
ω-3-PUFAS(DHA、EAP)	↓ SC、↑免疫细胞的吞噬活性、↑CD4+与 CD8+淋巴细胞、↓ SASP、↑端粒长度、↓ IL-6 等痰症因子
维生素 E、维生素 D、ZN^{2+}、MG^{2+}、多酚、益生菌	↓ SC、↑免疫细胞的吞噬活性、↑CD4+与 CD8+淋巴细胞、↓ SASP、↑端粒长度、↓ IL-6 等痰症因子、↓ROS、↓SA-β- GAL 活性、↑线粒体能量稳态、调节肠道菌群失调

4 结 论

衰老是人类自然发生的过程,与其他年龄相关的现象如免疫能力降低、肠道菌群失调、疾病易感性增强互为一体。养成健康的饮食习惯,可以减缓衰老的有害方面,包括慢性或致命性疾病的恶化或发生频率,对实现健康老龄化,很有帮助。

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