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炎性衰老在老年衰弱综合征中的发生机制

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摘　要

衰弱是一种与增龄相关的老年综合征，增加老年人不良健康结局的风险，减少预期寿命。炎性衰老(inflamm-aging)是机体在衰老过程中所显现出的慢性促炎症反应状态，并随着衰老而进行性加剧。研究表明，炎性衰老可能是导致衰弱的重要原因。本文对炎性衰老和老年人衰弱综合征的机制进行综述，为衰弱的早期诊断和干预提供理论依据。

关键词

衰弱，炎性衰老，机制

The Mechanism of Inflamm-Aging in Elderly Frailty Syndrome

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Abstract

Frailty is a geriatric syndrome associated with increasing age, increasing the risk of adverse health outcomes and decreasing life expectancy in older adults. Inflamm-aging is a chronic pro-inflammatory response state of the body that manifests itself during the aging process and progressively intensifies with aging. Research suggests that inflamm-aging may be an important cause of frailty. In this paper, we review the mechanisms of inflamm-aging and debilitating syn-

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dromes in the elderly to provide a theoretical basis for early diagnosis and intervention of frailty.

Keywords

Frailty, Inflamm-Aging, Mechanisms

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1. 引言

随着人类预期寿命的延长，全球老龄化人口正呈指数级别的增加。老年衰弱综合征是一种涉及多个系统和器官的形态和生理变化，以机体内部稳态消失、功能储备减少和脆弱性增加为特征的老年综合征[1]。衰弱在社区老年人群中非常普遍，亚太地区社区老年人衰弱的患病率为 3.5%~27.0% [2]，我国社区老年人衰弱的患病率为 10.0% [3]。衰弱增加老年人跌倒、残疾、抑郁和痴呆的风险，还是老年人死亡率的重要危险因素[4]。衰弱与否常与多种年龄相关疾病并存，严重影响了老年人的生活质量[4]，降低了其独立性，缩短了其预期寿命，增加了社会和家庭的照护负担。老年人普遍处于全身性的低度炎症状态，近年来提出的炎性衰老(inflamm-aging)被认为是与年龄相关疾病发展的重要驱动因素[5]。炎性衰老是机体长期慢性生理刺激的结果，可通过不同的炎症途径损害机体的功能，引发多种年龄相关的不良健康结局。炎性衰老在老年相关疾病中越来越受关注，本文综述了炎性衰老和老年衰弱综合征的相关研究进展。

2. 炎性衰老

炎症可能是一种进化选择，在生命早期和成年时期具有有益的影响，然而随着年龄的增长，炎症反应会逐渐失调，导致持续的低度炎症状态，即炎性衰老[5]。

老年人群中普遍存在慢性低度系统性炎症，以无症状、持续性、非特异性和全身性的轻度炎症状态为特点，表现为体内非特异性炎症因子水平轻度升高[6]。在炎性衰老过程中，随着衰老过程中衰老细胞的积累，先天免疫系统慢性激活，促炎介质的循环水平逐渐增加[7]。研究表明，炎性衰老在年龄相关疾病，如阿尔兹海默病、2 型糖尿病、心血管疾病、肌少症和衰弱等年龄相关疾病的发生发展中起着重要作用[5]。

3. 炎性衰老的机制

3.1. 遗传易感性

遗传易感性被认为是导致炎性衰老的因素之一，研究者已在涉及大量人群的研究中确定了影响炎症介质血液水平的多种遗传变异[8]。一些单核苷酸多态性与心血管疾病的低风险有关，而其他的则与心血管疾病的高风险相关联。例如，影响 IL6R1 的功能性遗传变异(Asp358Ala)与降低冠状动脉疾病的风险相关[9]，而 IL-6 基因 174G/C 多态性与冠状动脉疾病的风险增加相关[10]。端粒缩短是由于炎症引起的 DNA 损伤积累而发生的。并且已被证明通过复制衰老促进持续的 DNA 损伤，并进一步增加促炎性细胞因子[11]。潜在的介质，如 microRNA (miRNA)提供基因表达的调节，并且通过 NF-κB 信号通路诱导炎症[12]。有证据表明，miRNA 中与年龄相关的变化被认为会导致炎症，一些 miRNA 与炎症衰老和慢性疾病有关。例如，在 CVD 和糖尿病患者中观察到较低的 miR-126-3p 水平，而 miR-21 的 m5p 水平较高[13]。

3.2. 细胞衰老

衰老细胞在不同组织中的积累通常被认为是引起慢性炎症的生物学机制之一。细胞衰老是一种对损伤和压力的反应，会抑制细胞增殖，防止癌症扩散并有利于组织的良好愈合[14]。衰老细胞显示出与衰老相关的分泌表型(SASP)，其涉及多种可溶性分子的分泌，这些分子的列表目前尚不全面，它们根据细胞类型和触发因素发生变化[15]。这些分泌分子主要以旁分泌的方式起作用，可以促进邻近细胞中细胞衰老的发展，但是一些可溶性介质被释放到循环中并可能导致炎症[16]。随着衰老，在器官和组织中积累的衰老细胞数量呈指数增长，由于免疫系统的老化，从而导致机体持续的促炎状态[17]。

3.3. 免疫衰老

免疫衰老是指与免疫系统广泛的与年龄相关的免疫紊乱，影响先天和适应性免疫应答。免疫衰老影响免疫系统的所有功能，包括对病原体、异常细胞的防御以及长期免疫[18]。因此，老年人往往面临着更高的急性感染、慢性感染的重新激活和癌症的风险[19]。免疫衰老通过不同的途径影响老年人的先天和适应性免疫功能。研究表明，衰老影响先天免疫的所有成分，包括生理屏障、解剖屏障和吞噬作用等[18]。吞噬能力降低被认为是免疫衰老的标志，在老年小鼠和老年个体的嗜中性粒细胞中已经观察到呼吸爆发的损害，这是细胞内病原体破坏的关键机制[20]。目前的研究尚未完全阐明年龄影响免疫功能的潜在机制，还需进行更多的研究。

3.4. NLRP3 炎症小体的激活和线粒体功能障碍

NOD 样受体热蛋白结构相关蛋白(NLRP3)炎症小体复合物由 NLRP3，凋亡斑点样蛋白(ASC)和 pro-caspase 1 组成。在受刺激时，NLRP3 炎性体激活 caspase-1，其切割炎性细胞因子的前体，例如 IL-1β、IL-1α 和 IL-18 [21]。NLRP3 炎症小体的激活包括启动和触发两个基本步骤。NLRP3 启动是由应激信号引发的，包括内源性危险相关分子模式(DAMPs)和外源性病原相关分子模式(PAMPs)，这导致 NF-κB 激活和随后的 NLRP3 上调，而在未刺激的细胞中 NLRP3 的表达水平较低[22]。在不存在 NLRP3 和 ASC 的情况下，老年健康动物的 IL-1β 和 IL-18 的表达低于对照组，表明 NLRP3 炎症小体参与炎性衰老，并可能参与老年高血压的发病机制[23]。这种与年龄相关的 NLRP3 激活可能是由于随着年龄增长的 DAMPs 的积累，包括腺苷三磷酸，尿酸和胆固醇晶体[23]。

自噬和线粒体吞噬是细胞内去除功能失调的细胞质和错误折叠的蛋白质的过程，并最终调节炎症小体的激活[24]。由于自噬基因的表观遗传和转录调控的障碍，自噬活性在衰老中受损，从而导致受损细胞器的进行性积累[25]。线粒体吞噬，即受损线粒体的选择性去除过程在与年龄有关的疾病中起主要作用。由于 PINK-1 等关键因素的缺乏，线粒体吞噬在衰老中受损[26]。相关研究已证实受损的线粒体释放的 mtROS 和 mtDNA 参与 NLRP3 炎症小体的激活[27]。在这种机制中，caspase-1 进一步抑制线粒体吞噬，从而放大线粒体损伤，导致一种恶性循环[28]。

4. 炎性衰老与衰弱

流行病学研究表明，炎性衰老在多种年龄相关疾病中起作用，其中包括衰弱、心血管疾病、阿尔茨海默病、肌少症、癌症、2 型糖尿病和黄斑变性[29]。此外，血液中较高水平的炎症标志物与老年人肌肉质量和力量的较大损失，活动性下降相关[30]，这些都是目前最常用的定义衰弱的基本要素。

炎症是衰老相关疾病的焦点，也可能是衰弱的重要机制。研究显示，衰弱和衰弱前期与较高的炎症参数相关，尤其是 CRP 和 IL-6 [31]。高炎症水平和衰弱均与老年相关死亡率、发病率，残疾，多病等不良结局相关[32]。衰弱增加共病的风险，研究表明，高基线水平的 IL-6 和 IL-6 累积率增加可预测老年人

多种慢性疾病的加速纵向累积。衰老与多病症高风险的关联是非线性的，甚至比之前横断面分析中提出的相关性更强[33]。此外，研究发现一些衰弱相关的基因参与了炎症反应的信号转导通路，如 IL-18 rs360722、IL-12 rs9852519、IL-12 rs4679868、SELP rs6131 和 TNFrs1800629A，进一步说明炎症与衰弱之间的关联[33]。

坚持地中海饮食是唯一与较低的衰弱风险相关的行为因素，这可能是饮食固有的抗炎特性的结果[34]。长期使用非甾体抗炎药与≥80 岁社区居民患肌肉减少症的风险较低有关[35]。二甲双胍是一种对抗炎症和胰岛素抵抗的抗糖尿病药物，已被建议用于预防虚弱并减缓其进展[36]。

Ferrucc 等通过对炎症影响多种生理系统和表型的总体机制的描述，得出炎症会通过促进分解代谢并最终导致衰弱的结论[37]。在引发炎症反应的感染期间，机体的生理和代谢状态集中在防御上，所有其他合成代谢活动都被暂停，包括免疫系统的非防御功能，如依赖于生长因子的监测损伤和组织的持续修。如果这种情况是暂时的，机体会延缓大分子、细胞器和细胞的更新和修复，避免不可逆的损伤。然而，在老年个体中，低度慢性炎症持续存在，在缺乏大分子和细胞器再循环的情况下，损伤的累积可达到阈值，从而导致不可能逆转的严重功能性后果，从而导致衰弱的临床综合征。

5. 小结

随着全球人口老龄化不断进展，老年性疾病发病率逐年上升。衰弱在老年人群中普遍存在，严重影响老年人的生活质量。炎性衰老与老年衰弱密切关联，本文从遗传易感性、细胞衰老、免疫衰老、NLRP3 炎症小体的激活和线粒体功能障碍的层面阐述了炎性衰老的机制，并介绍了炎性衰老与衰弱的关联，为老年衰弱的机制研究和防治提供思路。

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