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细胞衰老标志物与衰老相关疾病的关系探讨

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摘　要

公共卫生和医学的不断进步推动着人类预期寿命的增长，目前老龄化持续加剧已成为我国乃至世界社会发展中不可逆转的趋势，据国家统计局最新数据显示我国65岁及以上人口20,056万人，占全国人口的14.2%，我国已进入深度老龄化阶段。神经退行性疾病、心脑血管疾病、癌症等的发生发展均与机体衰老密切相关，实现健康老龄化延缓衰老相关疾病的发生显得至关重要。细胞衰老是机体衰老和死亡的基础，因此，我们探究细胞衰老潜在标志物细胞周期抑制蛋白表达、端粒损耗、DNA损伤、衰老相关-*β*-半乳糖苷酶(SA-*β*-Gal)、衰老相关分泌表型(SASP)、核纤层蛋白B1 (Lamin B1)、衰老相关异色病灶(SAHF)、自噬与衰老相关疾病的关系，为后续探索更有价值的标志物来预测、延缓衰老相关疾病进展，实现健康老龄化奠基。

关键词

细胞衰老，健康衰老，标志物，老龄化，衰老相关疾病

Exploring the Relationship between Cellular Senescence Markers and Aging-Related Diseases

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Abstract

The continuous progress of public health and medicine has promoted the growth of human life expectancy, and aging has become an irreversible trend in the development of our country and even the world society. According to the latest data from the National Bureau of Statistics, China's population of 65 years old and above is 2005.6 million people, which accounts for 14.2% of the national population, and our country has entered into the stage of deep aging. The development of neurodegenerative diseases, cardiovascular and cerebrovascular diseases, cancer and others is closely related to the aging of the organism, to achieve healthy aging to slow down the occurrence of diseases related to aging seems to be crucial. Cellular senescence is the basis of aging and death, therefore, we explore the relationship between potential markers of cellular senescence, such as cell cycle inhibitory protein expression, telomere attrition, DNA damage, senescence-associated-*β*-galactosidase (SA-*β*-Gal), senescence-associated secretory phenotype (SASP), nuclear fibrillar laminin B1 (Lamin B1), senescence-associated heterochromatic foci (SAHF) and autophagy, and aging-related diseases, to provide a basis for the subsequent exploration of the development of healthy aging and slowing down of the development of aging-related diseases, laying the foundation for subsequent exploration of more valuable markers to predict and delay the progression of aging-related diseases and achieve healthy aging.

Keywords

Cellular Senescence, Healthy Aging, Markers, Aging, Aging-Related Diseases

1. 引言

细胞衰老是在 1961 年由美国生物学家 Leonard Hayflick 在体外培养正常人成纤维细胞时首次提出[1]。细胞衰老是指细胞正常生理功能和增殖能力伴随增龄和(或)面临外界应激压力时脱离细胞周期、丧失功能的过程，衰老细胞在不同组织器官中积累会导致机体出现各种功能衰退[2] [3]。细胞衰老分为复制性衰老和应激诱导性衰老两大类[4]，主要涉及 P53-P21-Rb 及 P16INK4A-Rb 通路[5] [6]。细胞衰老的标志包括：细胞周期抑制蛋白表达、端粒损耗、DNA 损伤、衰老相关-*β*-半乳糖苷酶(SA-*β*-Gal)、衰老相关分泌表型(SASP)、衰老相关异色病灶(SAHF)、自噬等。

2. 细胞衰老的生物标志物

衰老相关-*β*-半乳糖苷酶(SA-*β*-Gal)是最早用比色法测定来描述衰老的生物标志物之一，其可在衰老组织及细胞中被广泛检测到。衰老细胞最基本的特征之一是会发生不可逆的细胞周期停滞、表达大量细胞周期抑制蛋白，主要涉及 P53-P21-Rb 及 P16INK4A-Rb 通路[5] [6]。迄今为止，P16INK4A 的激活与表达已被证明是衰老最佳的体内标志物之一，作为细胞周期调节剂 P16INK4A 限制 G1 期通过抑制 CDK4 和(或) CDK6 激酶来促进细胞周期的 S 期进展[7]。有研究表面 p16 的表达是高度动态的，在健康的年轻组织中基本上检测不到，但随着衰老[8]或某些类型的组织损伤而表达急剧上升[9]。小鼠研究也表明，p16 导致特定组织的复制能力丧失与年龄呈高度相关，进而呈现出特定衰老相关表型[10]。细胞衰老体现出的

第一个表征即端粒缩短，端粒是位于染色体末端由形成“帽状结构”的 DNA 非编码重复序列组成，其功能是维持染色体的完整性[11]。端粒长度随着每次的细胞分裂而逐渐缩短，从而导致端粒 DNA 环结构稳定性丧失端粒结构破坏，进而激活 DNA 损伤应答，最终导致细胞周期停滞[11]。衰老细胞会分泌大量促炎因子、细胞因子、趋化因子、生长调节剂、血管生成因子和基质金属蛋白酶(MMP)，衰老相关分泌表型(SASP)介导了许多病理生理过程，SASP 可改变细胞微环境[12] [13]。其作用表现在：激活机体免疫系统清除衰老细胞和促进邻近受体细胞发生恶性转化。其他潜在标志物还包括核纤层蛋白 B1 (Lamin B1)及衰老相关异色病灶(SAHF)。细胞核形态标志物 Lamin B1 缺失时，其核完整性受损且呈现出衰老细胞会表现的形状不规则、体积增大改变[14]。衰老相关异色病灶(SAHF)可通过荧光显微镜观察到衰老细胞 DNA 在经过 DAPI 染料染色标记后出现染色质凝集，DNA 凝结成大小不一、致密的异染色质颗粒[15]。在 SAHF 的形成和维持过程里，组蛋白会出现甲基化修饰和互相结合蛋白等一系列变化，不仅 H3 组蛋白第 9 位赖氨酸三甲基化(H3K9me3)水平会提高，且其他[16]可作为检测细胞衰老的标志包括异染色质蛋白 1 (heterochromatin protein 1, HP1)、高迁移率 A 族蛋白(high-mobility group A protein, HMGA)和组蛋白甲基转移酶 Suv39h1 (suppressor of variegation 3-9 homolog 1)等的表达都会发生变化。有学者认为 SAHF 的形成与 P16 通路密切相关[17]。

3. 细胞衰老标志物与衰老相关疾病的关系

阿尔茨海默病(AD)涉及的神经退行性改变过程非常复杂。目前最广泛被接受的两个病因学假说是淀粉样蛋白级联假说和 *tau* 蛋白磷酸化假说[18]。淀粉样蛋白-β (Aβ)的积累和 tau 蛋白过度磷酸化被认为是该疾病发病的基石[19]。其他因素还涉及线粒体功能障碍、免疫功能退化，脂质稳态改变及蛋白质降解途径的失调等[20] [21]。近年来还有学者指出编码 ApoE4 载脂蛋白的等位基因是迟发性阿尔茨海默病(LOAD)的最强遗传危险因素。诸多流行病学证据已表明，ApoE4 通过影响 Aβ 沉积和清除而导致 AD [21]，其涉及的过程包括氧化应激通路及胆固醇转运等。因此检测 Aβ 蛋白的沉积及 tau 蛋白的过度磷酸化对该疾病有很好的预测作用。

年龄增长是动脉粥样硬化发生发展的独立危险因素且动脉粥样硬化还与过早衰老有关。动脉粥样硬化过程中显示出的衰老相关证据有：细胞增殖减少、不可逆的生长停滞和细胞凋亡、DNA 损伤增加、表观遗传修饰以及端粒缩短及功能障碍。在动脉粥样硬化中，衰老细胞会促进纤维帽变性并引发一系列炎症反应此时会促进 SASP 的产生，近来，已有学者发现：SIRT6 [22]是 III 类组蛋白脱乙酰酶 sirtuin 家族的成员。还有学者指出[23]，营养剥夺是自噬的强大激活剂，而自噬与细胞衰老密切相关。后来有学者通过小鼠喂食高脂肪实验在小鼠的血管组织中诱导自噬，并指出其和胰岛素抵抗和 ER 应激有关[24]，其机制在于通过抑制高血糖所致端粒损伤和氧化应激驱动的 AGEs 的形成并证实两者在基于氧化状态的血管疾病的发生和进展中起着至关重要的作用。自噬由 AGEs 触发，并通过大鼠主动脉血管平滑肌细胞(VSMC)中的 ERK，JNK 和 p38 信号传导促进细胞增殖，这表明 AGEs 诱导的自噬加速了糖尿病患者动脉粥样硬化的发展[25]。

骨质疏松的两个特征包括[26]：骨量减少和微结构破坏，从而使得骨折风险增加，老年性骨质疏松症(SOP)是与年龄相关的骨质流失和骨骼系统中特定生物的衰老，一般是指 70 岁以后的骨质疏松症。SOP 的发病机制十分复杂，目前尚未完全阐明。但越来越多的证据表明[27]，原发性骨质疏松症的主要原因是骨髓间充质干细胞(BMSCs)的衰老，扰乱 BMSCs 的成骨和脂肪生成之间的平衡[28] [29]。促进成骨分化和/或抑制 BMSCs 的成脂分化被认为是发展抗骨质疏松症的有希望的策略。

2 型糖尿病患者会出现胰岛素抵抗和胰岛素分泌受损，胰岛素抵抗是由肌肉、肝脏和脂肪等外周组织对胰岛素信号传导的反应受损引起的。同时伴随功能失调、脂肪组织的积累[30]。衰老细胞会释放大量

SASP，这一过程直接介导胰腺β细胞功能与脂肪组织功能障碍和外周组织胰岛素抵抗，从而促进2型糖尿病的发生[31]。此外，糖尿病患者的高血糖和代谢变化亦会促进细胞衰老。糖尿病诱导的细胞衰老会导致各种糖尿病并发症。因此，2型糖尿病既是细胞衰老的原因，也是细胞衰老的结果。随着年龄增长，胰岛β细胞出现数量减少及功能障碍也会进一步诱导β细胞衰老[30] [32]，曾有学者表示[33] [34]：p16Ink4a阳性细胞可靶向激活半胱天冬酶(INK-ATTAC)诱导小鼠模型凋亡[31] [35]，因此他们从全身选择性清除了p16Ink4a阳性细胞后发现此类衰老细胞群的葡萄糖代谢和胰岛素分泌有所改善，且有效降低了衰老和胰岛素抵抗模型中胰岛的衰老及SASP的表达[36]。

4. 小结

目前随着老龄化进程的不断加剧，我国乃至世界范围掀起了衰老相关研究的热潮，研究衰老与健康老龄化、保障生活质量预防衰老相关疾病密切相关，本文就细胞衰老潜在标志物及其与各个疾病之间的关系和价值做了初步说明，近年诸多学者通过衰老标志物验证衰老模型亦或建立衰老模型更进一步探究衰老已取得一定成果，探究细胞衰老相关研究任重道远，关乎新时代如何实现健康老龄化的远大目标。

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