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干细胞衰老与衰老微环境调控的研究进展 *

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摘要：干细胞衰老会损害机体组织的稳态，衰老的干细胞丧失修复能力从而引发衰老相关疾病。衰老微环境是促进机体衰老的重要因素之一。衰老相关分泌表型（SASP）是构成衰老微环境的主要成分，影响干细胞的组织修复能力，进而推动机体衰老进程。细胞外囊泡（EVs）被认为在衰老微环境中发挥重要作用，衰老细胞分泌的 EVs 通过运载 miRNAs 等非编码 RNA 及 SASP 在内的多种活性分子参与调控衰老微环境，本文就干细胞衰老的诱发因素以及衰老微环境的研究进展进行综述，以期为干细胞的临床应用提供实验基础和理论基础。

关键词：干细胞；衰老相关表型；微环境；细胞外囊泡

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The Progress on Researches in Stem Cell Aging and Regulation of Aging Microenvironment*

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ABSTRACT: The aging of stem cells impairs the homeostasis in the tissue. Aged stem cells lose their ability to repair tissue and cause the age-related diseases. Senescent microenvironment is one of the important factors which lead to organism aging. The senescence-associated secretory phenotype (SASP) is an important part of senescent microenvironment. The SASP affects the ability of stem cells to repair and drives the process of aging. Extracellular vesicles (EVs) are thought to play an important role in senescent microenvironment. EVs secreted by senescent cells carry non-coding RNA such as miRNAs and a variety of active molecules including SASP, which are involved in the regulation of senescent microenvironment. This paper reviews the reasons of the stem cells aging and the research progress of senescent microenvironment, so as to provide the experimental basis and theoretical basis for the clinical application of stem cells.

Key words: Stem cells; Senescence-associated secretory phenotype; Microenvironment; Extracellular vesicle

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前言

衰老（Aging）是器官功能和个体机能随时间推移而发生退化的过程，是引发多种慢性疾病的重要因素。细胞衰老与个体衰老密不可分。细胞衰老（Cellular Senescence）是细胞增殖周期永久停滞的现象，被视为个体衰老的关键因素[1]。衰老细胞参与衰老相关疾病，清除衰老细胞可以改善动物模型中动脉粥样硬化、骨关节炎和肿瘤等年龄相关疾病的病理过程[2-4]。因此，有效清除衰老细胞有望成为抗衰老的重要途径。组织器官和机体的整体衰老主要表现为对损伤应激能力及修复再生能力的下降。而作为组织修复的种子细胞，干细胞发生衰老将直接促使其更新及分化功能减弱，随后丧失对组织损伤的修复能力[5]。研究表明，衰老细胞主要通过累积在局部，形成特定衰老炎性微环境影响周围组织细胞及干细胞，从而将衰老表型扩散至局部或其他器官[6]。衰老微环境由细胞相关分泌表型（Senescence-associated Secretory Phenotype, SASP）和细胞外囊泡（Extracellular Vesicles, EVs）组成[7]。SASP 主要包括炎性因子、趋化因子、蛋白水解酶和生长因子。EVs 是所有细胞类型包括衰老细胞都会分泌的囊泡结构，可运载包括 miRNAs 等非编码 RNA 及 SASP 在内的多种活性分子。由于其运载分子种类丰富，且受细

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胞类别以及内环境影响显著,EVs 日益成为研究衰老调控及衰老细胞间通讯的热点[8]。基于近年关于衰老研究的飞速发展,本文阐述了干细胞衰老诱发因素及其对机体衰老的影响,着重讨论 SASP 组成因素及其在细胞衰老微环境中的作用,进一步通过调控干细胞衰老及细胞微环境为延缓衰老提出新思路,期望能为组织修复以及衰老相关疾病提供新的研究方向。

1 干细胞衰老及其诱发因素

1.1 DNA 损伤与干细胞衰老

DNA 损伤是导致干细胞等多种细胞衰老进而推动机体衰老进程的关键因素[9]。电离辐射、酶抑制剂和氧化应激等多种因素均可导致 DNA 损伤。DNA 损伤应答机制（DNA Damage Response Mechanism, DDR）包括细胞周期检验点（Cell Cycle Checkpoints）和 DNA 损伤修复通路（DNA Damage Repair Pathway）[10]。DNA 损伤首先激活 p53 等细胞检验点相关分子,导致细胞增殖停滞，进一步引起 DNA 损伤修复通路对损伤 DNA 进行修复;如细胞损伤严重,修复程序将会受阻,细胞周期可处于长期停滞状态,从而表现出细胞衰老表型。在此过程中,由于免疫细胞功能下降等原因,衰老细胞因无法被及时清除而在局部积累形成衰老微环境。

由于自身增殖与分化的功能特点，干细胞比成体细胞对 DNA 损伤反应更为敏感,轻微 DNA 损伤即可诱导干细胞功能下降、衰老或凋亡。研究发现,DNA 损伤通常会首先诱导胚胎干细胞分化,以充分激活 p53 等周期检验点分子,之后才会启动细胞凋亡及衰老机制清除衰老细胞 [11,12]。而造血干细胞的 DDR 机制可能更依赖于 DNA 损伤修复蛋白。当 DNA 损伤修复因子异常时,DNA 损伤可导致造血干细胞功能的明显下调[13]。

1.2 端粒缩短导致干细胞衰老

细胞分裂能力是有限的，经过大约 50 次分裂后细胞不能继续增殖,这被称为复制性衰老[14,15]。细胞端粒会随着细胞增殖周期不断变短,最终会触发 DNA 损伤应答机制,而导致细胞周期停滞[16]。具有较强增殖能力的细胞如干细胞及肿瘤细胞等比普通成体细胞具有较高活性的端粒酶,可维持端粒长度。端粒酶活性可直接通过诱导干细胞衰老等方式影响干细胞功能[17]。研究证实，缺失端粒酶的骨髓间充质干细胞功能明显下降,重新转染端粒酶逆转录酶（Telomerase Reverse Transcriptase, TERT）后,TERT 的活性得到恢复,不同程度的修复了骨髓间充质干细胞增殖、分化及免疫调节等功能[18]。

1.3 线粒体功能障碍与干细胞衰老

线粒体是细胞的动力来源，它包含独立的 DNA 等遗传物质。线粒体在通过有氧呼吸产生能量的同时还会产生活性氧（Reactive Oxygen Species, ROS）等氧化应激产物。而细胞内 ROS 不断积累可导致线粒体 DNA（mtDNA）突变,进而引起线粒体功能紊乱,最终导致细胞发生衰老、凋亡或死亡,当衰老细胞累积后器官出现功能退化,最终表现为机体衰老[5,19]。研究证实,mtDNA 突变小鼠会表现出脱毛、骨质疏松、寿命缩短等早老的特征[20]。此外,mtDNA 突变小鼠的造血祖细胞在胎儿发育过程中会受到影响,引起神经干细胞的衰老进程,最终导致神经干细胞会对 mtDNA 突变积累表现出自我更新能力的下降[5]。因此线粒体功能被破坏可能是干细胞衰老的原因之一,而如何通过减少氧化应激保护线粒体功能也日益成为防止和延缓衰老研究的热点。

2 细胞的微环境

衰老细胞的微环境主要由 SASP 和 EVs 构成。SASP 的主要成分包括炎性因子、趋化因子、生长因子和蛋白酶。而细胞外囊泡作用方式与 SASP 相似,被认为是调控衰老微环境的重要因素。衰老微环境相关因子通过两种方式来推动衰老进程,一种是它以自分泌方式促进生长阻滞,另一种是它以旁分泌方式将衰老表型传递给周围细胞[21]。衰老细胞的微环境不但能刺激相邻细胞发生病变,而且可以抑制肿瘤的发生和促进受损组织修复[22]。

2.1 炎性细胞因子

白细胞介素（Interleukin, IL）是常见的 SASP 炎性细胞因子,它包括 IL-1α、IL-1β、IL-6 和 IL-8 等等。SASP 炎性因子之间会相互影响,当跨膜受体 Notch 的活性上升时,SASP 的分泌作用被增强,IL-1α 以自分泌方式增加 IL-6 和 IL-8 的产物。IL-6 和 IL8 在衰老细胞中增强细胞生长阻滞[23]。此外,炎性因子还与干细胞的分化能力有关。BMMSCs 通过分泌 IL-6、IL-1β 等衰老炎性因子促进骨吸收和减少骨形成,导致其成骨分化能力下降[24]。有研究表明 IL-1β 通过激活 has-miR-496/FoxD3 来抑制 Wnt 信号通路,造成 hBMMSCs 的成骨分化能力被抑制,这表明 IL-1β 促进骨质丢失,骨质疏松的发生也与之相关[25]。

2.2 趋化因子和生长因子

趋化因子和生长因子也是 SASP 中重要成分,趋化因子包括 CC 和 CXC，已证实由衰老细胞分泌的趋化因子主要包括 CXCL-1、CXCL-2 以及 CCL-2,它们通过与自己 G 蛋白相关的跨膜受体（趋化因子受体）相互作用发挥其生物学效应[26,27]。SASP 中的生长因子包括转化生长因子 -β（TGF-β）、巨噬细胞集落刺激因子（GM-CSF）和肝细胞生长因子（HGF）。早期的 SASP 主要是由 TGF-β 家族成员组成,它可以诱导附近的细胞变老。癌基因激活诱导的细胞衰老伴随着 NOTCH1 动态波动,而 NOTH1 与 TGF-β 的分泌相关[28]。此外,TGF-β 很复杂,对不同干细胞分化功能的调控有差异。有研究表明，多能性因子 NANOG 通过激活 TGF-β 可以逆转衰老干细胞的肌源分化潜能[29]。但是对于脂肪间充质干细胞来说,miR-21 通过抑制 TGF-β 通路来促进它的成脂分化能力 [30]。子宫内膜间充质干细胞（eMSC）通过抑制 TGF-β 信号通路来促进其增殖、分化和细胞干性[31]。因此,是否有其他通路参与了 TGF-β 对于间充质干细胞的分化调控,还需要进一步研究。

2.3 蛋白酶

蛋白水解酶包括常见的金属蛋白酶（Matrix Metalloproteinases, MMPs）,例如 MMP-1、MMP-2 和 MMP-9 等。MMPs 与细胞衰老密切相关。有研究证实,成纤维细胞、血管平滑肌细胞、椎间盘细胞以及肝星状细胞中 MMPs 上调是导致这些细胞衰老的重要原因[7]。此外 MMPs 还参与调控干细胞的活性,位于骨髓部位的干细胞通常处于静息状态,但它也能对细胞外信号作出应答回到细胞增殖周期中。MMPs 是决定其增殖和分化的重要因子 [13]。在骨髓细胞中,MMP-9 使细胞释放可溶配体（sKitL）,造成内皮细胞和造血干细胞（HSCs）从休眠状态转变

到增殖状态，随后骨髓移植细胞开始向合适的血管壁龛转移，这有利于干/祖细胞池的分化和重组[32]。在造血干细胞的移植上，已有研究报道 MMP-9 是提升造血干细胞移植效率的重要靶点，有研究者利用 CXCR2 受体激动剂、趋化因子受体 CXCR4 拮抗剂 AMD3100 和 GROβ 增强 MMP-9 的释放，进而提升了造血干细胞的移植效率[33]。

3 细胞外囊泡

EVs 是由脂质双分子层构成的囊泡状小体，利用自身囊泡小体在细胞间担任细胞间的沟通交流作用，EVs 包裹着 miRNA，mRNA 和蛋白质，影响着多种疾病的病理和生理功能[34]。EVs 可以分为微囊泡（Microvesicles）和外泌体（Exosome），EVs 的直径范围在 40-1000 nm。Microvesicles 是细胞受到应激反应后产生的囊泡。Exosome 是与细胞膜融合后被释放到细胞外的小囊泡。很多证据表明衰老细胞分泌的 EVs 携带衰老信息，参与调节受体细胞的表型，这种发挥作用的方式类似于 SASP[8]。

3.1 细胞外囊泡与细胞衰老

很多细胞类型能够分泌 EVs，衰老细胞也不例外。热休克、缺氧、低体温、氧化应激和辐照等衰老刺激会改变 EVs 的数量和内容物成分[8,35]。研究证明，辐照引起的人类前列腺癌细胞、纤维母细胞的衰老，经过检测它们分泌的 Exosome 数量增加[36,37]。这表明，衰老细胞分泌的 EVs 的数量取决于不同的细胞类型和细胞衰老诱导因素。尽管目前还不清楚为什么处于压力状态的细胞会释放出更多的囊泡，但有一种解释是细胞利用囊泡释放出有毒物质或不必要的物质。有研究表明 EVs 是通过两方面在细胞衰老中发挥作用，一方面 EVs 的释放可以维持细胞内部的稳态。例如 Takahashi 等[38]发现细胞分泌的 Exosome 可以帮助清除有害的 DNA 片段，如果抑制 Exosome 的分泌则会导致细胞内 ROS 的水平增高。另一方面在应激状态下，EVs 作为重要的细胞间通讯物质与邻近细胞沟通交流。例如将细胞暴露于氧化应激下，它所产生的 Exosome 有能力向随后被暴露于氧化应激的受体细胞传递保护信号 [39]。关于 EVs 的释放机制，有研究提出它依赖于 p53 的激活。由 DNA 损伤引发的细胞衰老造成 EVs 生物发生增加。另有研究表明，由辐射引起人前列腺癌细胞的细胞衰老被检测到外泌体样的囊泡分泌物显著增加，这与 p53 的调控密切相关[37,40]。与外泌体生物发生有关的肿瘤抑制激活通路 6（TSAP6）基因，它的转录被 p53 的活化而调控[41]。这些证据表明 p53 信号通路调控着 EVs 的生物发生。

3.2 细胞外囊泡中 miRNA 与干细胞衰老

EVs 里包含的 miRNA 是一种短的非编码 RNA 大约 20 个核苷酸长，通过结合靶 mRNA 来调控转录后的蛋白表达。一些 miRNA 直接参与组织衰老和细胞衰老，因为它们的靶基因属于细胞衰老相关通路。SITR1 是调节细胞衰老的重要基因，有研究证明 miR-34a 通过抑制 SIRT1，进而活化 p53 信号通路参与细胞凋亡[42]。有研究将增殖和停滞状态的细胞进行对比，发现 miR-146 的表达水平在衰老细胞中明显增加，这是由于 miR-146 两个重要靶点是 IL-6 和 IL-8，它们是 SASP 中具有重要的促炎功能的炎性因子，这提示miR-146 直接调控衰老相关的炎症。另一些 miRNA 也被发现在组织老化过程中间接地进行差异表达[43]。在老年骨质疏松患者血浆中 miR-31 的升高，提示 miR-31 可作为骨质疏松疾病的血液标记物[44]。Machida[45]等人探究年轻个体与年老个体唾液中 miRNA 的差异表达，表明重要的衰老标志物是 miR-24-3p。此外在干细胞分泌的 EVs 中 miRNA 影响干细胞功能，EVs 中的 miR-31 抑制间充质干细胞的成骨分化能力 [44]。间充质干细胞成骨分化过程中，Exosome 中的 miR-199b、miR-218、miR-148a、miR-135b 和 miR-221 明显升高[46]。对比年轻和老年大鼠的 miRNA 在骨髓间充质干细胞的 EVs 的差异性表达，发现老年大鼠的 EVs 中的 miR-133b-3p 和 miR-294 表达下调，抑制 TGF-β1 介导的上皮间质转分化（EMT）[47]。因此 EVs 中的 miRNA 通过直接结合靶基因的方式来发挥其重要的调节作用，进而调控干细胞功能。

4 小结与展望

细胞衰老促进个体衰老进程，其中干细胞的衰老会导致组织损伤后无法得到有效修复，进而影响干细胞在组织工程和疾病治疗的应用。为了寻找有效的改善途径，我们需要关注到衰老细胞的微环境，由细胞分泌的炎性因子，趋化因子以及细胞外囊泡是影响干细胞功能的关键因素。虽然目前 SASP 和 EVs 在衰老进程中的关键作用已被阐述，但目前与衰老相关的细胞外囊泡的功能研究还处于起步阶段，尚需对其靶向的关键机制作进一步研究。研究干细胞衰老及衰老微环境有助于加深对机体衰老的认识，通过调控衰老微环境和维持干细胞功能，实现健康长寿的目的。

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