



口腔衰老的研究: 增龄性改变及其与全身衰老的关联*

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【摘要】 衰老并非由单一事件驱动,而是遗传稳定性下降、表观遗传调控异常、代谢失衡以及细胞应激反应紊乱等多种机制共同作用的结果。口腔衰老是全身衰老在口腔的体现,更是加快机体衰老的主要因素,不仅影响口腔局部稳态,还可通过炎症因子释放等途径与全身系统性衰老相互作用。口腔衰老性疾病,如根面龋、牙龈退缩、牙槽骨吸收、口干症、味觉减退、牙列缺失缺损等,严重危害老年人口颌系统功能,也可加重或引发全身性疾病。目前口腔衰老的研究面临基础与临床转化不足、口腔衰老与全身衰老关联机制不清以及早期诊断和有效干预手段缺乏等关键挑战。未来应通过多组学技术构建口腔衰老分子图谱,系统解析其发生发展机制及与全身衰老的互作网络,并加速衰老细胞清除药物等新型干预策略的临床转化。系统解析口腔衰老的生物学机制与发生规律,不仅为保留天然牙提供支持,更是理解口腔-全身共病互作、促进全身健康的核心,也为口腔衰老性疾病防治提供重要理论基础。

【关键词】 衰老 口腔疾病 细胞衰老 综述

Oral Aging: Age-Related Changes and Their Association With Systemic Aging

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[Abstract] Aging is not driven by a single event but results from the synergistic effects of multiple mechanisms, including genetic instability, epigenetic dysregulation, metabolic imbalance, and disrupted cellular stress responses. Oral aging represents a localized manifestation of systemic aging in the oral cavity and acts as a key contributor to the accelerated aging of the whole body. It not only affects local oral homeostasis but also interacts bidirectionally with systemic aging through pathways such as the release of inflammatory mediators. Age-related oral diseases, such as root caries, gingival recession, alveolar bone resorption, xerostomia, taste impairment, and tooth loss and dentition defects, severely compromise the function of the oral and maxillofacial system in older adults and may exacerbate or trigger systemic diseases. Current research on oral aging faces several critical challenges, including limited translation from basic to clinical studies, an incomplete understanding of the mechanisms linking oral aging to systemic aging, and lack of strategies for early diagnosis and effective intervention. Future efforts should be focused on leveraging multi-omics approaches to construct comprehensive molecular maps of oral aging, systematically elucidating its developmental mechanisms and networks for interactions with systemic aging, and accelerating the clinical translation of novel intervention strategies, such as senolytic drugs. A systematic understanding of the biological mechanisms and developmental patterns of oral aging will not only support the preservation of natural dentition but also provide critical insights into oral and systemic health interactions and promote overall health. Furthermore, it may pave the way for novel preventive and therapeutic strategies for age-related oral diseases.

[Key words] Aging Oral diseases Cellular senescence Review

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衰老是生物体随时间推移,生理功能逐渐下降、稳态维持能力减弱、对疾病和死亡的易感性增加的多维度生物学过程。衰老导致细胞、组织和器官的功能降低以及分子和细胞层面的损伤,如DNA突变、蛋白质错误折叠、

线粒体功能障碍等。口腔衰老是全身衰老在口腔的体现,也是加快机体衰老的主要因素。口腔衰老性疾病如根面龋、牙龈退缩、牙槽骨吸收、口干症、味觉减退、牙缺失缺损等,严重危害老年人口颌系统功能,影响咀嚼、吞咽、发音、美观等功能,也可能加重或引发全身性疾病,如心血管疾病、糖尿病、阿尔茨海默病、骨相关疾病等。随着全球人口老龄化进程,系统阐明衰老相关的分子机制,寻找潜在的干预靶点,延缓衰老进程并改善包括口腔健康在内的老年人群整体生命质量,已成为生命科学和医学研究领域的重要课题。

1 口腔衰老的生物学基础

1881年德国学者August Weissman首次提出生殖细胞系与体细胞系在胚胎发育早期就发生分离的假说,认为生殖细胞系携带遗传物质可代代延续,而体细胞系随个体死亡消失、其获得性状不能遗传,因而体细胞会衰老^[1]。1953年英国学者Peter Medawar提出自然选择的力量随年龄增长而减弱,将衰老从单纯的磨损理论提升至进化生物学理论,奠定了现代衰老生物学的开端^[2]。2013年西班牙学者Carlos López-Otín等将衰老标志归纳为三类共九项指标,包括①原发性标志:基因组不稳定、端粒磨损、表观遗传改变;②拮抗性标志:蛋白质稳态丧失、营养感应失调、线粒体功能障碍、细胞衰老;③综合性标志:干细胞耗竭、细胞间通讯改变^[3]。其中,细胞衰老(cellular senescence)是指细胞在应激后永久性停止分裂,并通过分泌促炎因子及蛋白酶破坏组织微环境、诱发慢性炎症,从而加速机体衰老。上述标志若在低水平持续存在或过度激活,均可损害组织稳态,导致功能衰退及多种老年疾病。2023年Carlos López-Otín团队进一步提出了三个新的衰老关键标志,涵盖了基因组不稳定性、端粒磨损等原有指标,并将组织物理微环境及心理社会因素纳入衰老的核心框架^[4]。衰老不仅是细胞内部问题,更是细胞与环境相互作用的结果。细胞外基质随增龄发生物理和化学改变(如弹性蛋白降解),影响机械转导信号及干细胞功能;长期心理压力与社交隔离则导致慢性应激激素水平升高,加速端粒磨损、诱发慢性炎症、降低免疫功能,并改变表观遗传状态。该理论将衰老的定义从细胞内扩展到了细胞外,从生物学扩展到了社会学。

衰老是一个跨越分子、细胞到组织、器官以至整个机体系统的复杂生物学过程。精准定位和干预关键靶点对于开发延缓衰老和防治相关疾病的新策略至关重要,疫苗靶向清除衰老细胞已显示出延缓衰老进程的潜力^[5]。此外,干细胞抗衰老治疗也展现出缓解衰老的潜力^[6]。单

细胞转录组研究揭示,机体约四分之一的细胞类型数量会随年龄而变化,不同器官间共享协调的细胞和分子动态,如免疫重塑、功能性细胞类型减少、炎症相关状态的出现及性别依赖性轨迹等,提示衰老以系统性方式重塑多个组织的细胞组成与调控区域^[7]。

口腔衰老既是机体整体衰老的局部体现,也是加速全身衰老的重要驱动因素。p16/p21阳性及衰老相关 β -半乳糖苷酶(senescence-associated β -galactosidase, SA- β -Gal)阳性的衰老细胞在口腔组织中积累,并通过分泌衰老相关分泌表型(senescence-associated secretory phenotype, SASP)驱动局部慢性炎症^[8]。口腔微生物组随年龄发生系统性演替,研究表明中国老年人群的唾液微生物组整体组成结构相较于年轻人相对稳定,但可识别出一系列与年龄显著相关的特定细菌属,包括梭杆菌属、细小单胞菌属、卟啉单胞菌属以及不动杆菌属^[9]。口腔间充质干细胞的功能衰退也是口腔衰老的重要特征,老年供体的口腔间充质干细胞出现细胞更新能力减弱、细胞形态从细长纺锤状向宽阔扁平状转变、胞内颗粒积聚增加以及伪足缩短等典型衰老特征,并表现出细胞增殖能力、活力、克隆形成能力以及多向分化潜能的显著下降^[10]。纵向循证研究证实,口腔健康问题与老年人身体机能、肌肉力量及身体表现的下降显著相关,且口腔疾病可预测后续更严重的功能衰退。一项针对中国西部农村中老年人群的研究显示,口腔衰弱患病率高达68.4%,且口腔衰弱指数每增加1分,肌少症风险升高30%^[11]。日本一项为期2年的纵向研究发现,口腔健康相关生活质量评分每提高1分,衰弱风险降低11%^[12]。本综述将系统总结口腔硬组织、软组织、感觉功能等增龄性改变(图1)以及与全身系统性衰老的互作,为老龄化背景下的口腔疾病防治与全身共病管理提供新思路。

2 口腔硬组织的增龄性改变

2.1 牙齿衰老

牙齿衰老是指随增龄发生的牙齿结构与功能不可逆退行性变化,主要表现为牙体硬组织磨损、牙髓萎缩、牙周退缩和功能减退。具体而言,牙釉质磨损变薄,表面光泽消失,牙齿切缘和牙尖变平,临床牙冠垂直高度降低;髓腔内成牙本质细胞持续分泌继发性牙本质,导致髓腔体积缩小、根管变细;牙本质小管矿化程度增加,使牙齿脆性上升,易发生隐裂或折裂;牙骨质随年龄增厚,可导致根面敏感并增加拔牙操作难度。

在微观结构层面,原子探针层析成像技术研究发现,牙釉质处于脱矿与再矿化循环,老年人牙釉质羟基磷灰石纳米晶体外壳的氟化物含量显著升高,而晶体核心或

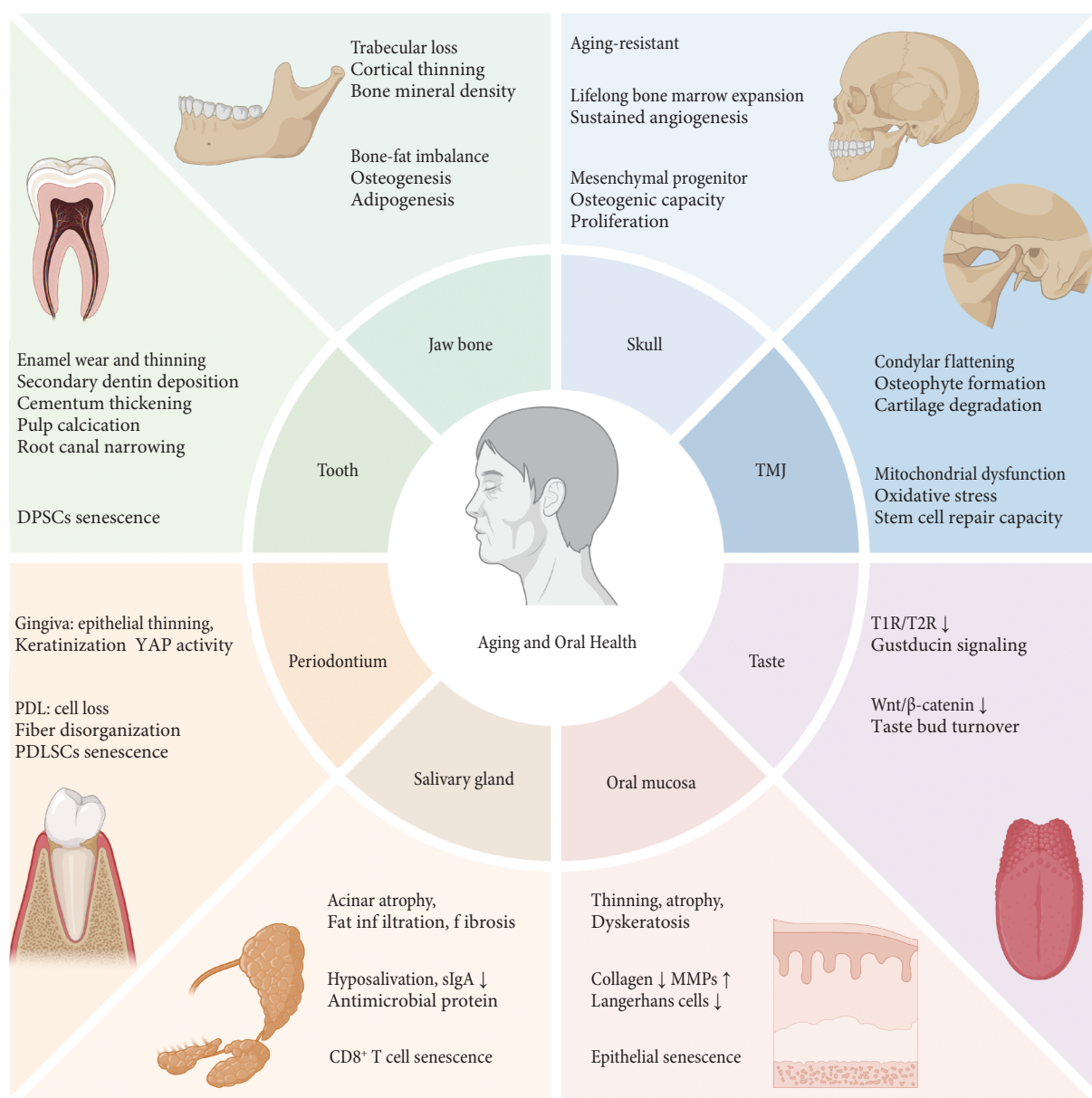


图1 口腔硬组织、软组织及感觉功能的主要增龄性改变

Fig 1 Key manifestations of oral aging: hard tissues, soft tissues, and sensory function

DPSCs: dental pulp stem cells; YAP: Yes-associated protein; PDL: periodontal ligament; PDLSCs: periodontal ligament mesenchymal stem cells; sIgA: secretory immunoglobulin A; MMPs: matrix metalloproteinases; T1R: taste receptor type 1; T2R: taste receptor type 2; TMJ: temporomandibular joint. The figure summarizes the key age-related degenerative changes in oral hard tissues (tooth, jaw bone, skull, and temporomandibular joint), soft tissues (periodontium, salivary gland, and oral mucosa), and sensory function (taste).

晶间相差异不显著,提示增龄使牙釉质纳米晶体外壳发生重塑^[13]。牙髓组织的增龄性改变主要表现为牙髓钙化:胶原纤维、基质变性或细胞坏死后成为钙化中心,钙盐在钙化中心周围呈同心板状或放射状沉积,导致髓腔和根管逐渐变小,脂肪可能沉积在牙髓中^[14]。在细胞层面,人牙髓干细胞(human dental pulp stem cells, hDPSCs)随传代次数增加出现衰老表型,WW域转录调节因子1(WW domain transcriptional regulator 1, WWTR1)可通过抑制p53、p21表达延缓其衰老,提高增殖和成骨分化能

力^[15]。线粒体动力学失衡,特别是线粒体融合与分裂失调,是炎症环境下牙髓干细胞功能衰退的关键分子机制^[16]。干预研究显示,衰老清除药物ABT-263可有效清除规模化长期培养的牙髓干细胞中的衰老细胞,从而维持其体外及体内的增殖与分化功能^[17]。

2.2 颌颌面骨衰老

颌颌面骨衰老是全身骨骼衰老的重要组成部分,主要表现为骨量丢失、形态改变、干细胞功能衰退及微环境失衡,不仅引起口腔健康问题,导致牙齿松动脱落、咀

嚼功能下降等,更是面部美学老化的核心驱动力之一。

颌骨衰老主要表现为骨微结构退变与力学性能下降。锥形束CT(cone-beam computed tomography, CBCT)显示衰老颌骨骨小梁数量减少、排列稀疏,下颌骨皮质厚度变薄、骨密度下降等特征性改变^[18]。在口腔功能重建中,颌骨衰老导致牙槽骨进行性吸收、骨量不足,增加了义齿修复及种植体植入的难度。骨密度降低与骨微结构恶化直接影响种植体的初期稳定性及远期骨结合质量,是种植修复失败的重要风险因素之一^[19]。与颌骨相似,颅骨在衰老过程中亦发生骨髓微环境重塑与骨量改变。近期研究发现,成人颅骨骨髓是一个持续扩张且具有较强修复潜能的造血储备库,其衰老特征与长骨存在显著差异。颅骨骨髓在衰老过程中呈现终身扩张趋势,血管持续生长,并对促炎因子上调、脂肪生成增加等衰老特征表现出保护性抵抗^[20]。单细胞水平研究揭示衰老过程中颅骨骨髓微环境受炎症性衰老影响,间充质祖细胞成骨分化能力下降、增殖功能减退,细胞间通讯网络在衰老过程中发生重构。此外,颅缝间充质作为颅颌面骨干细胞的特有生态位,其干细胞数量减少相对平缓但功能衰退显著^[21]。年龄增长是颞下颌关节(temporomandibular joint, TMJ)退行性变的关键风险因素,CBCT显示TMJ衰老最为常见的表现为髁突扁平、骨密度异常和骨赘形成。在细胞层面,TMJ衰老表现为表观遗传改变、SASP形成、线粒体功能障碍及氧化应激加剧,以及干细胞修复能力下降,共同加速软骨细胞外基质降解与凋亡^[22]。

机制调控方面,衰老改变骨髓干细胞命运转归,骨细胞的数量与功能随增龄显著下降,成骨分化减少而向成脂分化偏移,破骨细胞线粒体数量增加则导致衰老相关的骨微环境紊乱及骨吸收异常^[23]。在颌骨特有的修复机制方面,外周神经胶质细胞可通过神经胶质-间充质转化(glial-to-mesenchymal transition, GMT)参与骨修复,衰老抑制该转化过程导致骨再生障碍^[24]。精准调控的温和机械刺激可通过增强抗衰老基因FOXO1的染色质可及性,使衰老骨髓间充质干细胞恢复力学程序与机械信号转导,从而改善老年小鼠的骨质^[25]。上述机制提示,靶向细胞衰老的干预策略具有缓解颅颌面骨增龄性退变的潜力。以TMJ为例,间歇性给予衰老清除药物可选择性清除衰老细胞,保留衰老髁突软骨厚度、改善软骨下骨体积和降低组织病理学评分,提示靶向细胞衰老的干预策略可有效缓解增龄性TMJ退变^[26]。

3 口腔软组织的增龄性改变

3.1 牙周组织衰老

牙周组织的衰老涉及牙龈、牙周膜及牙槽骨的协同

退变。牙龈衰老主要表现为上皮层变薄、角化程度降低,牙龈上皮细胞数量减少,附着龈宽度随年龄增加而增加,而游离龈缘高度随牙槽骨退行性吸收而相应降低。牙周膜的增龄性改变表现为牙周膜细胞数量减少、纤维含量下降,Sharpey纤维附着变得不规整,牙周膜变窄,牙骨质增厚以及骨吸收增加。老龄个体牙周组织对正畸机械力的反应性降低,组织重塑和修复能力显著下降^[27]。

在细胞与分子机制层面,王松灵院士团队绘制了灵长类牙龈衰老的单细胞核转录组图谱,发现牙龈上皮细胞对衰老信号最为敏感,衰老导致的上皮细胞更新能力减弱和屏障功能破坏是牙龈衰老的显著特征,转录共激活因子Yes相关蛋白(Yes-associated protein, YAP)活性的降低是促进牙龈上皮细胞衰老的关键驱动力^[28]。此外,口腔病原菌牙龈卟啉单胞菌可通过脂多糖诱导人牙龈成纤维细胞衰老,表现为p53、p21和SASP相关因子白细胞介素(interleukin, IL)-6、IL-8表达升高和活性氧累积增加^[29]。多组学分析结合空间转录组学揭示了转化生长因子- β 1(transforming growth factor beta 1, TGF- β 1)信号在牙周组织中随增龄上调并驱动牙周膜干细胞(periodontal ligament mesenchymal stem cells, PDLSCs)衰老,表现为G₂期细胞周期阻滞和活性氧累积增加。衰老的PDLSCs功能障碍可破坏组织稳态、阻碍损伤修复,并最终导致牙齿脱落^[30]。衰老清除药物达沙替尼联合槲皮素可有效清除衰老细胞,减少SASP相关炎症因子表达,在老年小鼠中显著减轻牙龈组织的衰老细胞负荷并减缓自然进展的牙周骨丢失^[31]。针对PDLSCs的研究进一步证实,衰老清除药物可通过部分抑制YAP表达促进衰老PDLSCs的清除和凋亡,改善其成骨分化能力并促进基于PDLSCs的牙槽骨再生^[32]。

3.2 唾液腺衰老

唾液腺衰老是指随着年龄增长,唾液腺在结构、功能及分子层面发生的退行性变化,主要表现为腺泡萎缩、纤维化、脂肪浸润及唾液分泌减少。作为全身衰老的一部分,唾液腺衰老受局部神经调节和自身免疫因素的影响更为显著,是一个生理性退化与病理性因素交织的过程,严重影响老年人的咀嚼、吞咽、言语功能及口腔稳态,增加口腔感染和营养不良的风险^[33]。

在结构层面,增龄导致唾液腺实质减少,腺泡细胞数量下降,尤其以浆液性腺泡萎缩最为显著,而脂肪组织和纤维结缔组织增生性替代增多。同时,细胞外基质重塑失衡,基质金属蛋白酶(matrix metalloproteinases, MMPs)活性异常导致基质成分改变,破坏腺体正常微环境结构与功能^[34]。在功能层面,唾液腺衰老最直接的临床表现

是唾液分泌减少。研究显示, 静息唾液流率随年龄增长下降幅度较小, 但受刺激后的最大分泌能力显著降低, 同时唾液缓冲能力、分泌型IgA含量及抗菌蛋白浓度下降, 导致老年人对龋病、口腔念珠菌感染等疾病的易感性增加。细胞衰老及其伴随的SASP是驱动唾液腺结构和功能退化的关键因素。衰老细胞通过SASP因子刺激炎症、通过旁分泌效应传播衰老表型并促进纤维化, 加速唾液腺病理进展^[35]。衰老细胞中错误折叠蛋白的累积也会激活内质网的未折叠蛋白反应(unfolded protein response, UPR), 激活NF- κ B炎症通路^[36]。

在免疫层面, 唾液腺衰老伴随局部免疫微环境的改变。随着年龄增长, 唾液腺中出现导管周围局灶性淋巴细胞浸润, T细胞比例失衡, CD8⁺ T细胞功能衰退。以T细胞衰老为模型的研究发现, 唾液酸糖基化修饰缺失会抑制CD8⁺ T细胞功能, 具体表现为CD8⁺ T细胞中 α 2,6-连接唾液酸显著减少, 揭示了 α 2,6-连接唾液酸的年龄相关性缺失是调控T细胞功能衰退的新机制^[37]。增龄性唾液分泌不足还与自噬受损介导M1型巨噬细胞极化增加相关^[38]。IL-4诱导的下颌下腺细胞衰老则是IgG4相关性唾液腺炎纤维化的关键因素^[39]。免疫系统通过固有免疫反应清除衰老细胞, 对维持机体内环境稳态至关重要。核因子E2相关因子2(nuclear factor E2-related factor 2, Nrf2)是细胞内重要的抗氧化防御系统的主调节因子, Nrf2激活可保护下颌下腺免受增龄所致的氧化损伤及慢性炎症积累, 具有抗唾液腺衰老的作用^[40]。

3.3 口腔黏膜衰老

口腔黏膜衰老主要表现为黏膜普遍变薄, 弹性下降, 出现皱褶和萎缩, 颜色偏淡甚至呈灰白色, 易出现创伤、溃疡及愈合延迟。角化异常在老年口腔黏膜中较为常见, 表现为角化过度或角化不足, 尤其是在舌背和硬腭区域^[41]。此外, 唾液腺衰老导致的唾液分泌减少会加重黏膜干燥与脆弱性, 进一步加剧口腔黏膜衰老。

在微观机制层面, 口腔黏膜衰老的核心驱动因素是增龄相关的细胞衰老, 涉及上皮细胞、基质成分以及免疫细胞的多重改变。老年人上皮细胞增殖能力下降, 细胞周期调控异常, 伴随端粒缩短和DNA损伤累积, 导致细胞衰老标志物p16、p21表达增加^[42]。同时, 角蛋白家族和紧密连接蛋白表达下调, 使黏膜屏障功能减弱, 易受病原微生物侵袭^[8]。胶原纤维数量下降, 弹性纤维断裂, MMPs活性增加, 导致基质重塑失衡和组织弹性下降^[43]。免疫功能衰老在口腔黏膜中同样表现明显。黏膜固有免疫细胞如树突状细胞、朗格汉斯细胞及T淋巴细胞数量和功能均下降, 分泌抗菌肽及免疫活性因子如分泌型免疫球

蛋白A(secretory immunoglobulin A, sIgA)减少, 导致局部抗感染能力下降。促炎细胞因子如IL-6、肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)持续升高, 核因子 κ B(nuclear factor kappa-B, NF- κ B)、p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38 MAPK)及哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路在老年口腔黏膜中被过度激活, 促进炎症因子产生和细胞衰老^[44]。自噬功能随增龄下降, 导致错误折叠蛋白和受损细胞器累积, 进一步加剧细胞功能障碍^[45]。

4 口腔感觉功能的增龄性改变

味觉功能衰老又称味觉减退或老化, 是指随增龄发生的味觉系统生理性退行性改变, 主要表现为味蕾结构退化、神经传导效率降低, 导致对酸、甜、苦、咸、鲜的感知能力下降, 味觉阈值升高, 识别力下降及风味感知减弱, 是机体整体衰老在感官系统的重要表现。

味觉信号始于味蕾中的味觉细胞。G蛋白偶联受体(G protein-coupled receptors, GPCRs)家族中I型味觉受体(taste receptor type 1, T1R)家族负责感知甜味(T1R2+T1R3)和鲜味(T1R1+T1R3); T2R家族则负责感知苦味, 是识别相应味觉化学分子的关键受体^[46]。味觉素作为味觉细胞特异表达的G蛋白 α 亚基, 充当信号放大器和转换器^[47]。当味道分子与受体结合, 激活细胞内味觉素, 进而引发环磷酸腺苷(cyclic adenosine mono-phosphate, cAMP)或三磷酸肌醇(inositol 1,4,5-trisphosphate, IP3)等第二信使反应, 促使离子通道开放, 细胞去极化并释放神经递质, 将信号传递至大脑^[48]。随年龄增长, T1R和T2R受体的表达水平下调, 味觉素的mRNA表达及信号转导效率降低, 导致味觉细胞对刺激的敏感性下降^[49]。此外, 味蕾细胞的更新速度减慢, 部分归因于Wnt/ β -catenin信号通路的活性随增龄而减弱, 影响味蕾祖细胞的分化^[50]。面神经的轴突转运功能在衰老过程中减退, 轴突转运的慢性损害可消除味觉反应并导致味蕾消失。流行病学及临床研究证实, 面神经麻痹在老年人中更为常见, 约30%~50%的面神经麻痹患者伴随味觉障碍, 表现为舌前2/3味觉减退或丧失, 增龄加剧了面神经损伤相关的味觉障碍风险^[51]。

口腔微生物被称为味觉的“第二套受体系统”, 在味觉感知中发挥重要作用。增龄所致的唾液分泌减少和口腔菌群失调, 可通过多种途径干扰味觉感知: 牙菌斑生物膜可物理阻挡信号分子与味觉受体的接触, 细菌分泌的酶可降解味觉信号分子, 某些细菌代谢产物可直接下调

味觉受体的表达^[52]。动物实验证实,细菌脂多糖刺激可上调甜味受体T1R2的无功能异构体剪接变体,从而抑制甜味感知^[53]。此外,味觉受体(尤其是T1R和T2R)广泛表达于牙龈上皮细胞、成纤维细胞及口腔化学感应细胞中,参与口腔先天免疫和微生态稳态的维持,增龄所致的局部炎症可通过炎症因子下调味觉受体表达^[54]。

5 口腔衰老与全身系统性衰老的互作

口腔衰老是全身系统性衰老的重要组成部分,二者之间存在着多层次的双向互作关系。在免疫层面,衰老牙周组织中持续积累的衰老细胞通过分泌SASP因子破坏局部组织稳态,同时激活NF- κ B通路并释放IL-6、TNF- α 等促炎因子进入血液循环,进一步加剧全身炎症负荷。而免疫衰老(immunosenescence)深刻影响着口腔局部防御系统:增龄导致中性粒细胞趋化功能下降、抗菌活性受损及过度活化,表现为氧化应激增强和吞噬功能亢进,从而加剧牙周组织损伤和牙槽骨吸收^[55]。巨噬细胞在衰老过程中表现出向促炎表型的偏倚,对牙龈卟啉单胞菌等牙周病原菌的应答更为剧烈,导致炎症细胞因子分泌显著增加,加剧牙周组织破坏^[56],形成口腔衰老与全身免疫衰老相互促进的恶性循环。在骨骼层面,牙周炎与骨质疏松症均由炎症和骨重塑失衡所驱动,二者之间存在密切的双向关联。骨质疏松通过降低全身骨密度使牙槽骨更易受损,而牙周炎释放的炎性介质又可影响全身骨代谢,导致骨质疏松风险增加^[57]。在神经层面,牙龈卟啉单胞菌等口腔病原菌可通过血源性播散进入大脑,其产生的牙龈蛋白酶可促进 β -淀粉样蛋白聚集,导致神经细胞损伤^[58]。慢性牙周炎通过持续的全身炎症、微生物生态失调和血脑屏障改变,作为潜在的神经退行性病变上游驱动因素发挥作用^[59]。而阿尔茨海默病患者因认知功能下降导致口腔卫生恶化,又进一步加重牙周炎,形成口腔衰老与神经退行性变之间的双向脆弱性关联^[60]。在微生物层面,口腔菌群失调可通过口腔-肠道轴进入消化道,破坏肠屏障并诱发局部炎症;反之,肠道菌群紊乱也可经免疫和代谢途径加重牙周破坏,形成双向互作^[61]。

6 总结与展望

衰老是机体随增龄发生的复杂、多维度生物学过程。口腔衰老不仅是全身衰老的局部窗口,更是通过多种途径驱动全身性衰老进程的关键因素。口腔衰老性疾病,如根面龋、牙龈退缩、牙槽骨吸收、口干症、味觉减退及牙列缺失缺损等,不仅显著损害老年人口颌系统功能,还可能通过炎症反应等途径加重甚至诱发全身性疾病。

系统阐明口腔衰老的发生规律与生物学机制,对于开发精准防治策略具有重要指导意义。近年来,单细胞测序技术的快速发展为解析口腔组织衰老的细胞异质性提供了全新视角。基于单细胞测序,研究者能够系统描绘不同年龄阶段牙髓、牙周及颌骨组织中细胞亚群的转录组特征,识别SASP基因的动态变化,并解析细胞间通讯网络的增龄性重塑,从而为揭示口腔衰老的分子机制及筛选潜在干预靶点奠定基础^[62]。

口腔衰老研究虽已取得重要进展,但当前仍面临若干关键瓶颈。第一,动物模型与临床验证的断层:加速衰老模型在口腔研究中的应用较为有限,从健康动物模型到老年共病患者的临床转化是当前面临的主要障碍之一。第二,口腔-全身互作机制的证据碎片化:多系统衰老与口腔衰老的互作机制虽被提出,但多数证据来自横断面或短期纵向研究,缺乏长期前瞻性队列和干预性研究的支撑。第三,靶向干预的临床转化障碍:衰老细胞清除药物在小鼠模型中效果显著,但临床转化面临衰老状态异质性、生物标志物有限性等挑战,且干预手段的生物相容性评价与标准化评估流程仍需优化。

鉴于上述瓶颈,口腔衰老的研究可从以下几个方向开展:①通过单细胞转录组学、代谢组学及蛋白质组学等多组学数据,整合牙齿、牙周、颌骨、唾液腺、神经和免疫系统的衰老特征,构建口腔衰老整体图谱,描绘口腔衰老的细胞和分子网络,建立口腔组织衰老标志物检测与标准;②明确口腔来源的细胞特别是干细胞在衰老过程中的耗竭与功能障碍机制,探索细胞激活或再生策略;③依托大规模、长期纵向队列与随机对照试验,深入解析口腔与全身衰老之间的互作机制,重点阐明全身炎症及跨器官调控网络,为理解口腔-全身共病提供循证证据;④加速靶向衰老细胞干预策略的临床转化,重点筛选适用于口腔微环境的衰老细胞清除药物与递送系统,联合SASP抑制剂、口腔微生态调控、表观遗传药物等^[26, 31, 40],建立分层化的老年患者干预方案,并推进从动物模型到早期临床试验的阶梯式验证。多维度干预策略的联合应用与临床转化,有望为口腔衰老性疾病的防治提供新的思路,并为促进健康老龄化提供重要的理论与技术支撑。

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investigation, methodology, and writing--original draft. Zhou Chenchen is responsible for conceptualization, data curation, methodology, project administration, resources, supervision, and writing--review and editing. Fan Yi is responsible for conceptualization, data curation, funding acquisition, project administration, resources, supervision, validation, writing--original draft, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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