科学通报 2026 年 第 71 卷 第 7 期: 1369 ~ 1378
巾帼科苑·健康她力量专题 进 展
《中国科学》杂志社 SCIENCE CHINA PRESS

肝脏衰老及其相关疾病

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2025-12-17 收稿, 2025-12-31 修回, 2026-01-23 接受, 2026-01-23 网络版发表
国家重点研发计划(2022YFC3400900)、国家自然科学基金(82370615, 82588201)和肿瘤系统医学全国重点实验室开放课题(KF2303-93)资助

摘要 肝脏在机体代谢稳态中至关重要, 肝脏衰老则是引起人体其他器官系统疾病的重要风险因素. 肝脏衰老既是随着年龄增长, 肝脏血流量减少、再生能力减弱、免疫炎症增强、代谢能力减弱的生理表现, 也是肝脏在受到各种内外源侵害、应激或损伤情况下的病理性反应. 该过程涉及肝细胞、肝星状细胞、肝窦内皮细胞及免疫细胞等多种细胞类型的功能紊乱, 具体表现为肝脏再生能力下降、代谢失调以及免疫微环境失衡、衰老相关分泌表型, 进而引起衰老相关标志物的积累. 肝脏衰老不仅会增加代谢功能障碍相关脂肪性肝病、肝纤维化/肝硬化及肝细胞癌等多种肝病的发病风险, 还可将多种分泌因子经血液播散至远处组织, 引起人体其他器官系统疾病, 进而促进多器官衰老. 寻找肝脏衰老生物标志物, 深入研究衰老机制, 开发延缓肝脏衰老的干预策略, 包括生活方式调整、药物和营养干预、免疫及基因治疗、抗衰老干细胞改造和表观遗传调控等潜在手段, 有望为治疗肝脏疾病和延缓衰老提供新的治疗途径, 进而改善老年人群的肝脏健康, 推动健康中国发展.



陈瑶 海军军医大学国家肝癌科学中心肿瘤分子生物学研究室负责人, 研究员/博士生导师. 现任中华预防医学会临床预防分会副主任委员. 主要研究方向: 阐释肝脏细胞的代谢调控机制与肝损伤、肝脏肿瘤的关系, 并寻找新的干预靶点, 发展新的干预策略. 获国家自然科学基金优秀青年科学基金、上海市优秀学术带头人、上海市三八红旗手标兵、上海市青年科技英才、上海市青年科技启明星等; 在*J Hepatology*、*Hepatology*、*Gastroenterology*、*Cell Research*等期刊发表多篇SCI论文, 获国内外发明专利授权7项. 承担多项国家自然科学基金、国家重点研发计划子课题或上海市重点研究计划等项目. 参编参译专著5部.

关键词 肝脏衰老, 细胞衰老, 衰老相关分泌表型, 代谢功能障碍相关脂肪性肝病, 衰老细胞清除剂

随着全球人口老龄化加剧, 衰老与代谢紊乱和环境因素相互作用, 逐渐成为导致慢性肝病发生发展的重要风险因素. 随着年龄的增长, 肝脏再生和代谢能力不同程度地受损下降. 肝脏作为机体的代谢中枢, 易受脂毒性、酒精、病毒及药物积累等外源性刺激因素的影响而发生衰老[1~3], 具体表现为: 相比皮肤和肠道, 非

引用格式: 徐莹, 邓秋敏, 陈瑶, 等. 肝脏衰老及其相关疾病. 科学通报, 2026, 71: 1369–1378
Xu Y, Deng Q, Chen Y, et al. Liver aging and associated diseases (in Chinese). Chin Sci Bull, 2026, 71: 1369–1378, doi: 10.1360/CSB-2025-5918

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肝切除术等外围刺激下, 肝脏细胞很少增殖, 自我更新频率较低, 其DNA复制频率也较低, 上述外源性刺激因素所导致的隐匿性DNA损伤若未能及时修复, 易积累在非编码区从而引起肝脏衰老[4]. 典型的肝脏衰老在宏观上表现为体积缩小, 微观上出现肝细胞肥大、线粒体数量减少和功能下降、基因组不稳定性及DNA损伤累积[5], 同时肝血流与胆汁分泌下降、代谢酶活性降低、免疫炎症及纤维化倾向增强, 通常会伴有肝脏损伤修复与再生能力减弱, 以及对脂肪肝、肝纤维化及肝癌等疾病的易感性增加[6]. 此外, 肝脏衰老还与心血管代谢综合征(包括血脂异常[7]、胰岛素抵抗[8]和血管疾病[9])以及阿尔茨海默病等神经退行性疾病[10]相关. 因此, 深入探讨影响肝脏衰老的因素和信号通路, 阐述启动和维持细胞衰老的机制, 对于理解机体衰老和开发抗衰老疗法, 提高肝病患者的生活质量, 具有重要的科学意义.

1 肝脏衰老的特征

肝脏作为机体的重要代谢器官, 具有独特的衰老特性, 包括肝脏体积缩小、血流量减少, 脂褐素沉积, 细胞外基质成分改变[11]. 肝脏衰老伴随代谢、合成、解毒与再生功能的衰退, 具体表现为: 细胞色素P450 (cytochromep450, CYP450)活性降低导致药物代谢减慢, 葡萄糖/脂质代谢紊乱; 白蛋白、凝血因子合成轻度下降; 胆汁分泌与流动特性改变, 解毒效率降低; 肝脏部分切除或损伤后, 肝细胞增殖及组织修复能力显著减弱, 疾病易感性增加[12].

2 肝脏衰老的核心分子机制

肝脏衰老的机制纷繁复杂, 涉及基因组的不稳定性、端粒受损、线粒体功能下降、表观遗传学的改变, 再到蛋白质稳态的失调以及细胞衰老等多个方面. 本文将总结各类肝脏细胞衰老的变化特征, 阐述影响肝脏衰老的关键机制(图1).

2.1 肝细胞衰老

衰老的肝脏中, 肝细胞的数量相对减少, 而衰老的肝细胞数量持续增加[7], 伴随着细胞衰老相关标志物如SA-β-gal活性升高, p21、$p16^{INK4a}$、p53和γ-H2AX等表达增加[13,14], IL-6、TNF-α、IL-8等SASP(senescence-associated secretory phenotype)因子的释放[15]. 据报道, 多倍体肝细胞从不到15%增加到约42%[16], 细胞核更大, DNA密度更高. 然而, DNA复制和增殖相关的信号级联反应减少, DNA修复率也降低, 表现出更高的基因组和表观修饰的不稳定性[17]. 同时, 衰老肝细胞中蛋白质的稳态也面临严峻考验: 自噬囊泡数量显著减少且活性严重受损[18], 导致蛋白水解减少、氧化应激水平升高、蛋白质错误折叠和聚集, 形成脂褐素等蛋白质聚集体[19]. 此外, 有研究发现肝细胞亚群中染色质重塑体BAZ2B可以通过抑制PPARα信号通路损害脂质代谢, 促进肝细胞衰老与代谢功能障碍相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)进程[20].

肝细胞作为肝脏代谢的核心, 对物质转化与能量调节至关重要, 而衰老肝细胞常伴随着糖脂代谢以及能量代谢的失衡. 在糖脂代谢中, 一方面, 衰老的肝细胞有更高的脂质和葡萄糖摄取以及糖耐量异常, 同时胆固醇摄取和合成相关的基因表达增加[21]. 另一方面, 衰老肝细胞中脂肪酸β氧化通路相关分子表达下调, 且受到过度激活的晚期糖基化终末产物受体(receptor for advanced glycation end products, RAGE)的抑制, 上述两方面共同促进脂质积累[22,23]. 在能量代谢中, 衰老肝细胞的线粒体数量减少, 线粒体的嵴和内膜结构发生变化[12,24], 同时多种呼吸链相关酶减少且ATP合酶解离, 导致线粒体膜电位受损和质子泄漏, 最终引发ATP合成障碍[23], 随之累积的活性氧可引发线粒体DNA损伤, 进一步加剧氧化磷酸化失衡[22]. 此外, 肝脏内在生物节律通过磷酸戊糖途径(pentose phosphate pathway, PPP)调控细胞核苷酸从头合成, 影响肝脏损伤修复与肝脏衰老[25].

2.2 肝星状细胞衰老

衰老肝脏中肝星状细胞(hepatic stellate cells, HSCs)的数量并无明显变化, 但出现显著的端粒损伤[9], 同时细胞内脂滴数量和大小增加, 并呈现出自发的激活状态, 表现为以α-SMA和Acta2等为代表的激活标志物表达显著增加, 以及基质重塑相关基因的表达上调[26]. 此外, 衰老HSCs可释放IFNγ和IL-6等促炎因子以诱导肝内巨噬细胞向促炎型转变, 影响免疫微环境[27].

2.3 肝窦内皮细胞衰老

肝窦内皮细胞(liver sinusoidal endothelial cells, LSECs)是肝脏非实质细胞的主要组成部分, 其衰老常表现为$p16^{INK4a}$的表达上调和SIRT1的表达下调[28], 并出现“假毛细血管化”这种特征性变化: 窗孔数量减少、

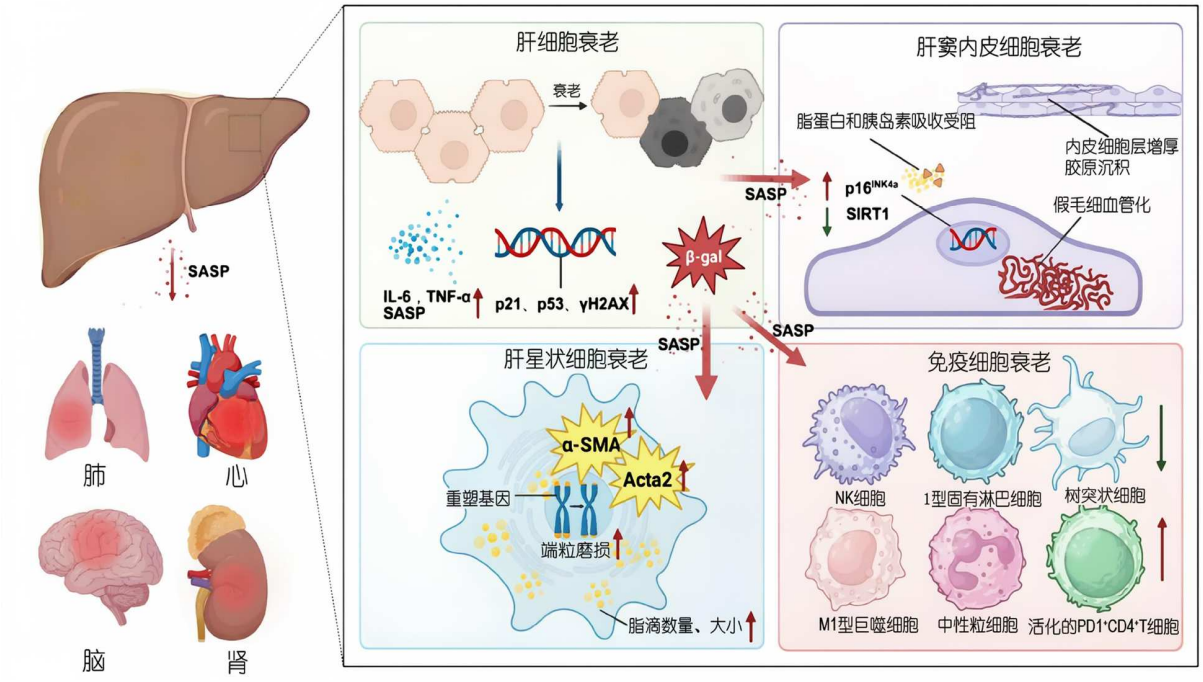


图 1 肝脏衰老的核心分子机制. 肝脏衰老涉及多种肝脏细胞类型, 包括肝细胞、肝星状细胞(HSCs)、肝窦内皮细胞(LSECs)和免疫细胞. 衰老肝细胞的特点是细胞周期抑制因子(如$p16^{INK4a}$、p21)的表达升高、β-半乳糖苷酶(SA-β-Gal)活性增加以及强烈的衰老相关分泌表型(SASP). 局部效应上, SASP会破坏组织特异性功能, 诱导邻近肝细胞的继发衰老、激活肝星状细胞、招募巨噬细胞和促进肝窦状内皮细胞毛细血管化, 促进肝病进展. 系统效应上, SASP因子进入血流, 影响肺、心脏、肾脏和脑等其他器官, 导致多器官功能障碍(使用BioRender.com制图)

Figure 1 Core molecular mechanisms of liver aging. Liver aging impacts various liver cells, including hepatocytes, hepatic stellate cells, liver sinusoidal endothelial cells, and immune cells. These cells show increased expression of cell cycle inhibitors (e.g., $p16^{INK4a}$, p21), elevated SA-β-Gal activity, and a strong senescence-associated secretory phenotype (SASP). Locally, the SASP impairs tissue-specific functions by inducing senescence in neighbouring hepatocytes, activating HSCs, recruiting macrophages, and promoting LSECs' capillarisation. Systemically, SASP factors enter the bloodstream and contribute to multiple-organ dysfunction, affecting organs such as the lungs, heart, kidneys, and brain (Created with BioRender.com)

孔隙率下降, 内皮细胞层增厚, 并伴有基底膜的异常出现和胶原的沉积, 导致窗孔吸收脂蛋白和胰岛素受阻[29,30], 以eNOS-NO-cGMP为代表的血管舒张途径失调与分泌能力受损[31]. 此外, 衰老的LSECs亦可通过分泌多种SASP因子(如vWF和ICAM-1)以及上调炎症因子受体(如CD68、MRC1、PD-L1)的表达, 参与促炎状态[31,32]. 衰老LSECs的调控作用呈现出空间特异性: 中央静脉周围区内皮来源的C-kit失活, 加速肝窦毛细血管化并促进脂肪变性[33].

2.4 免疫细胞衰老

总体上, 老年肝脏呈现免疫激活状态. 研究表明, 老年肝脏中NK细胞、1型固有淋巴细胞ILC1s、树突状细胞DCs的丰度减少[34], 但促炎M1样巨噬细胞M_{φ}[35]、中性粒细胞NEU[35]以及活化的$PD1^{+}CD4^{+}$ T细胞均存在显著累积[36]. 虽然初始$CD8^{+}$ T细胞的丰度降低, 但出现大量T细胞衰竭表型的$PD1^{+}TOX^{+}CD8^{+}$ T细胞亚群, 且可在TCR刺激下产生独特的促炎因子[34,37], 例如IFN-γ、IL-17和TNF-α, 其对老年肝脏的微环境产生不同的病理效应. IFN-γ通过激活HSCs的JAK-STAT1通路, 促使其转化为肌成纤维细胞并上调COL1A1等胶原合成酶表达, 促进细胞外基质沉积与肝纤维化. 同时, 持续高浓度IFN-γ可诱发肝细胞凋亡, 导致DNA损伤累积, 为肝癌发生提供病理基础[38]. IL-17A通过激活HSCs的STAT3信号轴, 上调成纤维细胞激活蛋白(fibroblast activation protein, FAP)表达, 直接促进纤维化进程. FAP介导的细胞基质重塑与血管新生, 共同塑造有利于肝癌侵袭的微环境. 临床数据提示, 肿瘤内$IL\text{-}17^{+}$细胞浸润程度与肝癌患者不良预后显著相关[39]. TNF-α则可以通过激活NF-κB/AP-1等信号通路, 促进肿瘤细胞存活、增殖和促纤维化基因表达[40]. 库普弗细胞(Kupffer)数量随着年龄的增长而增加, 表现为激

活状态[7,23], 伴有线粒体功能缺陷、吞噬活性降低以及炎症相关细胞因子生成增加[41,42].

3 肝脏衰老在慢性肝病中的作用

肝脏衰老与慢性肝病之间存在密切相互作用. 肝脏衰老通过端粒缩短、氧化应激及免疫衰老等机制降低肝脏再生与修复能力, 促进慢性肝病的进展; 而慢性肝病诱导的持续性炎症与纤维化则加剧肝细胞及肝星状细胞衰老, 共同驱动肝纤维化、肝硬化及肝细胞癌的发生发展(图2).

3.1 代谢功能障碍相关脂肪性肝病

肝脏衰老与代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)之间存在密切的双向关系: 肝脏衰老可加速MASLD的发生发展, 而MASLD也会反过来促进肝脏及全身衰老. 流行病学研究表明, MASLD(原非酒精性脂肪性肝病, nonalcoholic fatty liver disease, NAFLD)主要影响中老年人, 随着年龄的增长, 患病相关危险因素及各项临床指标异常显著增加[43,44]. 究其原因, 一是肝细胞衰老导致脂质合成增强而脂肪酸氧化减弱, 使得脂质更易在肝内积聚; 二是衰老的肝细胞线粒体功能障碍导致电子传递链受损, 引起活性氧(reactive oxygen species, ROS)的累积, 进一步导致DNA损伤, 加速衰老[45,46]; 三是大量促炎因子分泌介导的慢性炎症推动MASLD向脂肪性肝炎甚至肝纤维化进展[47,48]. 其他与年龄相关的变化因素, 如胰岛素[49]和瘦素抵抗[50]、生长激素和脂联素的减少、端粒缩短等[50], 也会导致老年人患MASLD的风险增加[1]. 目前, 有研究团队构建了衰老肝细胞的基因标签(senescent hepatocyte gene signature, SHGS), 证实其与MASLD进展显著相关[51]. 肠道菌群的变化也会引起MASLD的发生, 研究表明, 肠道菌群种类的改变和其所介导的肠道通透性改变, 共同参与了MASLD的脂肪变性及纤维化进程[52].

3.2 病毒性肝炎和肝纤维化

在病毒性肝炎的背景下, 各种类型病毒感染均可引起细胞应激, 诱导各类肝脏细胞发生衰老[53], 伴随促炎的细胞因子、生长因子和蛋白酶的分泌, 从而导致肝脏损伤、炎症和纤维化[54~58]. 一项老年患者队列

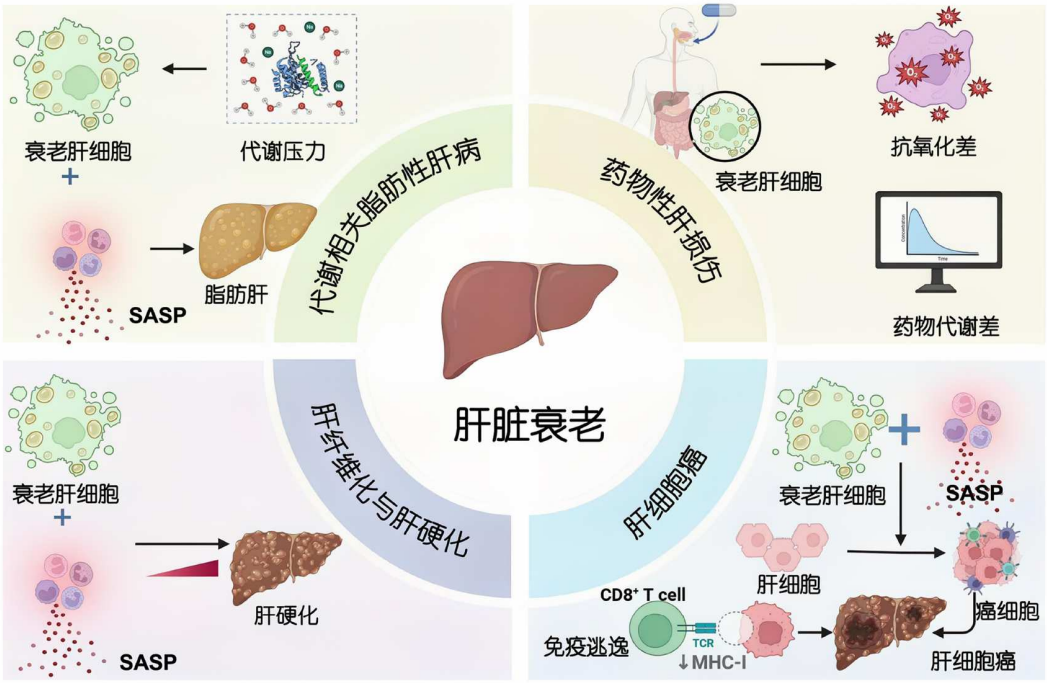


图 2 肝脏衰老与慢性肝病的相互作用. 肝细胞衰老是驱动多种肝脏疾病进展的关键机制, 其通过释放SASP并重塑肝脏微环境, 广泛参与代谢功能障碍相关脂肪性肝病(MASLD)、病毒性肝炎和肝纤维化、肝细胞癌等病理过程(使用BioRender.com制图)

Figure 2 Liver aging and chronic liver diseases: interactions and mutual impacts. Hepatocyte senescence drives the progression of various liver diseases by releasing SASP factors and remodeling the hepatic microenvironment, contributing to conditions such as metabolic dysfunction-associated steatotic liver disease (MASLD), viral hepatitis, liver fibrosis, and hepatocellular carcinoma (Created with BioRender.com)

研究显示, 与非老年NAFLD患者相比, 老年患者非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)和晚期纤维化的患病率更高[59]. 如前所述, HSCs在肝脏衰老的背景下可自发活化, 分泌SASP因子如IL-6、IL-1β等, 在局部微环境中形成慢性炎症反应, 进一步激活周围的HSCs, 形成正反馈, 加剧肝纤维化的进展[60].

3.3 肝细胞癌

研究表明, 衰老标志物p16^{INK4a}和p53经常出现在患者的癌前和良性肿瘤组织中, 而在晚期恶性肿瘤中, p16^{INK4a}和p53同时失活[61], 这一现象提示了细胞衰老在肿瘤中的关键作用. 在肝脏肿瘤领域, 细胞衰老最初被认为是一种阻止受损细胞增殖的肿瘤抑制机制. 但随着研究的深入, 衰老的双重作用被逐渐揭示: 衰老初期可通过细胞周期阻滞和免疫监视阻止肿瘤发生, 但持续衰老的细胞可以通过促进免疫逃避和促肿瘤微环境来促进肝细胞癌(hepatocellular carcinoma, HCC)的发生[21,62]. 与此同时, 免疫细胞衰老导致机体免疫监视功能显著下降, 共同削弱了免疫系统对早期肿瘤细胞的识别与清除能力, 进一步放大了癌变风险[63]. 此外, 肝祖细胞因持续耗竭而无法有效补充肝细胞, 这一过程不仅导致遗传不稳定细胞积累, 还使其获得促癌基因突变, 最终引发恶性转化及肝细胞癌[64].

4 肝脏衰老评估: 标志物的分类及应用

在健康老年人群中, 肝脏功能的常规临床指标通常仍保持在正常范围, 难以精确反映肝脏衰老的真实程度. 为了应对这一困境, 中国衰老标志物联盟最新发布的专家共识, 首次构建了覆盖功能、影像与体液三维度的肝脏衰老生物标志物体系. 功能维度, 将胆固醇代谢(血浆C4、LDL-C、PCSK9)及肝脏合成-抗凝蛋白(纤维蛋白原、凝血因子Ⅶ、抗凝血酶Ⅲ、肝素辅因子Ⅱ)列为Ⅰ级推荐指标, 以灵敏反映肝细胞合成与代谢功能的增龄性下降. 影像维度, 以MRI质子密度脂肪分数(MRI-proton density fat fraction, MRI-PDFF)量化脂肪变性, 联合CT/MRI经AI自动测定肝体积, 并以MRI评估肝脏血流量, 系统评估肝脏脂肪沉积、体积萎缩及血流减少等结构与功能衰老指标. 体液维度, 同步检测白蛋白、载脂蛋白APOE/APOC4、肝酶(ALT/ALP/GGT)、CRP、IGF-1等肝功能相关指标, 并纳入骨桥蛋白(osteopontin, OPN)与壳多糖酶3样蛋白1(chitinase 3-like protein 1, CHI3L1)等非肝功能相关指标, 综合评估肝脏衰老. 肝龄差(liver age gap, LAG)是指基于模型评估所得的肝脏预测年龄与实际年龄之间的差异[65,66], 该指标可作为预测肝脏衰老及评估相关健康风险的新型参考指标. 目前有研究表明肝硬化患者的肝龄差可达4岁以上[66]. 但肝脏衰老预测模型仍普遍面临大样本长期随访数据不足、特异性生物标志物缺乏及可靠计算模型缺失的局限, 难以独立应用于疾病预测, 常需结合疾病特异性标志物综合分析. 因此, 亟待建立有效的“肝龄”评估模型及“肝龄差”预测系统, 从而实现对肝脏衰老的早期预警与精准干预[6].

5 延缓或逆转肝脏衰老的干预策略

目前, 延缓或逆转肝脏衰老的治疗策略已从生活方式干预、分子靶向药物和免疫调控、药物和营养干预、干细胞疗法等多个层面展开(图3), 部分策略已在临床转化方面取得进展, 目前已步入动物实验或早期临床试验阶段.

5.1 干预生活方式

生活方式的干预是最有效且可行的基础策略. 热量限制(caloric restriction, CR), 即减少热量的摄入, 可以激活细胞修复机制、改善线粒体功能、抑制SASP等, 显著减缓肝脏衰老. 临床数据显示, CR可使健康成人衰老速度减缓2%~3%[67]. 规律的有氧运动可改善肝

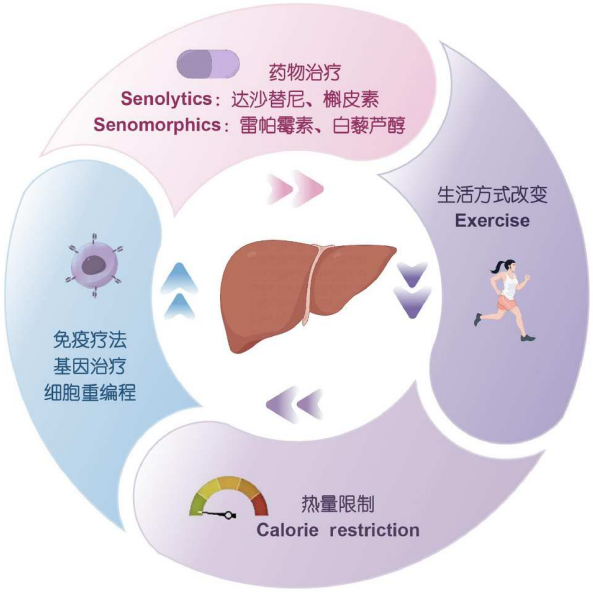


图 3 延缓或逆转肝脏衰老的干预策略(元素来源于FigDraw.com)
Figure 3 Therapeutic strategies targeting liver senescence (elements sourced from FigDraw.com)

细胞排列、降低肝内脂肪沉积, 延缓肝脏结构老化[67].

5.2 衰老细胞清除疗法

衰老细胞清除剂(senolytics)是直接诱导衰老细胞凋亡, 清除衰老细胞[68], 不影响正常细胞, 从而减轻组织炎症和纤维化[69]. 代表性的药物包括达沙替尼和槲皮素的组合(D+Q)[70]、Bcl-2家族抑制剂Navitoclax (ABT-263)以及黄酮类化合物非瑟酮(Fisetin).

衰老表型调节剂(senomorphics), 即抑制SASP的“表型调节剂”, 针对不适宜清除衰老细胞的场景, 通过抑制或减少有害的SASP因子分泌, 改善衰老细胞的毒性作用, 减轻肝脏的慢性炎症与组织功能障碍, 进而延缓肝脏衰老[71]. 目前的主要干预药物包括雷帕霉素[72]、NF-κB通路抑制剂[73]、JAK抑制剂等. 这些干预措施为延缓衰老相关疾病提供了潜在的治疗方向.

5.3 其他治疗策略

除上述策略外, 针对肝脏衰老的干预手段还包括免疫疗法、基因治疗、抗衰老干细胞改造和表观遗传调控等. 免疫疗法旨在增强天然免疫系统对衰老细胞的识别与清除能力, 通过恢复免疫监视功能以促进衰老细胞的及时清除[74]. 基因治疗则侧重于靶向调控细胞衰老相关的核心信号通路, 通过基因编辑或病毒载体递送等技术手段, 精确干预衰老细胞的特定基因表达, 从而诱导其凋亡或逆转衰老表型[75]. 在改造干细胞抗衰老方面, 最新研究发现, 利用“山中因子”(Yamanaka factors: Oct4、Sox2、Klf4、c-Myc)诱导细胞进入“部分重编程”阶段, 可恢复细胞年轻状态[76]. 此外, 改造人类间充质祖细胞, 使其具备抗细胞衰老的特性, 可以在灵长类动物中有效抵抗衰老. 这种“抗衰干细胞”在肝脏等组织中表现出显著的再生与修复能力, 为干预肝脏衰老提供了新策略[77]. 表观遗传调控方面, 组蛋白乙酰化(如H3K14ac)和甲基化(如H3K27me3)在调控肝脏代谢和衰老中发挥重要作用. SIRT家族蛋白(如SIRT1、SIRT6)可以通过去乙酰化作用参与DNA修复和抗氧化应激, 延缓衰老[78]. 以上治疗策略为开发精准抗衰老疗法提供了新的研究方向.

6 总结与展望

肝脏衰老是一个由多种分子机制共同驱动的复杂过程, 并与肝脏疾病的进程密切相关. 但是肝脏衰老相关研究目前仍面临关键挑战: 人类与模式动物在肝脏衰老特征上存在显著差异, 且缺乏特异性的肝脏衰老生物标志物, 同时Senolytics等人潜在抗衰老药物的长期安全性与有效性尚未得到充分临床验证. 基于这些现状, 未来研究应聚焦于多维度突破: 借助多组学技术构建人类肝脏衰老的动态分子图谱, 构建可量化的衰老评估体系, 开发针对肝脏的特异性抗衰老药物及靶向递送系统, 开展基于生物标志物的精准抗衰老临床前与临床试验, 并深入探究肝脏衰老与肠道、免疫系统等全身系统性衰老的相互作用机制, 以推动肝脏衰老相关基础研究向临床转化; 借助人工智能AI深度解读衰老时钟与衰老机制、开发新型药物与干细胞年轻化方案, 实现对肝脏等器官衰老的精准量化、靶点挖掘和个体化干预, 为抗衰老提供新的干预策略, 助力健康中国.

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Summary for “肝脏衰老及其相关疾病”

Liver aging and associated diseases

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Liver aging is a key risk factor for chronic liver disease, closely linked to metabolic disorders and environmental exposures. As the central metabolic organ, the liver is highly susceptible to stressors such as lipotoxicity, alcohol, viral infections, and drug-induced toxicity, all of which promote cellular senescence. Macroscopically, aging livers show volume loss; microscopically, they exhibit hepatocyte hypertrophy, mitochondrial depletion, and accumulating DNA damage. These changes lead to reduced blood flow and bile production, impaired metabolic enzymes, heightened inflammation, increased fibrosis, poor regeneration, and greater susceptibility to metabolic dysfunction-associated steatotic liver disease (MASLD), fibrosis, and hepatocellular carcinoma (HCC). Thus, understanding the molecular mechanisms of liver aging is crucial for uncovering systemic aging processes and developing interventions to prevent chronic liver diseases.

Liver aging involves distinct structural and functional changes. Key features include parenchymal atrophy, reduced hepatic perfusion, lipofuscin deposition, and extracellular matrix remodeling. Functionally, aging impairs metabolism, synthesis, detoxification, and regeneration, reflected in lower cytochrome P450 enzyme activity, disrupted glucose and lipid homeostasis, mildly reduced albumin levels, and a markedly regenerative response after injury.

The core molecular mechanisms of liver aging involve a tightly interconnected network of signaling pathways across major hepatic cell types. With age, senescent hepatocytes accumulate, showing increased SA-β-gal activity, elevated $p16^{INK4a}$, p21, p53, and γ-H2AX expression, and a strong senescence-associated secretory phenotype (SASP). In aged livers, hepatic stellate cells (HSCs) undergo telomere shortening and spontaneous activation, marked by higherα-smooth muscle actin (α-SMA) levels and a profibrogenic phenotype. The aging liver’s immune environment shifts toward chronic low-grade inflammation, characterized by more pro-inflammatory M1-like macrophages, activated T-cell subsets, including exhausted $PD\text{-}1^{+}CD8^{+}$ T cells and Kupffer cells with reduced phagocytosis but increased cytokine production, along with declining numbers and function of natural killer (NK) cells and type 1 innate lymphoid cells (ILC1s).

Liver aging and chronic liver diseases form a self-reinforcing cycle. Aging drives MASLD progression through disrupted lipid metabolism, increased mitochondrial ROS, and persistent inflammation. Conversely, MASLD accelerates hepatic senescence. In viral hepatitis, virus-induced stress promotes senescence, amplifying inflammatory and fibrotic responses. Aged HSCs sustain fibrosis via paracrine SASP signaling. Regarding HCC, senescence has a dual role: it initially suppresses tumors by halting damaged cells’ proliferation, but long-term accumulation of senescent cells creates an immunosuppressive, pro-tumorigenic environment that promotes cancer development, especially as immune surveillance declines with age.

Among healthy elderly individuals, the routine of liver function tests is typically normal, making it difficult to assess true liver aging. To address this, the Aging Biomarker Consortium of China has issued the first consensus on liver aging biomarkers, identifying 16 key indicators across functional, imaging, and humoral domains. These focus on cholesterol metabolism, coagulation factors, hepatic steatosis, blood flow dynamics, and hepatokines, providing a comprehensive framework for assessing liver age and guiding early interventions.

Therapeutic strategies targeting liver senescence are increasingly diverse and mechanism-based. Foundational approaches include lifestyle changes-caloric restriction and regular aerobic exercise, shown to slow liver aging. Pharmacologically, senolytic (e.g., dasatinib plus quercetin) eliminates senescent cells, while senomorphics (e.g., rapamycin, NF-κB inhibitors, JAK inhibitors) block harmful SASP effects. Emerging therapies include immunotherapies to boost clearance of senescent cells, gene therapies targeting aging pathways, stem cell-based regeneration using partial reprogramming or engineered mesenchymal stromal cells with anti-senescence properties, and epigenetic modulation via sirtuin activation.

In conclusion, liver aging is a multifactorial, dynamic process driven by complex molecular interactions among hepatic cells and deeply linked to the development of chronic liver diseases.

liver aging, cellular senescence, senescence-associated secretory phenotype (SASP), metabolic dysfunction-associated steatotic liver disease (MASLD), senolytics

doi: 10.1360/CSB-2025-5918