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卵巢衰老:女性系统性衰老的调控中枢与驱动机制

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摘 要:卵巢是女性最早发生功能衰退的器官之一,其衰老不仅标志着生育力下降,更可能构成女性系统性衰老的关键转折节点。目前,卵巢衰老的细胞与分子基础,以及其作为衰老信号源向全身多器官播散的具体路径,仍缺乏系统性的整合研究。本文围绕“卵巢衰老是否驱动女性系统性衰老”这一基础性科学问题,从卵巢细胞网络、分子通路与内分泌重塑层面进行系统梳理。在细胞层面,卵母细胞与卵巢多种类型体细胞在衰老过程中发生结构与功能重构,导致卵巢微环境稳态失衡。在分子层面,基因组不稳定、表观遗传重编程、蛋白质稳态破坏、线粒体功能衰退及代谢重塑等核心事件通过信号通路的交叉对话形成复杂的调控网络,共同促进慢性炎症微环境形成、组织纤维化进展以及细胞间通讯功能的渐进性紊乱。衰老卵巢能通过内分泌重塑、衰老相关分泌表型诱导的炎症扩散以及外泌体信号传递等多重通路,将局部衰老信号放大并传播至远端器官,加速心血管、骨骼、神经及代谢系统的功能退化。基于机体组织器官衰老时间顺序以及相关因果推断证据,本文提出卵巢衰老和卵巢早衰是连接生殖衰老与机体多系统衰老的关键因素。深入解析卵巢衰老的细胞与分子机制及其系统性效应,将为延缓女性生殖衰老、干预多器官协同衰老并促进全生命周期健康提供新的理论基础与潜在干预靶点。

关键词:卵巢衰老;内分泌失衡;衰老相关分泌表型;体细胞器官衰老
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Ovarian aging: A central driver of systemic aging in females

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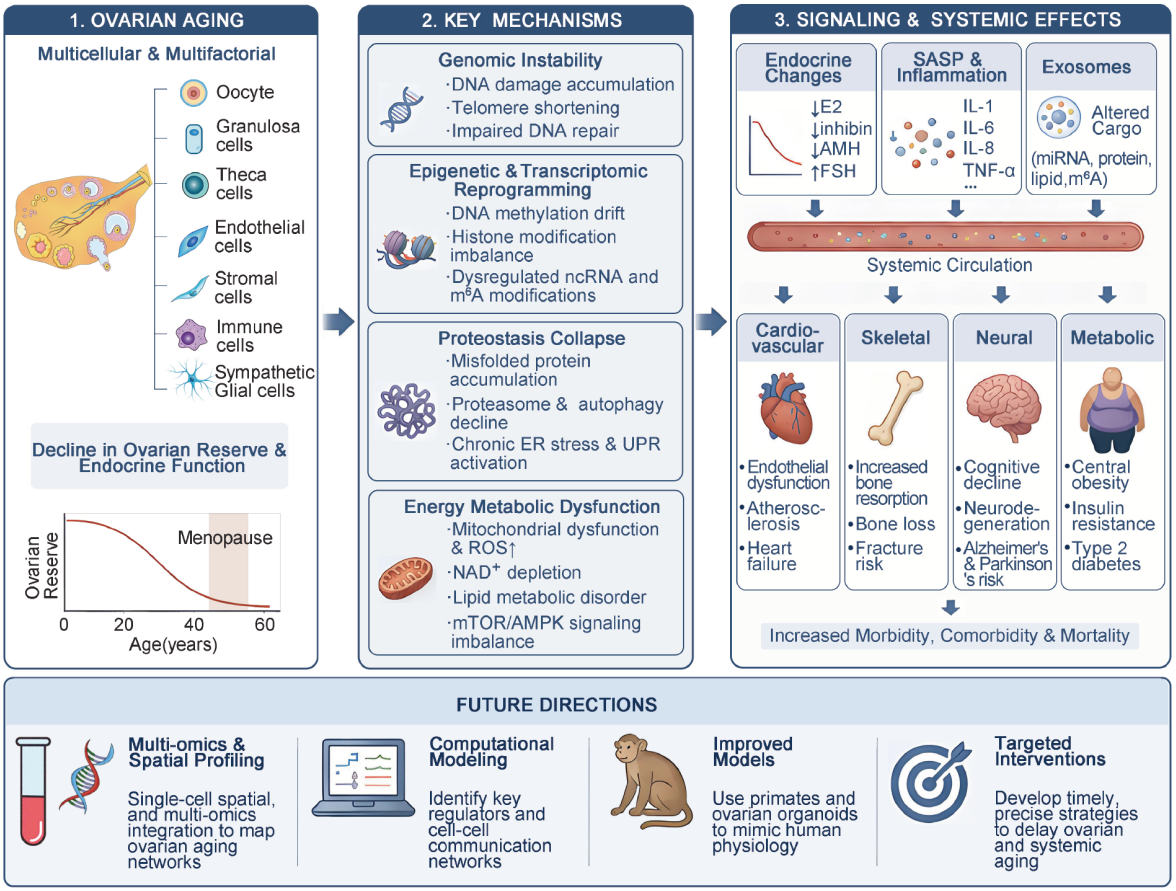
Abstract: Ovarian aging occurs significantly earlier than the overt aging of most somatic organs, indicating that it is not merely a passive consequence of systemic aging but a potential upstream regulator of female organismal decline. This review aims to comprehensively synthesize current evidence on the cellular, molecular, and systemic mechanisms underlying ovarian aging, to clarify how intra-ovarian changes reshape intercellular communication networks, and to elucidate how ovary-derived signals contribute to aging in distant organs. The ovary is a unique organ integrating reproductive and endocrine functions, maintaining a finite follicular reserve while secreting hormones such as estrogen, inhibin, anti-Müllerian hormone, and diverse bioactive factors. Unlike most somatic tissues, ovarian aging begins early, with a marked decline in ovarian reserve typically observed in women in their early thirties. Emerging single-cell and multi-omics studies reveal that ovarian aging is a dynamic, multicellular process involving coordinated dysfunction across oocytes, granulosa cells, theca cells, endothelial cells, stromal cells, immune cells, and neuro-glial networks. These cell types exhibit distinct yet interconnected aging phenotypes, including altered differentiation trajectories, inflammatory activation, fibrosis, and impaired vascular and metabolic support. At the molecular level, four convergent hallmarks dominate: genomic instability, epigenetic and transcriptional reprogramming, loss of proteostasis, and energy metabolic dysfunction. These mechanisms interact to create a self-reinforcing microenvironment characterized by oxidative stress, inflammation, hypoxia, and extracellular matrix remodeling. Critically, ovarian aging disrupts key intra-follicular communication systems—metabolic coupling, paracrine signaling, and steroidogenesis—leading to progressive follicular failure. Beyond the ovary, aging-related endocrine changes, senescence-associated secretory phenotype, and extracellular vesicles act systemically, promoting cardiovascular disease, osteoporosis, neurodegeneration, and metabolic disorders. Both clinical and experimental evidence supports a causal role, with timing-dependent effects observed in interventions such as hormone replacement therapy. We propose that ovarian aging functions as a central regulatory hub in female systemic aging. Future research should focus on high-resolution spatial multi-omics, computational modeling of intercellular networks, and development of human-relevant models such as ovarian organoids. Identifying critical transition points and early biomarkers will be essential for designing precise, time-sensitive interventions aimed at preserving ovarian function and extending female healthspan.



Key words: ovarian aging; endocrine dysfunction; senescence-associated secretory phenotype; somatic organ aging

卵巢是女性体内兼具配子生成与内分泌调节双重核心功能的关键器官。一方面,卵巢在胚胎期建立原始卵泡储备,并在成年后通过周期性募集、发育与排卵维持生殖潜能与生殖寿命;另一方面,卵巢持续分泌雌激素(estrogen)、抑制素(inhibin)、抗缪勒管激素(anti-Müllerian hormone,AMH)及生物活性因子,经血液循环参与调控全身多器官稳态。与多数体细胞器官相比,卵巢呈现更早启动的衰老进程,女性通常在32~35岁即出现卵巢储备下降,而心血管、骨骼及神经系统的显性衰老表型多在45~55岁后逐步显现[1]。这一时间差提示,卵巢衰老可能不仅是机体衰老的被动反映,更可能是女性系统性衰老的重要驱动因素。

近年来,单细胞转录组学、空间组学及多组学整合分析揭示,卵巢衰老是一个由多细胞类型协同失衡驱动的动态、渐进性级联过程[2,3]。尽管如此,该领域仍存在重要的认知缺口。在卵巢局部,不同细胞类型衰老的启动时序及其互作网络的重塑机制目前仍不清楚;在全身层面,卵巢衰老在多大程度上驱动远端器官衰老,卵巢来源的衰老信号通过何种路径介导全身效应,以及如何区分卵巢衰老作为驱动因素与全身同步衰老之间的因果关系,目前均缺乏系统性的整合研究。

基于此,本文系统整合当前研究进展,重点综述卵巢内不同细胞类型的衰老表型及其共性分子机制、解析细胞间互作网络的重塑,并探讨卵巢衰老在全身器官衰老中的潜在驱动作用。

1　卵巢组织内主要细胞类型的衰老特征

卵巢衰老并非单一细胞类型的耗竭,而是多个细胞群体在数量、结构、功能与互作层面的系统性重构(图1)。尽管不同细胞类型表现出各自特异性的退行性改变,但在时间进程和微环境驱动下,这些变化相互作用并形成协同级联反应。

1.1　卵母细胞衰老特征

女性生殖寿命由出生时建立的卵泡储备及成年后卵泡持续激活与闭锁速率共同决定。新生儿卵巢约含100万~200万个原始卵泡[4],至40岁初期降至

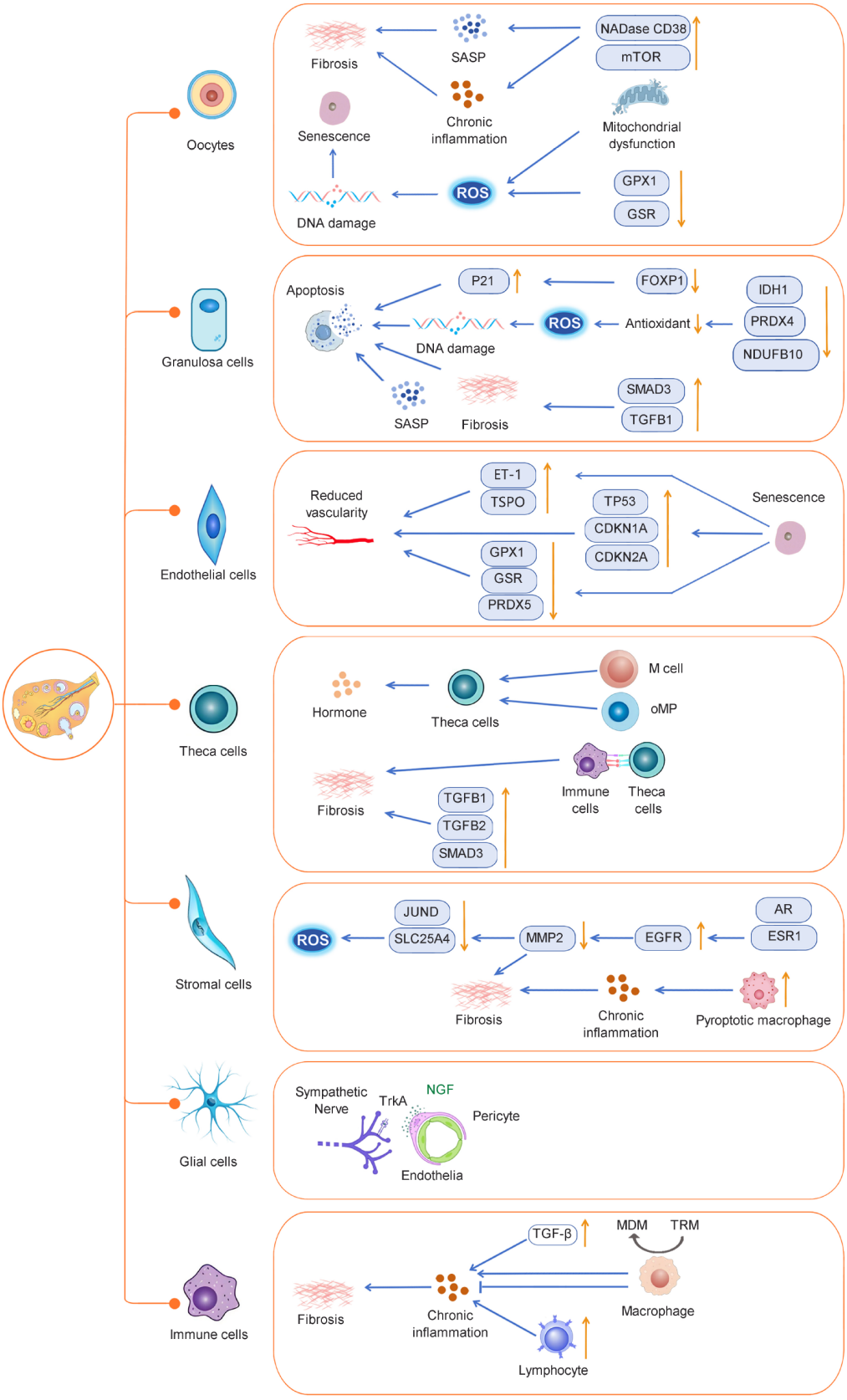


图1 衰老卵巢的单细胞分辨率衰老特征图谱

Figure 1 Single-cell-resolution atlas of aging-associated features in the ovary

约7 500个,自然绝经时通常不足1 000个[5]。在哺乳动物中,初级卵母细胞长期停滞于减数分裂I期前期双线期,使其成为DNA损伤累积和蛋白质稳态失衡的高风险细胞群体。临床上,女性约在34岁后会经历卵巢储备和卵母细胞质量的快速下降[6]。在形态学层面,衰老卵母细胞呈现透明带结构不均、胞质颗粒化增强、空泡形成及线粒体与脂滴异常聚集[7,8];在功能层面,则表现为减数分裂纺锤体结构紊乱及极体形成异常显著增加[9]。

跨物种比较显示,人类与小鼠在黏连蛋白复合体衰退、纺锤体组装检查点(spindle assembly checkpoint,SAC)功能减弱及线粒体功能下降等分子机制上具有高度保守性,但在衰老动力学方面存在显著差异(表1)。人类卵母细胞呈现染色体不稳定性的指数式累积,而小鼠则表现为渐进性衰退,提示"减数分裂停滞时间长度"可能是决定物种间生殖衰老严重程度的关键因素。

1.2　颗粒细胞衰老及亚群重塑

颗粒细胞(granulosa cell,GC)在卵巢衰老级联过程中发挥枢纽性作用。GC功能衰退不仅直接导致雌激素分泌下降,还可通过诱导卵母细胞活性氧(reactive oxygen species,ROS)水平升高及促进卵泡闭锁,间接加速卵巢功能衰退。在数量层面,GC随衰老逐渐减少[14,15];在结构与功能层面,更为关键的是其亚群组成的重编程。单细胞转录组研究显示,在年轻卵巢中GC主要由增殖型及类固醇生成型亚群构成,而在衰老卵巢中应激及凋亡相关亚群显著扩增(表2)。

跨物种比较表明,该重塑模式在总体趋势上具有保守性,但存在程度与时间尺度差异(表3)。具体

表1　人类与小鼠卵母细胞衰老相关分子特征的跨物种比较

Table 1　Cross-species comparison of aging-associated molecular features in human and mouse oocytes

比较维度	人类卵母细胞	小鼠卵母细胞	差异本质
减数分裂停滞时间	30~40年	6~12个月	时间尺度差异[3,9]
非整倍体率(年轻)	10%~20%	<5%~10%	人类本底更高[9]
非整倍体率(老龄)	50%~70%	20%~30%	人类上升更剧烈[9]
非整倍体率上升曲线	指数型	线性或缓慢	错误积累方式不同[9]
黏连蛋白耗损(REC8)	明显减少	减少但幅度较小	人类耗损更严重[10]
SGO2丢失	显著	存在但程度较低	着丝粒保护更脆弱[10]
SAC本底强度	天然较弱	相对更强	质量控制阈值差异[11]
BUB1B/MAD2功能	老龄显著减弱	部分保留	人类易突破检查点[3]
纺锤体异常率	高	中等	微管附着更不稳定[12]
DNA损伤积累	高	中等	停滞时间驱动[13]
线粒体功能下降	明显	存在但可代偿	能量代谢韧性不同[3]
卵泡耗竭节律	加速性耗竭	平稳下降	激活阈值不同[3]

表2　卵巢衰老过程中颗粒细胞亚群重编程及动态变化特征

Table 2　Dynamic reprogramming of granulosa cell subpopulations in ovarian aging

GC亚群	主要功能	标志基因	比例变化	分化轨迹
增殖型	细胞增殖与GC扩增;支持卵泡生长	MKI67、TOP2A、PCNA、BIRC5	显著下降	年轻:Mitotic、Preantral、Mural; 衰老:分化受阻或凋亡偏移
窦前-卵丘型	支持卵泡早期发育;维持代谢与细胞通讯	GJA1、IDH1、PRDX4、FSHR	明显下降	年轻:Preantral、Antral; 衰老:向凋亡样转向
窦状-卵丘型	促进卵母细胞成熟;调控卵泡液微环境	HAS2、PTGS2、TNFAIP6、EGFR	轻-中度下降	向衰老样终末重定向
壁层型	类固醇生成与LH响应调控	CYP19A1、STAR、INHA、INHBB、HSD3B1	明显下降	年轻:终末分化; 衰老:转入衰老样
Ghr^{+}过渡型	过渡分化状态;响应生长激素信号	GHR、IGF1R、ESR2	不稳定;部分停滞	分化轨迹分叉:部分凋亡,部分维持低活性
凋亡富集型	DNA损伤应答与凋亡执行	CDKN1A、BAX、BBC3、TP53	衰老时显著上升	来自Preantral或Mitotic亚群的重定向
SASP高表达型	分泌炎症因子与微环境重塑	IL6、TGFB1、CDKN2A、MMP3	显著增加(老年特异)	源自Mural/Antral终末转化

表3 人类与小鼠颗粒细胞衰老特征的跨物种比较

Table 3 Comparative analysis of aging-associated features in human and mouse granulosa cells

比较维度	人类	小鼠	启示
衰老节律	缓慢进展,伴阶段性断崖式下降	生命周期短,渐进式变化	小鼠适用于早期机制研究
GC总量	显著下降	下降较缓	人类衰退更剧烈
类固醇生成亚群	Mural亚群减少;CYP19A1显著下降	下降但保留部分活性	人类更易出现内分泌失衡
增殖亚群	明显减少	减少但仍可检测	小鼠保留一定再生潜力
氧化应激/代谢通路	NAD^+代谢/抗氧化通路显著下调	以氧化磷酸化紊乱为主	氧化应激为共同核心机制
SASP亚群扩增	显著扩增;炎症反应增强	存在但程度较轻	人类更易放大炎症
DNA损伤反应	γH2AX与p21信号显著增强	激活但幅度较低	人类更易进入不可逆衰老
免疫耦联	与M1型巨噬细胞高度相关	相关性较弱	人类更适用于炎症研究
神经调控敏感性	交感神经调控显著增强	调控存在但相对温和	人类调控网络更复杂
整体衰老模式	炎症主导+功能快速衰退	代谢主导+渐进性衰退	模型外推需谨慎

而言,在人类中,类固醇生成GC亚群比例下降更为显著,成熟壁层GC呈现“断崖式”功能衰退;而小鼠则表现为相对渐进的比例变化,部分功能亚群在高龄阶段仍保留一定活性。此外,人类GC在衰老过程中炎症及DNA损伤相关通路富集更显著,衰老相关分泌表型(senescence-associated secretory phenotype,SASP)样亚群扩增程度更高。

两物种均出现线粒体功能障碍与抗氧化能力下降,但人类GC中NAD^+代谢与氧化应激调控基因的下调幅度更大。研究发现,FOXP1[16]与NCOA7[17]的表达下调,进一步激活p53/p21和JNK/p38等信号通路,使功能型亚群向凋亡/衰老样(apoptotic/senescent-like)细胞状态偏移。拟时序分析显示,年轻状态下“增殖型(mitotic)、窦前(preantral)、壁层(mural)”的分化成熟轨迹在衰老过程中发生偏移,人类GC更早地向凋亡/衰老样细胞偏移,而小鼠则保留部分可塑性。

此外,炎症微环境在GC重编程中的作用在人类中更为突出。衰老卵巢中IL-6、TGF-β等炎症因子显著升高,与SASP样GC亚群扩增高度相关;尽管小鼠中亦存在类似趋势,但效应相对较弱。然而,即使是较低程度的炎症改变,也足以通过促进胶原沉积、增加组织刚度及降低跨透明带突起(transzonal projections,TZPs)密度,间接损害卵母细胞的代谢与信号整合能力[14]。

1.3 卵泡膜细胞结构重塑与功能重编程

在年轻卵巢中,卵泡膜细胞(theca cell,TC)有序分布于卵泡基底膜外侧,形成结构明确的双层组织:内层类固醇生成细胞负责雄激素合成,外层成纤维样和平滑肌样细胞参与机械支撑与局部血流调控。该结构单元通过与GC和血管网络的紧密互作,构成卵泡单元与内分泌及血管协同功能模块。随着卵巢衰老进展,TC排列逐渐紊乱,卵泡膜结构完整性受损[18]。单细胞转录组分析显示,类固醇生成型TC亚型减少,而基质样表型亚群比例相对增加,卵泡膜细胞发生“细胞身份漂移”或向间质样表型细胞转分化[19,20]。在功能层面,类固醇生成能力显著下降,表现为关键合成酶表达降低及胆固醇转运通路活性减弱,导致雄激素供给不足,从而限制颗粒细胞芳香化反应并降低雌激素生成[7,18]。此外,在闭锁卵泡中,内层TC可发生肥大并形成“次级间质腺”样结构。随着功能性卵泡数量减少,该类结构逐渐在卵巢中占据主导,使卵巢由周期性雌激素分泌模式转向持续性低水平雄激素分泌模式[7,21]。值得指出的是,衰老相关β-半乳糖苷酶活性主要集中于卵泡膜-间质细胞群体,提示TC对衰老刺激更为敏感。衰老TC获得典型SASP表型,分泌多种促炎细胞因子、趋化因子及基质金属蛋白酶,进而诱导颗粒细胞凋亡、破坏卵泡结构并促进卵巢纤维化[22,23]。跨物种比较显示,人类与小鼠在TC衰老的基本分子路径上具有保守性,但在人类中SASP相关基因富集程度更高,结构紊乱与功能退化更为显著。

1.4 卵巢内皮细胞衰老特征

卵巢内皮细胞(ovarian endothelial cell,OEC)通过调节血管通透性、局部血流灌注及氧供,并介导血管生成信号,维持卵巢组织微环境稳态。卵巢衰老在组织层面表现为血管密度下降、微血管稀疏化及毛细血管分支减少[19,23,24]。单细胞测序分析显示,OEC亚群比例随年龄下降,内皮标志基因(CD31、CD34和KDR)表达整体下调,血管生成相关转录网

络活性减弱[3]。VEGF-KDR轴是调控卵巢血管生成的核心通路,但其信号响应能力在衰老过程中显著下降,这一下降并非源于VEGF配体不足,而主要与卵巢血管内皮细胞自身的衰老密切相关[25]。在细胞层面,OEC端粒缩短导致其增殖能力下降并进入衰老状态[24],衰老OEC呈现典型SASP特征,包括炎症因子和趋化因子表达上调,SA-β-gal活性增强及NF-κB信号持续激活[26]。该状态不仅加剧卵巢慢性低度炎症,还通过促进局部缺氧与成纤维细胞活化,驱动胶原沉积及组织刚度增加,形成"血管退化-缺氧-纤维化"的正反馈环路[16,23]。跨物种研究表明,小鼠OEC衰老可早于卵泡储备显著下降,提示血管改变可能为早期驱动事件[24];而在人类中,OEC比例下降与卵泡耗竭更趋同步,呈渐进性变化[19]。

1.5 卵巢基质细胞衰老特征

卵巢基质细胞(包括成纤维细胞、间充质干细胞(mesenchymal stem cell,MSCs)和血管周细胞)构成组织结构支架及信号整合平台。随着年龄增长,基质细胞衰老以纤维化增强、炎症因子上调和机械微环境硬化为核心特征[14,27,28]。在数量层面,基质细胞相对比例随卵巢衰老逐渐增加[29,30]。在分子层面,胶原降解酶表达下降而胶原蛋白表达相对稳定,导致胶原异常沉积;同时,透明质酸(hyaluronic acid,HA)合成减少而降解增强,进一步改变细胞外基质组成[29]。这些变化显著提高组织刚度,并激活YAP/TAZ等机械感受通路,促进成纤维细胞向肌成纤维细胞转分化,从而加剧纤维化进程[31,32]。在细胞亚群层面,衰老成纤维细胞持续分泌促炎及促纤维化因子[2,33,34];间充质干细胞数量减少且功能退化,表现为修复能力下降而炎症分泌增强[35];血管周细胞减少并导致其与内皮细胞的相互作用受损,进一步破坏血管稳定性[36]。

1.6 卵巢组织中交感-胶质网络衰老特征

卵巢内存在由交感神经纤维与胶质细胞构成的神经-胶质网络,其在发育及卵泡调控过程中发挥重要作用。出生后,人类和小鼠卵巢中的酪氨酸羟化酶阳性交感神经纤维与S100B阳性胶质细胞主要定位于髓质;伴随发育进程,两者逐渐向皮质迁移,最终分布于卵泡膜及间质区域。功能研究表明,在发育早期阻断该网络可抑制卵泡激活,表现为原始卵泡储备增加而生长卵泡减少,提示其参与卵泡募集调控。在衰老过程中,该网络呈现显著的代偿性重塑特征,表现为交感神经轴突密度增加,并与卵泡储备耗竭呈同步变化[3]。这一现象提示,神经信号可能由生理调控转向应激驱动,参与卵巢衰老过程中的功能重编程。

1.7 卵巢组织中免疫细胞衰老特征

随着卵巢衰老,免疫系统呈现数量扩增与谱系重塑并存的特征,表现为由先天免疫向适应性免疫倾斜的"免疫衰老"模式[14,37]。单细胞研究显示,衰老小鼠卵巢中$CD8^+$ T细胞数量增加,$CD4^+$ αβ T细胞数量下降,导致$CD4^+/CD8^+$ T细胞比值下降;在$CD4^+$ T细胞亚群中,辅助性T细胞Th1及Th17比例上升,而调节性T细胞(Treg)和Th2比例下降[13,38]。此外,自然杀伤T细胞(NKT细胞)及γδ T细胞比例显著增加,而B淋巴细胞比例无显著改变[14]。巨噬细胞在衰老过程中数量显著增加,并发生功能重编程,表现为促炎因子分泌增强、吞噬功能下降,呈现促炎且代谢紊乱的衰老相关表型[28,39]。以上转变增强了炎症反应并破坏组织稳态。

2 卵巢衰老的共性分子机制

卵巢衰老涉及卵母细胞、颗粒细胞、基质细胞及血管内皮细胞等多种细胞类型的协同功能衰退。尽管各类细胞在衰老过程中的表型特征存在显著差异,但现有研究表明,其分子病理改变存在明显的共性。具体而言,DNA损伤修复效率下降导致的基因组不稳定累积、染色质可及性改变伴随的转录程序重编程、蛋白质折叠与降解系统功能受损,以及线粒体氧化磷酸化效率降低伴随的代谢重编程,在衰老卵巢的各类细胞中普遍存在。更为重要的是,这些过程并非孤立发生,而是通过信号通路的交叉对话形成正反馈调控网络,共同驱动卵巢功能的整体衰退,构成了卵巢衰老的核心分子基础(图2)。

2.1 基因组不稳定性

减数分裂质量控制失效。染色体稳定性下降是卵母细胞衰老的核心特征之一。随着年龄增长,黏连蛋白复合体关键组分REC8和SMC1β发生进行性丢失,同时着丝粒保护因子SGO2(shugoshin 2)定位异常,导致姐妹染色单体黏连稳定性下降[13]。此外,SAC关键分子BUB1B(BUB1 mitotic checkpoint serine/threonine kinase B)和MAD2(mitotic arrest deficient 2)表达及活性均显著减弱[11,40],从而削弱减数分裂质量控制能力,导致非整倍体发生率随年

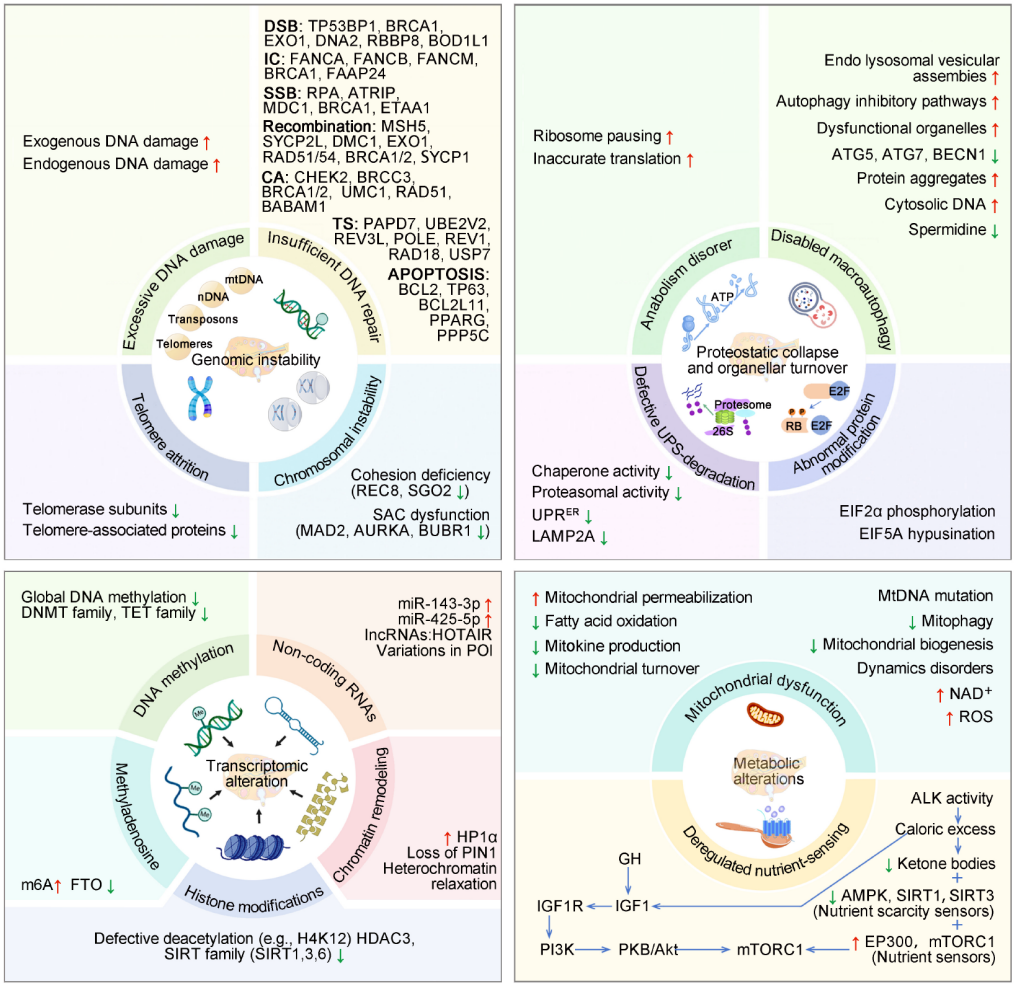


图2 卵母细胞衰老的分子特征与调控机制

卵母细胞衰老由多层级分子异常协同驱动，主要包括：基因组不稳定性增加、表观遗传与转录组异常、蛋白质稳态失衡以及能量代谢重编程。随着年龄增长，DNA损伤逐渐累积、DNA损伤修复能力衰退、染色体分离异常及端粒缩短共同促进基因组稳定性被破坏。在表观遗传层面，DNA甲基化修饰模式重构、组蛋白修饰异常以及RNA转录后修饰和非编码RNA调控网络重塑，通过整合遗传因素与环境信号，调控卵巢衰老进程。在蛋白质稳态层面，蛋白质合成、折叠及降解系统功能逐渐衰退，导致错误折叠蛋白积累及细胞应激反应增强。在代谢层面，线粒体功能障碍、能量生成能力下降及营养感知信号失衡共同削弱卵母细胞代谢稳态。DSB：双链断裂；SSB：单链断裂；IC：链内交联；TS：跨损伤合成；CA：检查点激活；SAC：纺锤体组装检查点；lncRNA：长链非编码RNA；UPS：泛素-蛋白酶体系统。

Figure 2 Molecular hallmarks and regulatory mechanisms of oocyte aging

Oocyte aging is driven by coordinated multi-level molecular abnormalities, primarily including increased genomic instability, epigenetic and transcriptomic dysregulation, loss of proteostasis, and metabolic reprogramming. With advancing age, the progressive accumulation of DNA damage, decline in DNA repair capacity, chromosomal segregation errors, and telomere shortening collectively contribute to the disruption of genomic stability. At the epigenetic level, remodeling of DNA methylation patterns, aberrant histone modifications, and alterations in RNA post-transcriptional modifications and non-coding RNA regulatory networks integrate genetic and environmental signals to regulate ovarian aging. At the level of protein homeostasis, the gradual deterioration of protein synthesis, folding, and degradation systems leads to the accumulation of misfolded proteins and enhanced cellular stress responses. Metabolically, mitochondrial dysfunction, reduced energy production capacity, and dysregulated nutrient-sensing pathways jointly impair metabolic homeostasis in oocytes. DSB: double-strand break; SSB: single-strand break; IC: intrastrand crosslink; TS: translesion synthesis; CA: checkpoint activation; SAC: spindle-assembly checkpoint; lncRNA: long non-coding RNA; UPS: ubiquitin-proteasome system.

龄呈指数式上升，在高龄卵母细胞中可高达50%~70%[9,41]。

DNA修复能力衰退。在高龄卵母细胞中，多种DNA修复通路功能受损，包括DNA双链断裂修复、同源重组、链间交联修复、单链断裂修复等DNA修复相关关键蛋白表达下降或功能异常[38]。由于卵

母细胞长期停滞于减数分裂前期，对DNA损伤的累积高度敏感。值得注意的是，携带*BRCA1/2*及*MCM8/9*等基因杂合致病变异的女性，常表现出卵巢储备下降及提前绝经的趋势[42]。

端粒-线粒体互作失调。随年龄增长，端粒酶及shelterin复合体相关组分表达下调，端粒T-loop结构的保护功能随之减弱[43,44]。端粒功能障碍可诱导ROS产生增加，而ROS的过量积累又反过来加剧端粒DNA的氧化损伤，使端粒缩短与氧化应激之间形成自我强化的恶性循环。这种交互作用显著加速了基因组不稳定性的渐进累积[45,46]。

2.2 表观遗传和转录组重塑

卵巢衰老伴随多层级表观遗传调控网络的系统性重编程，涵盖DNA甲基化、组蛋白修饰及RNA调控等多个维度。

随年龄增长，卵母细胞及颗粒细胞的DNA甲基化维持系统发生渐进性失衡。DNMT1表达下调削弱了复制依赖性甲基化记忆的稳定传递，而DNMT3A/3B的异常升高则促进了非预期的从头甲基化事件，加之TET1/2介导的氧化去甲基化效率下降，共同导致5-甲基胞嘧啶与5-羟甲基胞嘧啶的代谢比例失调[47-51]。在基因组层面，这种失衡表现为全基因组范围的低甲基化与特定调控区域的高甲基化并存。上述表观遗传改变的功能影响是双向的：一方面抑制了减数分裂调控、DNA损伤修复及线粒体稳态相关基因的表达；另一方面通过解除对炎症反应及mTOR、IGF等生长信号通路的表观遗传约束，驱动原始卵泡的过度耗竭。此外，甲基化结合蛋白MeCP2异常积累可介导rDNA启动子区域高甲基化，干扰甲基化阅读器功能，从而进一步加速衰老进程中早期卵泡的丢失[52]。

在染色质结构层面，衰老卵巢中组蛋白修饰酶系统亦发生显著改变。多种组蛋白甲基转移酶及Sirtuin家族成员表达下调[53-55]，伴随异染色质标记H3K9me3和H4K12ac水平降低[56]，导致染色质从致密结构向相对开放且不稳定的状态转变。这种异染色质完整性的丧失增加了转录噪声，破坏了基因表达的精确调控[57]，进而促进细胞衰老表型的形成。

在转录后调控层面，非编码RNA及RNA修饰网络亦发生广泛重塑。研究表明，原发性卵巢功能不全（primary ovarian insufficiency，POI）患者血浆中miR-22-3p显著下调[58]，且lncRNA *HOTAIR*基因多态性与POI易感性相关[59]，提示非编码RNA表达谱的改变可能参与调控卵巢储备下降。此外，N^6-甲基腺苷（m^6A）修饰水平整体升高，而去甲基化酶基因*FTO*表达显著降低[60-61]，表明RNA修饰介导的转录后调控效率在衰老过程中受到明显干扰。

2.3 蛋白质稳态失衡

蛋白质稳态网络在卵巢衰老过程中发生系统性崩解，涉及蛋白质合成、折叠及降解等多个关键环节。

翻译与蛋白质折叠失调。在卵巢衰老过程中，蛋白质合成与折叠调控发生显著紊乱。衰老细胞普遍存在核糖体生物发生障碍[6,52,62]。尽管mTORC1活性升高，但eIF4F复合体组装受抑，形成“调控信号与执行机制脱节”的异常状态[63]，从而选择性抑制含复杂5′UTR（untranslated region）结构的mRNA的翻译效率，由此导致错误折叠蛋白逐渐积累，持续激活内质网应激及未折叠蛋白反应（unfolded protein response，UPR）。长期UPR经CHOP（C/EBP homologous protein）介导的通路诱导细胞凋亡，促进卵泡闭锁[64]。

蛋白质降解系统功能衰退。随着年龄增长，细胞内泛素-蛋白酶体系统活性逐渐下降[65,66]，导致受损及异常蛋白清除能力减弱，进而加剧氧化应激。同时，自噬-溶酶体系统功能亦显著受损[67]。溶酶体功能障碍甚至可直接诱导POI表型[68-70]。此外，高龄卵母细胞中分子伴侣蛋白（如HSP70与HSP90）表达下降，进一步削弱蛋白质折叠纠错能力，使蛋白质质量控制网络处于高负荷状态[71]。

2.4 能量代谢紊乱

在卵巢衰老过程中，能量代谢网络发生系统性重编程。线粒体功能衰退、代谢辅因子渐进耗竭以及营养感知信号失调相互交织，共同构成卵巢衰老的代谢病理基础。

在线粒体层面，衰老卵母细胞呈现数量减少及结构异常比例升高，线粒体DNA拷贝数与膜电位显著下降[72-75]。线粒体动力学亦发生改变，融合过程减弱而分裂活动增强，引起线粒体碎片化及功能退化。融合蛋白MFN1/2表达异常或分裂调控蛋白Drp1活性失调，均可加速卵泡储备耗竭并阻碍卵母细胞成熟[76-78]。此外，线粒体自噬清除效率下降造成ROS过度积累，进一步加重细胞损伤[79-81]。

在代谢辅因子层面，衰老卵巢微环境中的基质

细胞及巨噬细胞呈现CD38表达上调，加速NAD^+水解[82,83]。NAD^+水平下降导致Sirtuin家族成员活性受损，不仅削弱细胞的抗氧化与代谢调控能力，还促进炎症信号放大。这种代谢失衡、氧化应激与炎症反应之间的交互强化，构成了卵巢衰老进程的重要机制基础[84]。

在脂质代谢层面，老龄卵母细胞中脂滴异常积累[85]，同时肉碱棕榈酰转移酶1A(CPT1A)表达下调，限制脂肪酸向线粒体的转运及β-氧化效率[86]。脂质储存增加与氧化利用能力下降并存，代谢灵活性的降低削弱了卵母细胞应对能量需求变化的适应能力。

在营养感知层面，mTOR、AMPK及IGF-1信号通路协同调控卵泡激活与能量代谢稳态[87,88]。衰老卵巢中AMPK活性下降，使细胞对能量应激的感知能力减弱[89]；而mTORC1持续活化则抑制自噬起始，并驱动原始卵泡过度激活[90]。遗传学证据表明，*Pten*或*Tsc1*/*Tsc2*缺失可导致原始卵泡同步启动并快速耗竭[91,92]；相反，抑制mTOR信号能够显著延缓卵泡消耗及卵巢衰老进程[93,94]。

3 卵巢内细胞间互作的衰老重塑

近年来，单细胞转录组、空间转录组和功能遗传学研究表明，卵巢衰老本质上是多细胞网络结构的系统性重构，是涉及卵母细胞与神经、血管、免疫及基质细胞之间复杂互作关系的动态再平衡。

3.1 卵泡核心互作单元的内源性失稳

越来越多证据提示，卵巢衰老的早期驱动因素并非单纯卵母细胞数量减少，而是卵泡核心单元内跨细胞耦联系统的渐进性失稳。

首先，卵母细胞与颗粒细胞之间的代谢与信号通讯发生“双重阻断”。在生理状态下，两者通过Cx37/Cx43介导的缝隙连接交换NAD^+前体、丙酮酸、cAMP(cyclic adenosine monophosphate)等关键代谢物与第二信使，从而实现代谢支持和信号调控的高度协同。在衰老过程中，缝隙连接功能受损，导致代谢物转运效率下降，卵母细胞ATP生成不足，以及第二信使传递受阻，进而导致减数分裂阻滞维持与解除失衡，并产生离子交换障碍，使得卵母细胞内钙信号与膜电位调控紊乱；同时，透明带突起数量减少及结构异常[95]，与缝隙连接功能障碍叠加，进一步削弱GC-卵母细胞之间的直接通讯能力，形成“代谢-通讯双重阻断”；最终，使得卵母细胞在生理以及功能上处于“支持剥夺”状态[96]。代谢支持下降与通讯失效相互强化，构成局部恶性循环。

其次，卵泡旁分泌调控网络发生双向衰减。卵母细胞分泌的GDF9(growth differentiation factor 9)和BMP15(bone morphogenetic protein 15)在维持GC增殖、分化及促性腺激素(Gn)反应性中发挥关键作用，其中GDF9调控卵丘细胞特异性基因表达，BMP15增强GC对促卵泡激素(FSH)的敏感性并参与卵泡膜细胞分化及类固醇生成[96]。在衰老过程中，卵母细胞分泌能力与GC响应性同步下降[97]，导致这一正反馈调控回路逐步瓦解。

此外，类固醇合成体系亦呈渐进式失衡。卵泡内类固醇合成依赖GC-TC“双细胞-双促性腺激素”精密协同机制，而衰老可导致TC雄激素生成能力下降及GC芳香化效率降低，从而改变局部雌激素微环境，削弱优势卵泡选择机制并降低卵泡资源利用效率。

综上，卵泡核心单元的衰老可概括为“代谢-信号-类固醇”三元耦联系统的整体退化，其中代谢支持模块(线粒体功能、糖酵解效率、代谢物转运)提供能量和底物；信号通讯模块(缝隙连接、TZPs、旁分泌)协调时空调控；类固醇合成模块(TC雄激素合成、GC雌激素合成、细胞间协作)输出激素并反馈调节上游模块。三者相互依赖，其协同失衡构成卵巢功能衰退的内源性基础。

3.2 神经-血管-免疫-基质细胞网络的重塑

卵泡嵌入于高度耦合的神经-免疫-血管-基质网络，其稳态依赖多细胞间信号、代谢及结构支持的精密协同。衰老导致该网络发生多层级重编程，从而驱动卵泡微环境失稳。

首先，神经-血管耦联发生功能失配。交感神经释放去甲肾上腺素(norepinephrine，NE)，通过α1-肾上腺素能受体(α1-adrenergic receptor，α1-AR)调控血管收缩[98]，通过β2-AR刺激TC类固醇生成并在GC中激活β-AR-cAMP-PKA通路上调血管内皮生长因子(vascular endothelial growth factor，VEGF)表达[99]。然而，在衰老卵巢中，交感神经异常增强[3]，而血管内皮对VEGF的响应(如VEGFR2磷酸化)减弱[25]，血管生成与舒张反应功能衰退，形成“神经输出增强-血管响应迟钝”的功能失配状态。

其次，血管衰老与炎症反应形成正反馈环路。血管结构退化早于卵泡耗竭[24]，血管稀疏化导致

局部低氧与ROS升高,进而激活HIF-1α(hypoxia-inducible factor-1 alpha)与NF-κB通路,诱导OEC进入SASP状态[100]。SASP相关因子进一步促进单核细胞募集及巨噬细胞向促炎表型偏移,并激活NLRP3(NOD-like receptor family pyrin domain containing 3)炎症小体,导致IL-6、TNF-a等炎症因子持续释放。此外,中年小鼠卵巢(仍处生殖活跃期)已出现淋巴细胞谱系扩张,提示适应性免疫亦参与卵巢炎性衰老进程[3,14]。

最后,基质重塑驱动"纤维化-炎症-血管退化"恶性循环。衰老过程中胶原及层粘连蛋白沉积增加,组织硬度上升[101]。衰老成纤维细胞持续分泌TGF-β、IL-6及基质金属蛋白酶(matrix metalloproteinases,MMPs),在促进炎症及纤维化的同时抑制血管生成信号,从而导致持续性微环境恶化。

总体而言,卵巢衰老可视为卵泡内耦联系统解体与间质网络重编程的协同过程,形成多节点正反馈网络,推动卵巢从功能可塑性阶段向维持性衰老状态转变。这一过程具有非线性特征,可能表现为跨越临界阈值后的网络相变。识别该临界点及其分子标志,对于延缓卵巢功能衰退具有重要意义。

4 卵巢衰老驱动体细胞器官衰老的核心信号通路

4.1 经典内分泌途径

卵巢衰老导致雌二醇(estradiol,E2)、抗缪勒管激素、抑制素和激活素(activin)等关键卵巢分泌激素发生系统性改变。这些变化通过下丘脑-垂体-卵巢轴的反馈调节,引发FSH等激素代偿性升高,从而形成全身性内分泌失衡状态。

其中,E2缺失被认为是驱动全身性衰老最直接且核心的信号之一。E2通过雌激素受体(estrogen receptor,ER)介导其生物学效应,而该受体在心血管系统、骨组织及中枢神经系统等多种器官中广泛表达,使得E2缺失可对全身多器官功能产生广泛影响[102]。

与此同时,FSH水平升高不仅是内分泌反馈的结果,还被认为是多器官衰老的主动调控因子。其受体FSHR除在卵巢颗粒细胞中表达外,还存在于骨组织、脂肪组织及中枢神经系统中,从而赋予FSH直接参与多器官系统调控的能力[103]。研究表明,血清FSH可通过激活破骨细胞的MEK/ERK、NF-κB和Akt等信号通路促进破骨细胞活化并增强骨吸收[104];在脂肪组织中,FSH通过上调脂肪生成相关基因表达并抑制棕色脂肪细胞中Ucp1(uncoupling protein 1)活性,促进脂质合成和中心性肥胖的形成[105,106];在神经系统中,FSH可上调大脑皮层及海马神经元中C/EBP的表达,促进淀粉样前体蛋白累积和Tau蛋白异常磷酸化,从而诱导神经元凋亡并增加阿尔茨海默病(Alzheimer's disease,AD)发生风险[107]。

4.2 卵巢衰老相关分泌表型与炎性衰老

随着卵巢衰老进程推进,卵巢内不同细胞类型呈现出差异化的衰老相关分泌表型。这些细胞协同作用后可过量分泌白细胞介素(IL-1、IL-6、IL-8等)及趋化因子等多种炎症介质,并以自分泌或旁分泌方式在卵泡局部乃至整个卵巢微环境中发挥作用,导致促炎反应增强、纤维化进展及组织稳态失衡。

进一步地,随着卵巢衰老进展,大量SASP因子释放进入循环系统,诱导全身性慢性低度炎症状态,从而在系统层面促进多器官功能衰退及年龄相关疾病的发生[82,108,109]。

表4对卵巢内不同细胞类型来源的SASP差异进行了比较 。

4.3 卵巢外泌体在卵巢衰老过程中的变化

卵巢组织中多种细胞类型分泌的外泌体及其他细胞外囊泡共同构成卵巢微环境中重要的细胞间通讯网络。GC来源的外泌体向卵母细胞递送多种生物活性分子,参与调控卵母细胞的生长发育和成熟[114,115]。卵泡液细胞外囊泡(follicular fluid-derived extracellular vesicles,FF-EVs)作为卵泡液的重要组成部分,可全面反映卵泡整体生理和代谢状态[116,117]。在卵巢衰老过程中,FF-EV的数量、粒径分布及携带物等均发生显著改变,这些变化被视为卵巢储备功能下降及卵母细胞质量降低的重要分子标志[118]。卵巢间充质干细胞来源的外泌体通常富含促进组织修复与再生的分子,但随着卵巢衰老,间充质干细胞的数量与功能逐渐衰退,其外泌体组成也由促修复型向促衰老型转变[119]。

5 卵巢衰老对全身多个器官系统的影响

5.1 心血管系统

5.1.1 相关性证据

卵巢衰老导致的雌激素缺失被认为是全身多器

表4 卵巢内不同细胞类型来源的衰老相关分泌表型(SASP)差异比较

Table 4 Differences in senescence-associated secretory phenotypes across distinct ovarian cell types

细胞类型	标志性SASP因子	功能偏向	特征	作用范围
卵母细胞	待深入解析(推测MDK)	自主衰老维持、微环境破坏信号启动	SASP强化自身衰老状态[16]	卵泡局部,自分泌为主
颗粒细胞	IL-1β、IL-6、IL-8、CCL2	卵泡功能抑制、卵母细胞质量下降、激素合成失调	SASP强化自身衰老状态,37至39岁阶段IL-8显著升高[16]	卵泡内,自分泌+旁分泌
卵泡膜细胞	CCL5(标志性)、DLK1	卵泡发育阻滞、颗粒细胞凋亡、血管交互调控	SASP扩散至邻近细胞,诱导继发性衰老;CCL5在早期就诱导表达[16,22]	卵泡周围,局部高浓度效应
基质/成纤维细胞	IL-1α、IL-6、MMP12、PAI-1、IGFBP3	基质纤维化、旁分泌衰老传播、ECM重塑	SASP扩散至邻近细胞,诱导继发性衰老;在中年向老年的过渡期,从促炎通路向TGF-β/SMAD纤维化信号转变[23,110-112]	卵巢间质广泛,旁分泌为主
内皮细胞	抗原呈递分子(MHC Ⅰ/Ⅱ)、IL-6、IL-8	血管功能障碍、免疫激活、屏障破坏	兼具局部和系统性效应[23,113]	连接卵巢局部与全身性炎性衰老
免疫细胞	IL-6、TNF-α,及多种趋化因子(CCL2-5)	维持慢性炎症、促进纤维化	兼具局部和系统性效应[110]	连接卵巢局部与全身性炎性衰老

官衰老的驱动因素之一(图3)。绝经后心血管疾病风险升高与卵巢衰老显著相关。大规模前瞻性研究结果表明,绝经年龄与冠心病(coronary heart disease,CHD)患病风险呈负相关:绝经每提前1年,CHD风险增加约2%~3%,手术绝经女性较自然绝经女性患CHD风险增加25%(HR=1.25,95% CI:1.10~1.42)[120];而早绝经女性心衰风险增加33%(HR=1.33,95% CI:1.15~1.53)[121]。这些研究支持"激素骤降"假说,即E2突然缺失比渐进性下降更易破坏血管稳态。激素替代治疗(hormone replacement therapy,HRT)呈现显著时间依赖性,WHI(Women's Health Initiative,WHI)的年龄分层分析显示,<60岁或绝经≤10年内启动HRT者CHD风险下降,而≥60岁或延迟启动则风险升高[122]。长期随访数据表明,绝经10年内启动HRT可降低全因死亡率约30%,心血管死亡率下降40%~50%,确立"启动时机"是HRT干预的决定性变量[123]。

5.1.2 因果性证据

双侧卵巢切除(ovariectomized,OVX)动物模型为E2的血管保护作用提供直接因果证据。OVX大鼠对乙酰胆碱诱导的血管舒张反应下降50%~60%[124],且OVX主要损害乙酰胆碱诱导的内皮依赖性舒张,而自然衰老更多涉及非内皮依赖机制[125]。人群研究亦显示,急性E2剥夺能通过增强环氧合酶(COX)依赖性收缩因子生成而损害内皮功能[126]。E2早期替代处理可部分逆转OVX大鼠的氧化应激、代谢紊乱及血管功能异常[127-130];而延迟治疗则难以逆转血管壁结构重构[131]。在ApoE$^{-/-}$小鼠中,OVX显著加速主动脉根部粥样硬化斑块形成,而E2干预可完全阻断该加速效应[132,133]。

5.2 骨骼系统

5.2.1 相关性证据

骨质疏松是卵巢衰老最明确的器官效应。50岁以上女性约30%经历过骨质疏松性骨折[134],且髋部骨折风险随绝经年龄增加呈指数级增长[135]。45岁前绝经者骨折风险增加36%(OR=1.36,95% CI:1.11~1.66)[136];SWAN队列的22年随访数据显示,绝经年龄每提前1年,骨折风险增加约5%[137,138]。

卵巢储备标志物与骨密度(bone mineral density,BMD)存在剂量依赖关系。AMH<100 pg/mL对早期快速骨丢失的预测敏感性达80%[139]。AMH每降低1个标准差,腰椎快速骨丢失风险增加45%[140];生育中期AMH<1.0 ng/mL者在绝经过渡期后腰椎与髋部BMD显著更低[141],提示骨丢失启动早于显性雌激素下降阶段。

促性腺激素与抑制素构成的内分泌调控轴可相对独立地调控骨转换。在围绝经期和绝经早期,FSH水平与骨吸收标志物CTX(C-terminal cross-linked telopeptide of type Ⅰ collagen)及骨形成标志物PINP(N-terminal propeptide of type Ⅰ procollagen)显著正相关,且FSH>35 IU/L时骨丢失风险显著增加[142]。此外,在围绝经期阶段,抑制素A/B较FSH或E2更能敏感地反映骨转换变化[143,144]。整体证据提示,围

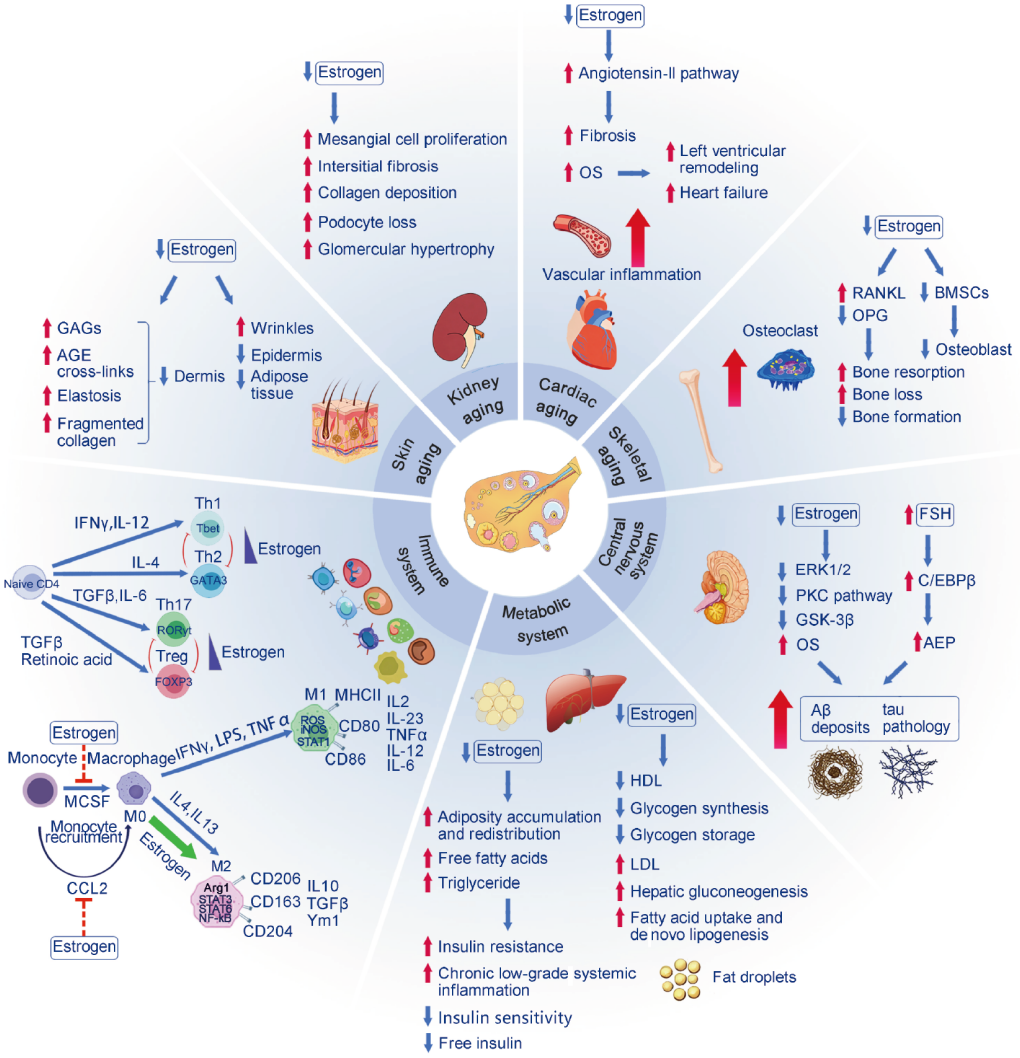


图3　卵巢衰老后雌激素缺失驱动多器官协同退化

衰老卵巢通过内分泌信号重塑以及持续释放SASP因子，在全身范围内放大卵巢衰老的生理影响。该过程促进心血管系统、骨骼系统和中枢神经系统等多个组织器官的协同衰退。

Figure 3　Ovarian aging-induced estrogen deficiency triggers systemic multi-organ decline

The aging ovary amplifies the systemic physiological impact of ovarian aging by reshaping endocrine signaling and persistently releasing senescence-associated secretory phenotype (SASP) factors throughout the body. This process promotes coordinated functional decline across multiple organ systems, including the cardiovascular, skeletal, and central nervous systems.

绝经期骨脆弱性的早期发生，可能主要源于卵巢储备下降所引发的多肽类调控信号失衡，而非单纯由雌激素缺乏所致。

HRT对骨折具有明确保护作用。来自WHI的汇总分析（n=25 389）显示，HRT显著降低任何临床骨折、主要骨质疏松性骨折及髋部骨折风险，风险比分别为0.72、0.60和0.66[145]。在随机对照试验（n=16 608）中，5.6年HRT使骨折发生率由11.1%降至8.6%（HR=0.76）[146]。然而，该保护作用在停药后迅速减弱[147]。一项纳入80 955例受试者的队列研究亦显示，停药女性髋部骨折风险较持续用药者增加55%，且该风险在停药后2年内即开始上升[148]。

5.2.2　因果性证据

OVX模型作为研究绝经后骨质疏松的标准试验体系，被广泛用于评估骨量变化及微结构损伤。显微CT（micro-computed tomography，micro-CT）纵向研究显示，术后4周内即出现显著松质骨丢失，骨体积分数下降幅度可达约40%[149-151]。这一过程伴随骨小梁数量减少、厚度变薄及分离度增加，呈现出典型的骨质疏松微结构退变特征[150]。骨丢失主要

集中于术后4~6周,随后进入相对稳定期[152-154]。在C57BL/6小鼠模型中,该骨丢失模式在松质骨与皮质骨层面均具有良好的重复性[153],并在6周内形成显著结构性损伤[155]。

5.3 中枢神经系统

5.3.1 相关性证据

绝经相关内分泌变化与认知功能下降密切相关。围绝经过渡期认知表现呈动态波动,其中绝经后第1年在语言记忆、工作记忆及精细运动功能方面出现显著下降[156]。流行病学研究进一步表明,绝经年龄偏离正常范围(<40或>55岁)与长期认知不良结局相关[157],提示神经系统对生殖衰老时间轴具有高度敏感性。手术绝经构成更强风险暴露:绝经前OVX女性认知障碍风险增加46%[158],而40岁前切除且未使用HRT者风险升高超过2.5倍[158]。此外,在*APOEε4*携带者中,认知障碍风险会进一步放大[159,160]。

在干预层面,观察性研究支持HRT在特定时间窗口内可降低AD风险。Cache County队列研究显示,长期(≥10年)使用HRT的女性AD风险降低59%[161];进一步的随访分析表明,仅在绝经后5年内启动HRT且持续≥10年的个体中观察到显著保护作用[162],而终生E2暴露与认知功能呈正相关[163]。相反,在晚年启动HRT则与AD风险增加48%相关[164]。这些结果共同支持"机会窗"假说,即E2干预对神经系统的影响取决于启动时机及持续时间。

5.3.2 因果性证据

多模态神经影像学证据表明,绝经过渡期构成女性脑结构与功能网络重塑的关键转折点。磁共振成像数据显示,绝经后海马年萎缩率达3.3%(绝经前<1%,P≤0.001)[165],且其萎缩速度与血清E2水平呈显著负相关[166]。在EPAD(European Prevention of Alzheimer's Dementia consortium)队列研究中,携带*APOEε4*且接受HRT的女性,其内嗅皮层与杏仁核体积增加约6%~10%;且HRT启动越早,海马体积越大[160]。此外,大规模群体影像数据库分析亦表明,HRT使用年限与海马旁回体积呈正相关[167]。

动物实验进一步揭示了相关潜在机制。OVX模型显示,E2在维持血脑屏障完整性方面发挥重要作用,但老年(18月龄)动物对激素的反应性显著减弱[168]。离体脑动脉研究发现,E2可维持年轻大鼠脑血管扩张功能,而在老年个体中则表现为相反的血管收缩效应[169],提示脑血管对激素的敏感性存在年龄相关逆转。此外,E2的神经保护作用具有明确"关键期":在OVX后0~10天内补充E2可产生显著保护效应,而延迟至≥21天则该效应基本丧失[170]。

在神经退行性疾病模型中,上述时间依赖性同样得到验证。灵长类猕猴OVX模型研究显示,术后30天黑质致密部酪氨酸羟化酶(TH)阳性神经元显著减少,而HRT可完全阻断该多巴胺能神经元退行性改变[171]。在AD小鼠模型中,OVX可加重海马与皮层β-淀粉样蛋白(amyloid-beta,Aβ)沉积,而HRT处理可有效阻止Aβ异常积累[172,173]。总体而言,这些证据表明,卵巢功能衰退通过脑血管调控、血脑屏障稳定性、神经元代谢及Aβ代谢等多通路协同作用,影响神经退行性风险,且具有显著时间依赖性特征。

临床试验进一步体现了这一时间效应。在WHIMS(Women's Health Initiative Memory Study)中,65~79岁女性启动HRT与痴呆风险增加相关[174,175],确立了晚期启动HRT的不利认知效应。相比之下,围绝经早期人群的随机对照研究(如ELITE队列及KEEPS-Cog队列)均未观察到HRT对认知功能的显著获益或损害[176,177],且在长达14年的延续随访中亦未显示长期认知差异[178]。

5.4 代谢系统

5.4.1 相关性证据

绝经后女性代谢综合征(metabolic syndrome,MetS)患病率显著升高约54%~58%[179-182]。围绝经期过渡期队列研究表明,FSH水平与体重指数(body mass index,BMI)、躯干脂肪质量、腰围及空腹血糖等多项代谢指标呈显著正相关[183-185],当FSH>40 IU/L时,6年内腰围平均增加约6 cm [186]。与此同时,AMH水平下降亦与代谢异常密切相关:AMH <0.7 ng/mL的女性的MetS患病率显著高于对照组(25.0% vs 14.8%,P<0.001)[187]。值得注意的是,荟萃分析显示肥胖可反向降低血清AMH浓度[188],提示肥胖与卵巢储备下降之间存在双向耦合关系。

在临床结局方面,早绝经女性发生2型糖尿病的风险较自然绝经者增加32%(HR=1.32,95% CI:1.04~1.69)[189],而手术绝经则进一步将该风险提高至57%(HR=1.57,95% CI:1.03~2.41)[190]。反之,2型糖尿病女性呈现出卵巢衰老加速的表型特

征[191]。二者形成代谢-卵巢功能衰退恶性循环。

5.4.2 因果性证据

SWAN(Study of Women's Health Across the Nation)队列随访3.5~6年显示,绝经后脂肪量平均增加约6%,并逐渐形成以中心性脂肪积聚为特征的"隐性肥胖"表型;磁共振成像定量分析进一步证实,绝经后内脏脂肪体积增加达36.5%[192-195]。在动物模型中,OVX小鼠于术后12周内体重增加超过30%,脂肪量接近翻倍[196]。干预研究显示,不同给药模式的E2对代谢调控产生显著差异。周期性E2替代(每4天一次,模拟动情周期)可完全逆转OVX所致体重增加,并恢复动情周期依赖性的摄食节律;相比之下,持续性E2给药仅部分降低体重,且无法重建生理性摄食波动[197]。这些结果提示,除激素水平本身外,其"动态节律"亦是维持代谢稳态的关键调控因素。

6 结论、研究不足与未来方向

6.1 结论

本综述阐述了卵巢功能衰退不仅标志着生殖能力的丧失,更是深刻影响着机体多个器官系统的健康与稳态。卵巢衰老的核心特征表现为卵母细胞数量与质量的不可逆下降,并伴随卵巢微环境中多细胞群体,包括颗粒细胞、卵丘细胞、卵泡膜细胞、基质细胞、内皮细胞及免疫细胞的协同衰老重塑,这些变化加速卵泡闭锁和内分泌功能衰退,构成卵巢衰老的组织学与功能学基础。

更为重要的是,卵巢衰老所产生的信号并非仅作用于卵巢器官,而是通过内分泌调控、细胞衰老相关分泌表型及外泌体等多层次通讯网络被系统性放大,并作用于远端器官,因此,卵巢衰老成为连接生殖衰退与多系统老化的关键节点,显著增加心血管疾病、骨质疏松、神经退行性疾病等年龄相关疾病的发生风险。

6.2 研究不足

尽管已有研究取得重要进展,但仍存在若干重要局限。首先,现有证据主要来源于小鼠模型,而啮齿类与灵长类在卵泡发育动力学及激素节律调控等方面存在本质差异(表5)。其次,卵巢组织内细胞异质性及其空间微环境的动态变化尚未得到充分解

表5　小鼠、灵长类(猴)与人类卵巢结构与衰老特征差异比较

Table 5　Comparative differences in ovarian structure and aging characteristics among mice, non-human primates (monkeys), and humans

参数	小鼠(C57BL/6)	食蟹猴	人类
性成熟时卵泡数量	~4 000个(2月龄)	~150 000个(4~5岁)	30~40万个(青春期)
卵巢储备耗竭模式	出生后急剧下降,随后稳定缓慢下降,6月龄后加速	持续缓慢下降	指数下降,37岁后加速
生殖寿命终点	~12月龄(不育)	~25岁(绝经)	~51岁(绝经)
围绝经期及其特征	无;发情周期不规律;原始卵泡<200个	有(约18~23岁);月经不规律;原始卵泡<3 000个[198]	有(约47~51岁);月经紊乱、潮热;原始卵泡<1 000个
生殖周期	4~5天发情周期	28~30天月经周期	~28天月经周期
端粒长度与端粒缩短速度	长度:50~150 kb;缩短速度~7 kb/年[199]	长度平均14.4 kb[200]	长度:10~15 kb;缩短速度:43~72 bp/年[201]
端粒长度与生殖衰老关系	端粒极长但缩短极快[202]	端粒长度与人类相似,围绝经期端粒仍维持~14 kb[200]	端粒缩短与卵巢衰老相关,绝经时(~51岁)端粒约6~7 kb
解剖结构差异			
皮质卵泡池	缺失	类似结构,卵泡区域萎缩[15]	年龄依赖性萎缩[3],OvaRePred 整合卵泡袋特征[203]
卵泡分布			
基质/卵泡比例	卵泡均匀分散分布[3]	区域性聚集	区域性聚集
组织硬度	变化相对温和	显著增加(老年期30%~40%纤维化)	年龄相关性显著增加
卵巢体积	中度增加	显著增加	显著增加(5~10 kPa)
	0.003~0.005 cm^3	2~4 cm^3	3~5 cm^3
细胞类型特异性反应			
卵母细胞	人类成熟阶段变化更显著 vs. 小鼠早期阶段变化更显著[3]		
基质细胞反应	人类/灵长类纤维化主导 vs. 小鼠炎症主导[3]		
卵泡膜细胞反应	小鼠卵巢衰老的细胞类型敏感性排第一 vs. 人类卵泡膜细胞的转录变化相对温和[3]		
内皮细胞反应	人类年龄敏感性最高 vs. 小鼠相对稳定[3]		

析，特别是在单细胞与空间组学整合层面仍有待突破。最后，现有关于卵巢衰老与多系统慢性疾病关联的证据多来源于观察性研究，缺乏纵向随访及干预性机制研究支持，尚难明确卵巢衰老在系统性衰老中的驱动作用与伴随现象之间的界限。

6.3 未来研究方向

未来研究需在单细胞分辨率和空间维度上，系统描绘卵巢衰老过程中各类细胞的多组学特征，包括基因表达谱、表观遗传修饰、染色质可及性和蛋白质活性变化，从而构建全景式的动态调控图谱。在此基础上，亟需发展整合多组学数据的计算模型，以识别驱动衰老进程的关键调控节点和细胞间通讯网络。

进一步而言，研究应突破传统生殖和内分泌范畴，深入探索卵巢功能与机体其他器官系统之间的长期相互作用机制，以揭示其在全身性衰老中的系统性角色。同时，有必要优化并建立更接近人类生理特征的灵长类动物模型，并发展和完善体外培养系统，通过构造卵巢类器官以模拟卵巢三维结构和微环境，为解析人类卵巢衰老机制及开发干预策略提供关键试验平台。

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