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细胞外基质对衰老标记物的调控及透明质酸的介导机制

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摘 要:细胞外基质(ECM)是由透明质酸(HA)、胶原蛋白、弹性蛋白等生物大分子构成的动态三维网络,兼具结构支撑与微环境调控功能。ECM的独特之处在于,它不仅呈现原发性衰老特征(即其成分与结构随年龄增长而发生改变),还具备整合性调控能力,能够跨系统调控细胞内外衰老进程。其中,HA作为ECM的核心糖胺聚糖成分,是ECM调控衰老过程的关键介质。本文系统综述了ECM在四类典型衰老标记物中的作用机制,包括营养感知失调、线粒体功能障碍、细胞间通讯改变和慢性炎症,特别强调了HA在其中的核心枢纽作用。这些发现揭示ECM作为衰老调控整合枢纽的关键作用及HA的核心介导价值,为开发新型抗衰策略提供理论基础。

关键词:细胞外基质;透明质酸;衰老标记物;整合性调控;抗衰策略
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Regulation of senescence markers by the extracellular matrix and the mediating mechanisms of hyaluronan

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Abstract: Aging is a complex, multi-system, and multi-level dynamic biological process involving intricate crosstalk between cellular and tissue components. In 2025, *Cell* officially added the extracellular matrix (ECM) as a novel hallmark of aging, marking a pivotal shift in aging research from intracellular to extracellular regulatory networks. The ECM is a dynamic three-dimensional macromolecular scaffold composed of glycosaminoglycans (such as hyaluronan), collagens, elastin, proteoglycans, and glycoproteins, which not only provides structural support for tissues and organs but also serves as a core hub for micro-environmental signal integration and transduction. Its unique biological characteristics lie in two aspects: on one hand, it exhibits primary aging features, with its components and structural architecture undergoing progressive alterations with advancing age; on the other hand, it possesses integrated regulatory capability that can cross-systemically modulate intracellular and extracellular aging processes, thereby constructing a “structure-signal-function” cascade regulatory network that links traditional aging hallmarks. Among all ECM components, hyaluronan (HA), a core glycosaminoglycan, acts as an indispensable mediator in the ECM-mediated regulation of aging. Emerging studies have further confirmed that enhancing high-molecular-weight HA levels *in vivo* can effectively extend healthspan and reduce the risk of aging-related diseases such as cancer and chronic inflammation. Against this backdrop, this review aims to systematically elucidate the regulatory mechanisms of the ECM in four representative aging hallmarks, i.e., deregulated nutrient sensing, mitochondrial dysfunction, altered intercellular communication, and chronic inflammation. In terms of nutrient sensing regulation, the changes in modulates the activity of the mTORC1 signaling axis through integrin-mediated focal adhesion (FAs) assembly and mechanical transduction, where HA participates by interacting with its receptor CD44 to regulate the PI3K-AKT-mTORC1 pathway, thereby affecting cellular nutrient perception and metabolic homeostasis; moreover, abnormal HA accumulation under obese conditions can impair insulin sensitivity, further verifying its role in metabolic regulation. For mitochondrial dysfunction, change in mechanical properties (such as stiffness and acidification) and chemical composition of ECM can regulate mitochondrial fission, mitophagy, and reactive oxygen species (ROS) production, while HA degradation (driven by overexpressed degrading enzymes like TMEM2)

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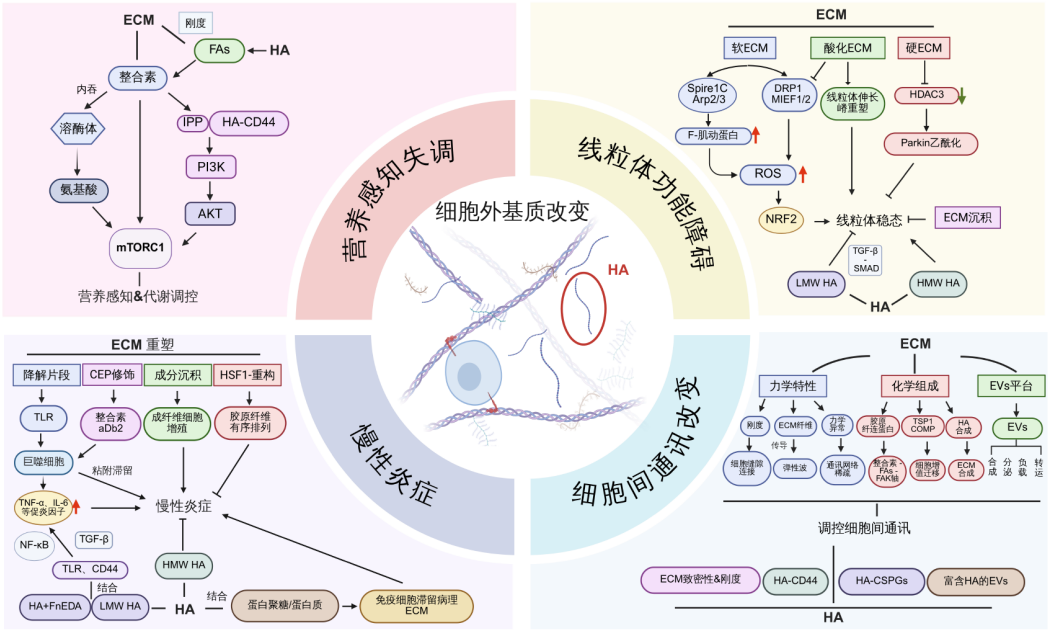
generates low-molecular-weight fragments that activate the TGF-β-SMAD pathway to induce mitochondrial dysfunction, whereas high-molecular-weight HA exerts a protective effect by promoting mitophagy and restoring mitochondrial membrane potential and ATP levels. In the context of altered intercellular communication, the ECM regulates gap junction activity, mechanical signal transmission, and extracellular vesicle (EVs) secretion and transport; HA influences ECM stiffness to alter intercellular mechanical communication and directly binds to receptors such as CD44 to modulate cell-cell interactions, and it can also be packaged into EVs to participate in long-distance signal transduction. Regarding chronic inflammation, the ECM exerts a bidirectional regulatory effect: its degraded fragments act as inflammation amplifiers by activating Toll-like receptors (TLRs), while intact macromolecules (including high-molecular-weight HA) inhibit inflammatory responses; notably, the imbalance between HA synthesis and degradation is closely associated with the progression of chronic inflammation. Collectively, these findings comprehensively demonstrate that the ECM serves as an integrative regulator of aging by constructing a multi-dimensional regulatory network for aging hallmarks, and HA acts as the core mediator in this network. Based on these insights, this review proposes key directions for future aging research: first, to clarify the molecular mechanisms underlying the molecular weight-dependent functional switching of HA and its precise regulation via specific receptors and signaling pathways; second, to develop advanced tools (such as single-cell spatial omics and biomimetic mechanical scaffolds) for dynamically monitoring ECM-cell interactions during aging; third, to explore precise anti-aging strategies targeting HA, including regulating its synthesis and degradation, designing molecular weight-controllable HA derivatives, and combined targeting of downstream receptor pathways (e.g., CD44); fourth, to evaluate the potential of ECM-related indicators (especially HA and its metabolites) as biomarkers for early aging diagnosis and individualized anti-aging intervention efficacy assessment.



Key words: extracellular matrix; hyaluronan; senescence marker; integrative regulation; anti-aging strategy

衰老进程涉及多系统、多层面的动态变化。2025年发表在*Cell*上的文章《From geroscience to precision geromedicine: understanding and managing aging》，新增了“细胞外基质(ECM)改变”作为衰老标记物[1]。ECM由糖胺聚糖、胶原蛋白、弹性蛋白、蛋白聚糖及糖蛋白等构成，通过持续的重塑过程维持组织稳态。

ECM随年龄发生的成分和结构变化，可通过生物物理与生化信号的耦合作用跨系统调控传统的十二大衰老标记物，形成“结构-信号-功能”的级联调控网络。在所有ECM成分中，透明质酸(HA)是ECM调控衰老的核心因子。最新研究显示，来源于裸鼹鼠的*Has2*基因能够提高小鼠体内高分子量HA水平，从而延长健康寿命并降低癌症和炎症发生风险，进一步凸显了HA在衰老调控中的独特地位[2]。因此，本文将围绕“ECM调控衰老标记物”这一核心主线，聚焦营养感知失调、线粒体功能障碍、细胞间通讯改变和慢性炎症与ECM，尤其是HA密切相关的标记物，系统总结其作用机制与研究进展，为理解衰老进程及开发靶向干预策略提

供参考。

1 ECM对衰老标记物的调控

1.1 对营养感知失调的调控

营养感知失调作为衰老的核心标记物，指细胞和组织对营养物质(如氨基酸、葡萄糖和脂类)丰度或缺乏的感知能力失调，往往导致代谢紊乱、氧化应激和加速衰老进程[3]。ECM作为动态微环境，会随年龄发生重塑，从多层机制调控营养感知网络。mTORC1(mechanistic target of rapamycin complex 1)是蛋白激酶复合物，在细胞营养感知和代谢调控中起核心作用，整合素介导ECM被内吞并送入溶酶体降解，ECM被降解后释放氨基酸，为mTORC1激活提供条件[4]。黏着斑(focal adhesions, FAs)是细胞营养感知和信号转导的关键信号枢纽，ECM通过整合素为FAs提供空间平台，mTORC1在营养充足时定位于FAs附近，与溶酶体、生长因子受体(如IGF受体)及氨基酸转运蛋白(SLC3A2)共定位，从而增强营养信号整合。此外，ECM刚性影响FAs介导的整合素-mTORC1信号轴，可以动态调控细胞铺展与黏附成熟，直接影响糖酵解酶活性、细胞内pH及转录过程[5]。ECM动态重塑还通过整合素受体-IPP(ILK-PINCH-Parvin)及HA-CD44蛋白调控细胞形态和信号转导，抑制蛋白激酶(AKT)磷酸化，导致葡萄糖转运和胰岛素信号转导障碍[6]。而缺乏ECM的蛋白聚糖(Decorin)会导致心肌细胞对营养缺乏的感知能力下降，进而影响自噬和代谢重编程，最终影响心脏功能[7]。

HA参与ECM对营养感知的调节，HA与CD44相互作用可激活磷脂酰肌醇3-激酶(PI3K)-AKT信号通路，调节mTORC1活性，从而影响细胞的营养感知和代谢[8]。一种自组装HA-结合肽单层膜，可以特异性结合HA，会加速局部细胞-基底FAs的形成，进而改变细胞黏附结构和营养感知能力[9]。另外，在肥胖状态下，HA的积累会影响胰岛素敏感性，这进一步表明HA在ECM调控营养感知中的作用[6]。

1.2 对线粒体功能障碍的调控

线粒体功能障碍被视为衰老标记物，是因为线粒体功能随着衰老逐渐退化，使得能量代谢受损、活性氧(reactive oxygen species，ROS)过量生成及膜通透性异常，从而诱发炎症和细胞死亡，最终推动机体功能衰退与衰老进程[10]。ECM对线粒体功能具有显著调控作用，在马凡综合征动脉瘤形成过程中，ECM-线粒体稳态的破坏会导致线粒体功能障碍，从而促进动脉瘤的发展[11]。在柔软的ECM上培养的细胞中，Spire1C和Arp2/3成核因子促进线粒体周围F-肌动蛋白增加，以及依赖动力相关蛋白1(dynamin-related protein 1, DRP1)和线粒体延长因子(MIEF1/2)的线粒体分裂增强，上述的线粒体动力学改变，导致线粒体ROS增加，激活核因子e2相关因子2(nuclear factor erythroid 2-related factor 2，NRF2)介导的抗氧化转录应答，通过胱氨酸摄取和谷胱甘肽代谢调节细胞氧化还原稳态[12]。而ECM硬化会下调组蛋白去乙酰化酶3(HDAC3)，促使蛋白连接酶(Parkin)乙酰化，从而过度激活线粒体自噬，加速软骨细胞衰老[13]。同时，在肾纤维化中，线粒体结构功能失调也与ECM沉积有关[14]。此外，轻度ECM酸化可以抑制DRP1介导的线粒体分裂，促进线粒体伸长和嵴重塑，维持缺氧状态下ATP水平和细胞存活[15]。由此可知，ECM通过其力学和理化性质的改变显著影响线粒体分裂、自噬和代谢稳态。

HA在ECM信号通路调控线粒体功能的过程中起重要作用。HA降解酶(TMEM2)过度表达会降解ECM中的HA，将高分子HA转变为低分子片段，而HA片段激活TGF-β-SMAD信号通路，引发线粒体分裂、呼吸速率下降及氧化应激增强等多重线粒体功能障碍[16]。高分子量HA可通过激活线粒体自噬来保护线粒体功能，减轻氧化应激引起的线粒体功能障碍，HA处理后线粒体膜电位($\Delta\psi m$)和ATP水平显著恢复，同时，在牛椎间盘器官培养模型中，高分子量HA能减轻机械应力引起的细胞凋亡和ECM降解，以缓解线粒体功能损伤[17]。

1.3 对细胞间通讯改变的调控

在衰老过程中，细胞间通讯改变作为典型的衰老标记物之一，表现出显著的功能异常，其根本原因在于衰老伴随着通讯效率下降和信号传递失衡[3]。ECM作为细胞间结构支撑，对细胞间通讯产生重要影响。

首先，ECM的力学特性对细胞间通讯具有显著调控作用。在骨质疏松小鼠模型中，ECM刚度降低导致成骨细胞缝隙连接活性下降，并伴随缝隙连接蛋白connexin 43表达下调[18]。细胞主动收缩产生的弹性波可通过ECM纤维传播，放大信号并被相邻细胞接收，从而实现长距离的机械通信[19]。心脏组织

ECM力学传导异常可能导致细胞间通讯网络稀疏,表现为配体-受体对总数减少及整合素β1信号通路配体和受体显著下调[20]。

其次,ECM的化学组成也会影响细胞间通讯。ECM的胶原和纤连蛋白表达水平的升高,会通过整合素-黏附复合物-FAK信号轴调控细胞骨架重构和下游基因表达,从而影响细胞间的信号传递和通讯网络[21,22]。而ECM的重要蛋白血小板反应蛋白1(TSP1)和软骨寡聚基质蛋白(COMP)的降解会影响内皮细胞增殖/迁移及血管平滑肌细胞迁移,进而改变细胞间相互作用[23]。通过口服HA合成抑制剂4-甲基伞形酮(4-MU)破坏大鼠神经元周围网(PNNs)和弥散性ECM,可影响细胞外空间中神经活性物质的扩散,从而调控突触外信号传递[24]。

再次,胞外囊泡(extracellular vesicles,EVs)传递分子实现细胞间信号传递,而ECM作为EVs的附着和运输平台,间接调控细胞间通讯。在刚性较高的ECM基质上培养的细胞,其EVs分泌水平高于柔软基质上的细胞,这表明ECM刚度可通过机械转导被转化为细胞内信号级联反应,进而调控EVs的生成与释放[25]。ECM还可调控EVs的负载,ECM大分子(如胶原、层粘连蛋白和纤连蛋白)可被选择性地包装入EVs,参与细胞通讯并调节受体细胞的行为[26]。此外,ECM重塑通过形成物理屏障或促进EVs扩散,影响EVs的摄取及在组织内的分布,改变其到达靶细胞并发挥作用的能力[27]。

HA在细胞间通讯中起到重要作用。一方面,HA影响ECM的刚度。高分子量HA在较高浓度下能够使ECM结构更加致密并显著提高刚度,最高可达无HA对照组的3倍[28]。另一方面,HA直接与受体结合,调节细胞通讯。HA可结合CD44(s型或v6型)介导细胞-ECM以及细胞-细胞的相互作用,调控下游信号通路(如整合素、细胞骨架重塑),改变细胞间接触和通讯状态[22]。此外,HA-CD44复合物还参与了EVs与靶细胞表面的结合过程,促进信号分子传递[29]。HA作为PNNs的主要成分,与硫酸软骨素蛋白聚糖(CSPGs)结合形成三联体结构,通过稳定突触结构和调控神经元可塑性影响神经系统通讯[30]。HA合成酶(HAS3)的过表达可促进细胞释放富含HA的EVs,提示HA不仅通过ECM结构与受体信号调控通讯,还可能作为细胞外囊泡介导的信息分子,参与远距离信号传递[31]。

1.4 对慢性炎症的调控

慢性炎症是一种持续存在的炎症状态,随年龄增长而加剧且与多种衰老相关疾病(如动脉粥样硬化、关节炎等)的发展相关,故被认为是重要的衰老标记物[32]。ECM动态重塑在炎症平衡中发挥“开关”作用,通过成分与结构变化响应并反馈炎症信号。结肠炎模型结合患者样本的研究表明,ECM在疾病症状出现前就已经发生结构、刚度和成分的改变,且由免疫细胞的亚临床浸润及重塑酶活化所驱动[33]。ECM的弹性蛋白降解片段可通过神经氨酸酶1(NEU1)介导的先天免疫激活,进而引发系统性炎症反应,促进炎症相关基因表达并加速机体衰老[34]。而胶原蛋白等ECM成分的过度沉积增强了成纤维细胞的增殖,使炎症和纤维化持续产生[35]。ECM对炎症的双向调控体现在:降解片段作为慢性炎症放大器,通过激活Toll样受体(Toll-like receptor,TLR)刺激巨噬细胞释放TNF-α、IL-6等促炎因子;而高分子量HA、胶原蛋白等抑制TLR信号或激活免疫抑制受体,减少炎症因子产生,发挥抗炎效果[36]。热休克因子1(HSF1)调控的ECM重构通过维持胶原纤维有序排列,限制炎症细胞浸润和活化。在炎症性微环境中,ECM会发生持续的重塑与改变,逐步诱导癌症发生[37]。二十二碳六烯酸(DHA)氧化产生的羧乙基吡咯(CEP)修饰ECM蛋白,通过整合素aDb2增强巨噬细胞的黏附和滞留,促进慢性炎症[38]。

HA合成和降解失衡与慢性炎症的严重程度相关,HA可与ECM中的蛋白聚糖及蛋白质相互作用形成网络,在损伤和炎症时影响免疫细胞行为,导致免疫细胞在病理组织ECM中滞留,从而延长炎症病程[39]。HA和纤维连接蛋白EDA剪接变体(FnEDA)等可作为损伤相关分子模式,通过与免疫细胞表面的TLR4、整合素及CD44等受体结合,刺激TGF-β信号通路,导致IL-8、TNF-α等促炎细胞因子的表达增加,进而促进慢性炎症的持续和慢性疾病的发展[40]。高分子量HA具有抗炎和组织保护作用,而低分子量HA通过TLR2/4和CD44激活NF-κB(核因子 κB)、TGF-β信号,促进免疫细胞活化、炎症反应及ECM沉积[41]。HA降解酶HYAL2在肝纤维化中过表达使HA降解,其降解产物刺激促炎基因表达[42]。

2 结论与展望

ECM通过其力学特性、化学组成及结构重塑过

程，对衰老标记物发挥多层次、多机制的调控作用。具体而言，ECM通过整合素- FAs信号及力学传导调控营养感知，影响mTORC1活性和细胞代谢稳态；ECM力学性质及化学组成的改变调控线粒体分裂、自噬及ROS生成，从而维护或破坏线粒体功能；ECM通过力学传导、化学成分及EVs载体作用，影响缝隙连接、受体-配体信号及EVs传递效率，进而调控细胞间信息交流；同时，ECM的动态重塑与炎症信号交互，既可抑制慢性炎症，又可能在降解片段累积时加剧炎症反应。这些作用机制共同构建了ECM对衰老进程的“结构-信号-功能”级联调控网络。

HA作为ECM核心糖胺聚糖，在调控衰老标记物中发挥关键枢纽作用。HA不仅通过调节ECM刚度影响细胞的信号感知和转导，还可通过与CD44、整合素和TLR等受体结合，介导胞外-胞内信息传递和信号放大，广泛参与营养感知、氧化还原稳态调控、细胞间通讯以及炎症反应。同时，HA的动态代谢在衰老进程中至关重要：其降解产物——低分子量HA片段往往激活TGF-β信号通路，引发炎症反应和线粒体分裂失调，而HA合成增强或高分子量HA补充则可以稳定细胞黏附与通讯网络、抑制促炎因子过度释放，从而逆转衰老相关代谢与炎症功能退化。因此，HA可被视为ECM介导衰老进程中最具潜力的核心调控因子。

展望未来，ECM研究亟待解决若干关键问题：一是明确不同成分通过特定受体和信号通路实现精细化调控的分子机制，尤其是HA分子量依赖性的功能转变；二是发展可动态解析ECM-细胞互作的新型工具，如单细胞/空间组学结合可控力学仿生支架，以捕捉衰老过程中信号动态变化；三是探索以HA为靶点的精准干预策略，包括调控其合成与降解、设计分子量可控的HA衍生物或联合靶向受体通路（如CD44）；四是评估ECM作为生物标记物的潜力，用于早期衰老诊断、个体化风险预测及抗衰干预。

参考文献

[1] Kroemer G, Maier AB, Cuervo AM, et al. From geroscience to precision geromedicine: understanding and managing aging. Cell, 2025, 188: 2043–62.

[2] Zhang Z, Tian X, Lu JY, et al. Increased hyaluronan by naked mole-rat Has2 improves healthspan in mice. Nature, 2023, 621: 196–205.

[3] López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: an expanding universe. Cell, 2023, 186: 243–78.

[4] Rainero E. Extracellular matrix internalization links nutrient signalling to invasive migration. Int J Exp Pathol, 2018, 99: 4–9.

[5] Hamidi H, Ivaska J. Food for thought: how cell adhesion coordinates nutrient sensing. J Cell Biol, 2021, 220: e202103128.

[6] Musale V, Wasserman DH, Kang L. Extracellular matrix remodelling in obesity and metabolic disorders. Life Metab, 2023, 2: load021.

[7] Gubbiotti MA, Seifert E, Rodeck U, et al. Metabolic reprogramming of murine cardiomyocytes during autophagy requires the extracellular nutrient sensor decorin. J Biol Chem, 2018, 293: 16940–50.

[8] Bourguignon LYW. Matrix hyaluronan-activated CD44 signaling promotes keratinocyte activities and improves abnormal epidermal functions. Am J Pathol, 2014, 184: 1912–9.

[9] Pang X, Li W, Chang L, et al. Hyaluronan immobilized on surfaces via self-assembled monolayers of HA-binding peptide modulates endothelial cell spreading and migration through focal adhesion. ACS Appl Mater Interfaces, 2021, 13: 25792–804.

[10] Somasundaram I, Jain SM, Blot-Chabaud M, et al. Mitochondrial dysfunction and its association with age-related disorders. Front Physiol, 2024, 15: 1384966.

[11] Marcos-Rios D, Rochano-Ortiz A, Sebastián-Jaraba I, et al. Mitochondrial dysfunction: a new hallmark in hereditable thoracic aortic aneurysm development. Cells, 2025, 14: 618.

[12] Romani P, Nirchio N, Arboit M, et al. Mitochondrial fission links ECM mechanotransduction to metabolic redox homeostasis and metastatic chemotherapy resistance. Nat Cell Biol, 2022, 24: 168–80.

[13] Fu B, Shen J, Zou X, et al. Matrix stiffening promotes chondrocyte senescence and osteoarthritis development through downregulating HDAC3. Bone Res, 2024, 12: 32.

[14] Zhao X, Li Y, Yu J, et al. Role of mitochondria in pathogenesis and therapy of renal fibrosis. Metabolism, 2024, 155: 155913.

[15] Khacho M, Tarabay M, Patten D, et al. Acidosis overrides oxygen deprivation to maintain mitochondrial function and cell survival. Nat Commun, 2014, 5: 3550.

[16] Zhang H, Tsui CK, Garcia G, et al. The extracellular matrix integrates mitochondrial homeostasis. Cell, 2024, 187: 4289–304.e26.

[17] Zhang F, Wang S, Gao M, et al. Hyaluronic acid

ameliorates intervertebral disc degeneration via promoting mitophagy activation. Front Bioeng Biotechnol, 2022, 10: 1057429.

[18] Zhang D, Li X, Pi C, et al. Osteoporosis-decreased extracellular matrix stiffness impairs connexin 43-mediated gap junction intercellular communication in osteocytes. Acta Biochim Biophys Sin, 2020, 52: 517–26.

[19] Panchenko AY, Tchaicheeyan O, Berinskii IE, et al. Does the extracellular matrix support cell-cell communication by elastic wave packets? ACS Biomater Sci Eng, 2022, 8: 5155–70.

[20] Larson A, Codden CJ, Huggins GS, et al. Altered intercellular communication and extracellular matrix signaling as a potential disease mechanism in human hypertrophic cardiomyopathy. Sci Rep, 2022, 12: 5211.

[21] Valiente-Alandi I, Schafer AE, Blaxall BC. Extracellular matrix-mediated cellular communication in the heart. J Mol Cell Cardiol, 2016, 91: 228–37.

[22] Horwacik I. The extracellular matrix and neuroblastoma cell communication—a complex interplay and its therapeutic implications. Cells, 2022, 11: 3172.

[23] Kessler T, Sager HB, Mann M. Role of the extracellular matrix in cell-cell communication: a new therapeutic target? Eur Heart J, 2023, 44: 3495–7.

[24] Syková E, Vořišek I, Starčuk Z, et al. Disruption of extracellular matrix and perineuronal nets modulates extracellular space volume and geometry. J Neurosci, 2025, 45: e051724.

[25] Dawson TR, Weaver AM. Niche tension controls exosome production. Nat Cell Biol, 2023, 25: 377–8.

[26] Piperigkou Z, Mangani S, Koletsis NE, et al. Principal mechanisms of extracellular matrix-mediated cell-cell communication in physiological and tumor microenvironments. FEBS J, 2026, 293: 26–41.

[27] Arif S, Moulin VJ. Extracellular vesicles on the move: traversing the complex matrix of tissues. Eur J Cell Biol, 2023, 102: 151372.

[28] Unnikandam Veettil SR, Hwang D, Correia J, et al. Cancer cell migration in collagen-hyaluronan composite extracellular matrices. Acta Biomater, 2021, 130: 183–98.

[29] Arasu UT, Deen AJ, Pasonen-Seppänen S, et al. HAS3-induced extracellular vesicles from melanoma cells stimulate IHH mediated c-Myc upregulation via the hedgehog signaling pathway in target cells. Cell Mol Life Sci, 2020, 77: 4093–115.

[30] Zhu K, Fu Y, Zhao Y, et al. Perineuronal nets: role in normal brain physiology and aging, and pathology of various diseases. Ageing Res Rev, 2025, 108: 102756.

[31] Rilla K, Oikari S, Jokela TA, et al. Hyaluronan synthase 1 requires higher cellular UDP-GlcNAc concentration than HAS2 and HAS3. J Biol Chem, 2013, 288: 5973–83.

[32] Baechle JJ, Chen N, Makhijani P, et al. Chronic inflammation and the hallmarks of aging. Mol Metab, 2023, 74: 101755.

[33] Shimshoni E, Adir I, Afik R, et al. Distinct extracellular-matrix remodeling events precede symptoms of inflammation. Matrix Biol, 2021, 96: 47–68.

[34] Yi J, Wang Y, Sui H, et al. Elastin-derived extracellular matrix fragments drive aging through innate immune activation. Nat Aging, 2025, 5: 2390–8.

[35] Lin S N, Wang J, Mukherjee P K, et al. The functional role of the extracellular matrix in inflammatory bowel disease associated gut fibrosis. Matrix Biol, 2025, 139: 29–48.

[36] Levi-Galibov O, Lavon H, Wassermann-Dozorets R, et al. Heat shock factor 1-dependent extracellular matrix remodeling mediates the transition from chronic intestinal inflammation to colon cancer. Nat Commun, 2020, 11: 6245.

[37] Marangio A, Biccari A, D'Angelo E, et al. The study of the extracellular matrix in chronic inflammation: a way to prevent cancer initiation? Cancers, 2022, 14: 5903.

[38] Casteel JL, Keever KR, Ardell CL, et al. Modification of extracellular matrix by the product of DHA oxidation switches macrophage adhesion patterns and promotes retention of macrophages during chronic inflammation. Front Immunol, 2022, 13: 867082.

[39] Rosales P, Vitale D, Icardi A, et al. Role of hyaluronic acid and its chemical derivatives in immunity during homeostasis, cancer and tissue regeneration. Semin Immunopathol, 2024, 46: 15.

[40] McKeown-Longo PJ, Higgins PJ. Hyaluronan, transforming growth factor β, and extra domain A-fibronectin: a fibrotic triad. Adv Wound Care, 2021, 10: 137–52.

[41] Garantziotis S, Brezina M, Castelnuovo P, et al. The role of hyaluronan in the pathobiology and treatment of respiratory disease. Am J Physiol Lung Cell Mol Physiol, 2016, 310: L785–95.

[42] Kim SM, Song GY, Shim A, et al. Hyaluronan synthase 2, a target of miR-200c, promotes carbon tetrachloride-induced acute and chronic liver inflammation via regulation of CCL3 and CCL4. Exp Mol Med, 2022, 54: 739–52.