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心成纤维细胞在心脏衰老中的研究进展

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摘　要

心血管疾病是全球发病率和死亡率的主要原因，心脏衰老的特征是细胞和分子变化的集合体，年龄驱动的心脏再生能力下降加剧了这种变化。尽管心脏衰老的表型得到了很好的表征，但潜在的分子机制却很少被探索。最近的研究表明，盘状蛋白结构域受体2 (DDR2)是一种主要位于心脏成纤维细胞中的胶原激活受体酪氨酸激酶，在心脏成纤维细胞功能和心血管纤维化中具有专性作用。对衰老心脏中心血管衰老和成纤维细胞功能失调的分子基础的敏锐研究将为缓解快速增长的老年人口心血管疾病的有效策略铺平道路。

关键词

DDR2，老化，心脏成纤维细胞，心脏纤维化，心脏细胞，胶原蛋白，衰老

Research Progress of Cardiac Fibroblasts in Cardiac Aging

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Abstract

Cardiovascular disease is a leading cause of morbidity and mortality worldwide, and cardiac aging is characterized by a conglomeration of cellular and molecular changes exacerbated by age-driven declines in the heart's regenerative capacity. Although the phenotype of cardiac aging is well characterized, the underlying molecular mechanisms have been little explored. Recent studies have shown that disc protein domain receptor 2 (DDR2), a collagen-activated receptor tyrosine kinase

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located primarily in cardiac fibroblasts, has an obligate role in cardiac fibroblast function and cardiovascular fibrosis. Acute research into the molecular basis of vascular senescence and fibroblast dysfunction in aging hearts will pave the way for effective strategies to mitigate cardiovascular disease in the rapidly growing elderly population.

Keywords

DDR2, Aging, Cardiac Fibroblasts, Cardiac Fibrosis, Cardiac Myocytes, Collagen, Senescence

1. 引言

心脏衰老的特征是心脏收缩器官、冠状动脉脉管系统和心脏成纤维细胞的老化，以及 ECM 的沉积和老化[1]-[3]。心肌细胞结构、生物化学和生理学的主要改变包括心肌细胞增大、肌细胞衰老增加、成纤维细胞增生、ECM 蛋白(如胶原蛋白)的周转和物理特性改变、心脏纤维化增强、左心室(LV)质容比和左心房大小增加、舒张功能障碍、瓣膜变性、心外脂肪组织沉积、心房颤动患病率增加和最大值降低运动能力[2] [4]-[7]。本综述概述了心脏衰老与成纤维细胞变化，重点关注盘状蛋白结构域受体 2 (DDR2)，这是一种胶原激活的受体酪氨酸激酶，主要位于心脏成纤维细胞中，可潜在地靶向预防或减少心肌纤维化。

2. 心脏成纤维细胞与衰老

心肌成纤维细胞是心肌的主要基质细胞。它们是未分化细胞，占心脏间质细胞的 90%以上，约占心肌细胞群的 2/3 [8]。除了是心肌的主要纤维 I 型和 III 型胶原的主要心内来源，还是几种生长因子和细胞因子的“来源和靶标”，这些生长因子和细胞因子对共存的心肌细胞具有显著的旁分泌作用[9]-[11]。但是多年来的研究主要集中在心肌细胞在衰老中的作用，而心脏成纤维细胞在心脏衰老和衰老中的作用在很大程度上被忽视了。

3. 老年心肌的伤口愈合受损和纤维化

与以不适当的增殖和过度 ECM 沉积为特征的传统心脏纤维化不同，衰老相关性纤维化的特征是心肌胶原含量升高的退行性改变[12]。人们对心脏中的转录程序和成纤维细胞增殖如何随着年龄的增长而变化并影响这些过程知之甚少。对动物模型和人体尸检标本的研究表明，衰老过程中胶原含量增加[13]-[16]，而对 80 岁人群的尸检显示，与年轻受试者相比，心脏中胶原 I 含量增加，胶原 III 含量减少[17]。然而，早期的观察表明，随着心脏衰老，I 型和 III 型胶原的转录水平降低或保持不变[18] [19]。与这一发现一致的是，尽管大鼠左心室胶原的羟脯氨酸含量和组织学定量随着年龄的增长而增加，但 I 型和 III 型前胶原的 mRNA 水平均降低[20]。在衰老相关纤维化的发病机制中，减少胶原降解可能比增强从头胶原合成更重要[21]。衰老过程中心肌胶原蛋白升高似乎最有可能与合成后或降解过程有关[20]。酶活性、信号通路之间的相互作用、蛋白质合成和翻译后修饰也可以驱动 ECM 沉积的增加。

4. 胶原蛋白更新失调会促进老年心肌中胶原蛋白过度沉积

基质保留信号和基质降解信号之间的精细平衡决定了心肌胶原的水平，是心脏结构完整性的必要条

件[21]。有证据表明，老年心肌中 I 型和 III 型胶原的胶原合成和 mRNA 水平降低与 MMP 1 型和 MMP 2 的水平和活性降低有关，表明基质降解途径的衰减可能是衰老心脏中胶原过度沉积的主要原因[21]-[24]。此外，参与心脏成纤维细胞合成和加工胶原纤维的酶(脯氨酰羟化酶、赖氨酰羟化酶)和分泌的酸性和富含半胱氨酸的分泌蛋白(SPARC，一种母细胞蛋白)的产生在衰老的心脏中也会上调，导致成熟的胶原沉积和 ECM 僵硬[20]-[24]。还需注意的是，胶原蛋白的非酶促糖基化或糖化水平随着年龄的增长而逐渐增加，这会影响心脏僵硬[25] [26]。这一点尤为重要，因为胶原蛋白的形成涉及酶促过程，这些酶促过程产生交联，由葡萄糖和其他糖类促进[26]。因此，老年心脏中胶原蛋白含量增加的可能机制如下：(1) 减少胶原蛋白降解；(2) 新生的胶原蛋白随着年龄的增长而发生交联，使得胶原纤维的硬度增加，增强了对胶原酶或 MMPs 蛋白水解的抵抗力；(3) 随着基质交联程度越来越高，可能会对调控交联的基因产生负反馈效应；(4) 胶原蛋白在老年心脏中的积累本身可能对心脏成纤维细胞中胶原蛋白基因的表达产生负反馈作用。

Achkar 等[27]的一项研究表明，老年小鼠的心脏纤维化和成纤维细胞表型存在性别依赖性差异模式。他们表明，虽然在雌性小鼠的老年心脏中观察到心肌和心外膜中的反应性纤维化，但在雄性心脏中观察到血管周围纤维化和替代纤维化。Pappritz 等[28]报道，雌性心脏成纤维细胞的胶原含量在 12 月龄动物中较高。这些观察结果表明，需要对老年人群进行性别依赖性抗纤维化管理。此外，来自雄性动物的心脏成纤维细胞产生更高水平的趋化因子，如 CC 基序趋化因子配体(CCL) 2 和 7，这表明它们比雌性动物具有更高的炎症能力。

5. 心脏成纤维细胞对衰老心脏损伤反应失调

除了正常衰老的心脏中与基质转换相关的过程发生显着改变外，衰老的心脏对大量不同损伤引起的急性和慢性损伤的反应失调也显着导致不利的结构和功能性心肌重塑[29]。如前所述，心肌损伤后伤口愈合的效率取决于成纤维细胞的表型变化及其成熟为功能性肌成纤维细胞的能力。然而，随着心脏年龄的增长，这种效率会受到影响，这促进了不利的重塑并危及结局[29]。除了心脏成纤维细胞的变化对 ECM 的影响外，ECM 张力还可以通过机械传感直接影响心脏成纤维细胞表型和活化状态。有人认为，基质下游发生的事件，如参与机械转导的各种蛋白的激活或表达水平的变化，可以负向改变衰老成纤维细胞成为肌成纤维细胞的能力[30]。Angelini 等[30]在他们的综述中讨论了 ECM 受体(整合素或非整合素)、黏着斑、细胞骨架和机械传感中涉及的转录因子随着衰老而发生的变化。在老年男性心脏成纤维细胞中，最近有报道称 Kindlin/ERK/actin/α-SMA 机械传感轴的主要效应子存在缺陷[31]。

此外，损伤后，心肌修复机制会增加间充质干细胞(MSC)或成纤维细胞前体的数量，这些前体最终可分化为成纤维细胞并成熟为肌成纤维细胞[32]。然而，源自老年心脏的间充质干细胞会产生功能和分化受损的成纤维细胞。这些细胞从成纤维细胞到肌成纤维细胞表型的转变不仅有缺陷，而且它们分化为收缩性肌成纤维细胞的分化能力很差，细胞对 TGF-β 受体 I 的表达降低导致对 TGF-β 的反应减弱和典型 TGF-β/SMAD 通路的减弱。这会影响肌成纤维细胞向需要替代纤维化的区域的迁移。在愈合性梗死中，α-SMA (一种 β TGF 敏感基因)的表达也降低，肌成纤维细胞分化受到抑制[33]。所有这些都导致心肌梗死后疤痕不足的形成。Trial 和 Cieslik [29]指出，存在一种自相矛盾的情况，即修复性纤维化受损，但间质性不良纤维化增强。在未受伤的心脏中，活化的成纤维细胞具有促纤维化表型，导致间质纤维化、心室僵硬和舒张功能障碍，最终导致心力衰竭[32]。

值得注意的是，Jo Ann Trial 等[34]报道，衰老小鼠心脏的病理性纤维化与干性降低和异常分化为功能失调的炎性成纤维细胞引起的驻留间充质干细胞失调有关。来自老化间充质干细胞的成纤维细胞分泌更高水平的 1 型胶原蛋白，直接导致纤维化，MCP-1 从血液中吸引白细胞，IL-6 促进单核细胞向髓系成纤维细胞的转化。

研究还表明，与从年轻心脏中收获的成纤维细胞相比，从衰老心脏分离的大鼠成纤维细胞中，Ang II对胶原合成的刺激作用不那么明显[35]。看似矛盾的是，尽管老年心肌暴露于氧化应激增加[36]，氧化应激诱导的 Ang II 产生有望增强胶原蛋白表达[36]，但实际上老年心脏中胶原蛋白合成减少，至少部分原因是对 Ang II 的反应缺陷。一种称为骨膜蛋白的 ECM 蛋白是一种参与细胞粘附的整合素结合蛋白[37]，它改变成纤维细胞的表型，从而影响肌成纤维细胞的分化，也会影响成纤维细胞在心肌损伤部位的运动或粘附[37] [38]。因此，骨膜蛋白表达可以被认为是成纤维细胞活化的标志物，并且参与成纤维细胞介导的伤口愈合的多个方面，包括迁移、分化和胶原沉积。然而，成纤维细胞通过 αv 整合素对骨膜蛋白产生反应，其表达在衰老心脏梗死中较少[39]。这表明，由于骨膜蛋白的表达或可用性降低，肌成纤维细胞的分化在老年心肌中可能受到损害。

6. 盘状蛋白结构域受体 2——减轻心脏纤维化的潜在治疗靶点

上述事实明确指出，无论年龄大小，心成纤维细胞介导的心肌纤维化都是导致心功能不全的主要原因。显然，确定可以作为治疗靶向的心脏成纤维细胞特异性机制或因素来预防或减少心肌纤维化具有巨大的科学意义和临床意义。

在这方面，DDR2 参与大量的细胞过程，包括基质产生、细胞增殖和细胞死亡[40]-[44]。一些研究者已经证实了其在组织纤维化和癌症中的作用[43]-[45]。最近，在恒河猴代谢综合征模型中发现，在恒河猴代谢综合征模型中，外定成纤维细胞和 VSMC 中 DDR2 表达的增加与腹主动脉内侧层和外层内侧和外层胶原蛋白的沉积和重塑增加相关[46]。此外，白藜芦醇减弱了饮食诱导的 I 型胶原沉积和重塑，同时减少了 DDR2。此外，发现高血糖通过 TGF-β1/SMAD2/3 信号传导增加离体大鼠血管外膜成纤维细胞和 VSMC 中 DDR2 和 I 型胶原的表达，白藜芦醇减弱了 DDR2 和 I 型胶原。基因敲低和过表达方法证实了 DDR2 在高血糖诱导的这些细胞中 I 型胶原表达增加中的专性作用。观察结果表明，DDR2 可能作为代谢综合征和动脉纤维化之间的分子联系，这将使其成为潜在的治疗靶点。

在心脏成纤维细胞中，Ang II 已被证明通过氧化还原敏感转录因子 NF-kB 刺激 DDR2 表达，据报道，DDR2 在这些细胞中对 Ang II 刺激的 α-SMA 和胶原基因表达具有专性作用[47] [48]。此外，在暴露于 Ang II 的心脏成纤维细胞中，DDR2 增加了抗凋亡 cIAP2 的表达，从而保护这些细胞免受细胞凋亡，这不仅可以在短期内促进它们在伤口修复中的作用，而且可以促进它们在长期内以活性形式持续存在，导致损伤后胶原蛋白沉积过多。DDR2 还通过转录和翻译后机制在心脏成纤维细胞的细胞周期进程中起着不可或缺的作用[49]。有趣的是，也有报道了心脏成纤维细胞对 H9c2 细胞整合素-β1 表达的 DDR2 依赖性旁分泌作用[48]。DDR2 在心脏成纤维细胞的表型转化以及心脏成纤维细胞的细胞周期进程、胶原蛋白和纤连蛋白表达以及细胞凋亡抵抗的调节中发挥着专性作用，因此成为不良心脏纤维化和心肌重塑的关键。DDR2 作为 Ang II 的下游靶标在心脏纤维化中的关键作用、DDR2 在心脏成纤维细胞中的主要定位以及 Ang II 靶向药物在限制不良心肌重塑方面的广泛认可功效为探索 Ang II-DDR2 与正常和受伤老年心脏中纤维化的联系提供了令人信服的理由。人们很容易假设，这些研究可能会导致靶向 DDR2 的新策略，以特异性控制衰老心脏的心血管纤维化。

7. 总结与展望

人口老龄化推进了对心肌细胞衰老的研究。心肌细胞衰老发生机制复杂，涉及广泛，仍需要继续探究机体变化对于心肌细胞的影响；探究衰老心肌细胞在心脏发育、重塑和再生过程中发挥的作用；阐明衰老心肌细胞如何导致心血管疾病。中医学历史悠久，抗衰老理论经验丰富，其疗法具有多靶点、多通路、多成分的特点，且安全有效。可通过中医学与现代医学结合，更深入挖掘其发生机制；亦可通过网

络药理研究中医药对于衰老心肌细胞的作用机制，寻找关键的信号通路及靶点蛋白。深入开发相关靶点蛋白的抑制剂以及防治心肌细胞衰老的策略，以预防和改善与年龄有关的心血管疾病。

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