核仁素在心血管疾病中的研究进展

涂均楚# 王燕丽# 陆琳 吴诚洁 张瑜 李杨欣*

(苏州大学医学院心血管病研究所, 苏州大学附属第一医院心脏大血管外科, 苏州 215006)

摘要 心血管疾病是目前危害全球人类健康的首要风险因素。传统的治疗手段虽能延长患者寿命, 但也存在着诸多风险, 因此对于心血管疾病的治疗人们需要寻找更为有效的靶点。核仁素是一类广泛表达且高度保守的蛋白质, 在多种心血管疾病病理过程中异常表达, 直接影响细胞的相关功能, 提示核仁素是心血管疾病的潜在治疗靶点。该文就核仁素在心血管疾病发生、发展中的作用加以综述。

关键词 核仁素; 心血管疾病; 分子调控机制

Research Progress on Nucleolin in Cardiovascular Disease

TU Junchu#, WANG Yanli#, LU Lin, WU Chengjie, ZHANG Yu, LI Yangxin*

(*Institute for Cardiovascular Science and Department of Cardiovascular Surgery, First Affiliated Hospital and Medical College of Soochow University, Soochow University, Suzhou 215006, China*)

Abstract The cardiovascular diseases are the leading cause of death worldwide. Although traditional treatment can prolong the life of patients, it is associated with many risks. Therefore, new treatments targeting a universal target are needed to achieve a better effect. Nucleolin is a widely expressed and highly conserved protein, which is abnormally expressed in the pathological process of various cardiovascular diseases. Its abnormal expression directly affects the function of the cells, suggesting that nucleolin is a potential therapeutic target for cardiovascular diseases. This paper reviews the role of nucleolin in the occurrence and development of cardiovascular diseases.

Keywords nucleolin; cardiovascular disease; molecular mechanism

心血管疾病目前是危害全人类健康的首要风险因素, 死亡人数占我国居民总死亡人数的40%以上, 居首位, 并且今后十年心血管疾病患病人数仍将快速增长, 可能成为重大的公共卫生事件[1]。因此, 发现并鉴定新的疾病预测因子或治疗靶点对于心血管疾病的预防与治疗有重要意义。核仁素是真核细胞核仁中含量最为丰富的非核糖体蛋白之一, 在胞质和细胞膜上亦有分布[2], 其进化保守, 在心血管疾病发生发展中发挥诸多重要的生物学作用。本文就核仁素及其在心血管疾病中的研究进展作如下综述。

1 核仁素概述

核仁素(nucleolin, Ncl)又称C23, 是真核细胞中进化高度保守的多功能磷酸化蛋白质, 自1973年

收稿日期: 2022-04-13 接受日期: 2022-05-14

国家自然科学基金(批准号: 91849122、81870194)、江苏省“六大人才高峰”创新团队项目(批准号: BU 24600117)、中国博士后基金(批准号: 2021M 702394)和江苏省卓越博士后基金资助的课题

#共同第一作者

*通讯作者。Tel: 15950019729, E-mail: yangxin_li@yahoo.com

Received: April 13, 2022 Accepted: May 14, 2022

This work was supported by the National Natural Science Foundation of China (Grant No.91849122, 81870194), the Jiangsu Province Peak of Talent in Six Industries (Grant No.BU 24600117), the Postdoctoral Research Foundation, China (Grant No.2021M 702394) and the Excellence Postdoctoral Research Foundation of Jiangsu Province

#These authors contributed equally to this work

*Corresponding author. Tel: +86-15950019729, E-mail: yangxin_li@yahoo.com

ORRICK等首次发现核仁素以来, 它一直是研究的焦点[3-6]。人类*Ncl*基因由2号染色体长臂末端的14个外显子和13个内含子组成。该蛋白在脊椎动物中高度保守, 植物和酵母中也有与其类似的蛋白质存在, 且在人体多种组织中均有表达, 以淋巴结中表达最高[7-8]。哺乳动物Ncl由707个氨基酸组成, 预测分子质量约为77 kDa, 而其表观分子质量约为100 kDa, 这归因于其N-端结构域的多重磷酸化[9]。Ncl的多重作用与其具有多种结构域是密不可分的, 它主要有N-端结构域、中心结构域和C-端结构域。Ncl的N-端结构域含有可磷酸化的酸性氨基酸: 谷氨酸、天冬氨酸和酪氨酸等, 能够被周期蛋白依赖激酶1(cyclin-dependent kinase, CDK1)、酪蛋白激酶2(casein kinase 2, CK2)等激酶磷酸化, 参与细胞周期的转变[10]。N-端结构域能够通过参与rRNA的转录, 与前rRNA加工复合体的组分相互作用参与核糖体新生, 还能够与染色质或mRNA非翻译区(untranslated region, UTR)相互作用调控rDNA转录。中心结构域包含四个RNA结合域(RNA binding domain, RBD), RBD可直接与rRNA或含有G-四链体的RNA结合, 参与核仁周围染色质的转录、细胞早期发育等重要的细胞生物学事件[11-12]。C-端结构域富含甘氨酸、精氨酸、苯丙氨酸残基, 又称为甘氨酸精氨酸富集区(glysine and arginine rich region, GAR)或精氨酸–甘氨酸–甘氨酸重复结构域(arginine-glycine-glycine repeat domain, RGG), GAR可通过驱动蛋白轻链和富含精氨酸序列的质膜关联的直接作用来驱动Ncl的定位, GAR结构域的缺失或突变, 显著减少了Ncl在细胞膜或核仁的定位[12-13]。

Ncl在细胞中具有广泛的亚定位。核仁的致密纤维区(dense fibrillar component, DFC)和颗粒区(granular component, GC)是其主要分布区域, 但许多刺激可以改变核仁素的亚细胞定位, 使其分布到核浆、细胞质和细胞膜等不同部位, 并发挥不同的作用[14-16](表1)。核仁是核糖体生物发生的中心, 作为核仁中含量最丰富的的非核糖体蛋白质, 核仁中的Ncl通过参与核糖体新生的多个阶段, 如rRNA的DNA(rDNA)转录、核糖体组装以及增加RNA聚合酶I(RNA Pol I)转录活性等过程实现了对细胞增殖的调控[17-18]。RhoGTP酶活化蛋白ARHGAP30与Ncl相互作用促进Ncl的泛素化, 导致pre-rRNA、5.8s rRNA和28s rRNA水平显著降低, 进而抑制宫颈癌细胞的增殖与侵袭[19]。运动神经元生存蛋白(survival motor neuron protein, SMN)的缺乏主要影响核糖体蛋白的合成[20-21]。最新的研究表明, SMN与*Ncl-mTOR* mRNA复合物相互作用。SMN蛋白水平的降低会诱导*mTOR* mRNA的核招募, 以及其翻译效率的降低, 而所有翻译为核糖体蛋白的mRNA都受到mTOR的特异性调控[23], 提示Ncl可通过多种机制网络参与核糖体新生。

机制上, 应激会使Ncl以p53依赖的方式迁移到核质, 一方面激活的p53蛋白Dux DNA激活偶联, 进而激活小鼠胚胎细胞中基因和内源性逆转录病毒的表达; 另一方面, LIN28介导Ncl/转录抑制因子TRIM28复合体在Dux DNA上的结合减少, 导致Dux基因表达抑制作用被解除、rRNA转录被抑制[18,24-25]。细胞质中的Ncl在转录后调控中发挥重要作用, 如乳腺癌细胞中, Ncl与基质金属蛋白-2(matrix metalloproteinase-2, MMP-2)的3′UTR结合, 影响MMP2的稳定性, 促进乳腺癌细胞增殖[26]。胞质Ncl的异常上调促进了Wnt/β-Catenin信号转导, 继而全面影响核糖体生物发生的多个步骤, 并通过myc依赖的途径

表1 核仁素亚细胞定位的不同生物学功能

Table 1 The functions of nucleolin in different cell compartments

亚细胞定位 Subcellular localization	功能 Biological function
Nucleolar	Promote rDNA transcription and rRNA synthesis, pre-RNA maturation and ribosome assembly; regulate RNA pol I transcription; interact with rDNA chromatin and chromatin remodelers; and facilitate chromatin transcription activities
Nucleoplasmic	Regulate RNA pol II activation; interact with G- & C- rich sequences and telomeric repeats; DNA helicase activity; participate in DNA repair and mRNA pre-cursors splicing
Cytoplasmic	Bind to target RNA and protein; maintain centrosomes integrity; regulate cell cycle and autophagy; regulate miRNA biogenesis; mediate nuclear-cytoplasmic transport of ribosomal proteins
Cell surface	Regulation of cell adhesion; internalization of pathogenic microbes, toxins and mt-DNA; as targets of tumor inhibitor molecules; as receptors of cell proliferation, angiogenesis and apoptosis related ligands

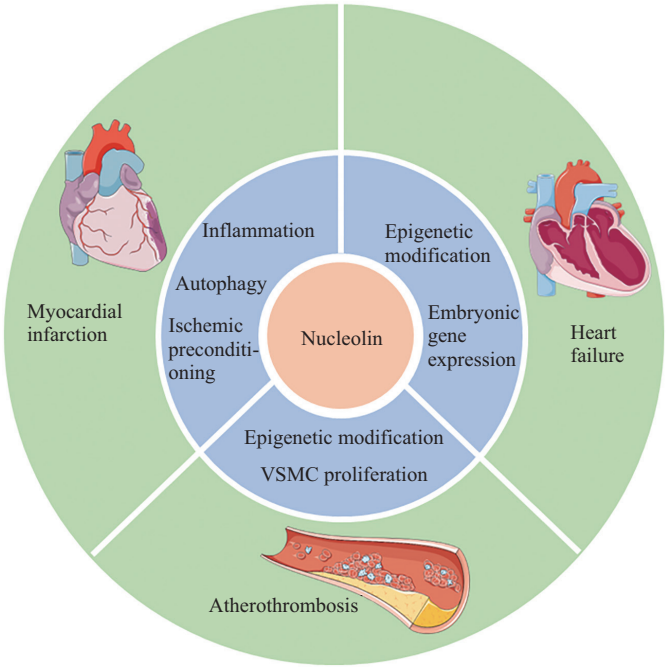


图1　核仁素在心血管疾病中的研究进展

Fig.1　Research progress on nucleolin in cardiovascular disease

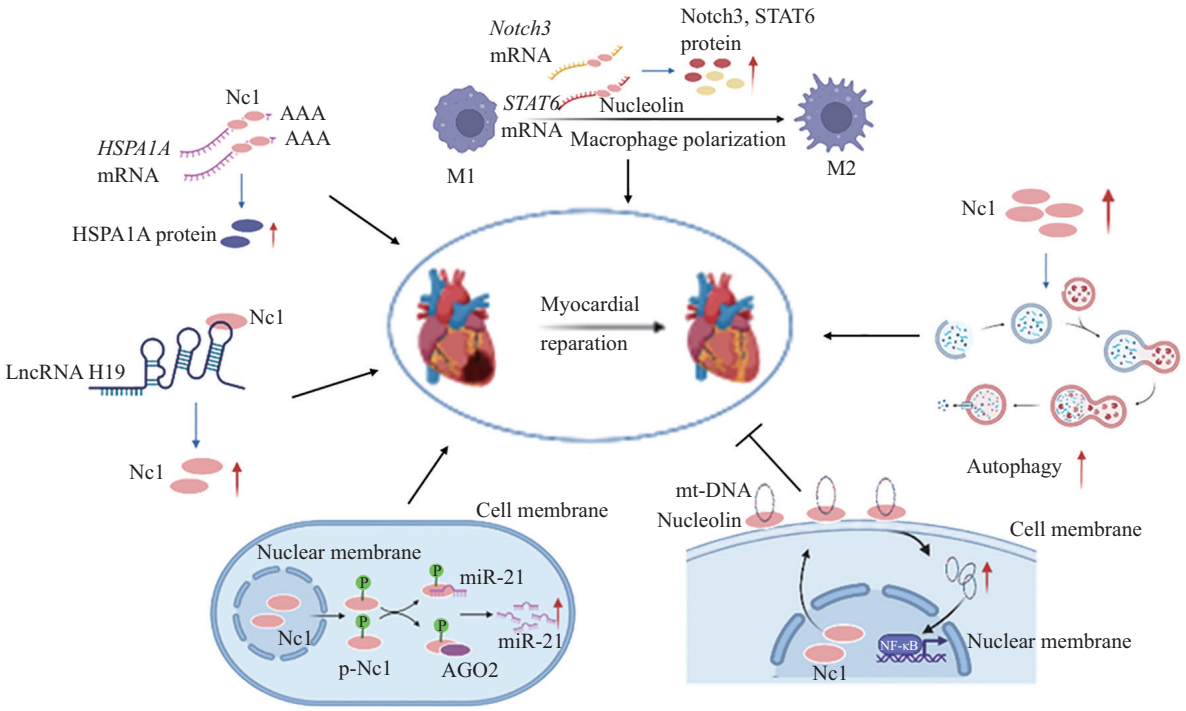
增强几乎所有核糖体蛋白的表达能力，促进细胞癌变[27]。细胞表面Ncl与多种细胞外抗肿瘤/抗血管生成蛋白形成受体配体复合物，如在血管生成过程中，细胞表面Ncl是细胞外金属蛋白酶ADAMTS5的一种新型高亲和力内皮细胞表面受体，介导ADAMTS5在内皮细胞中的促凋亡作用。机制上，TS5-p45与内皮细胞表面Ncl的RBD结构域相互作用后，通过网格蛋白和小泡蛋白依赖性的内吞作用被内化，并通过晚期核内小体被运输到细胞核，而TS5-p45的核转运对其促凋亡活性至关重要[16,28]。

Ncl是一种穿梭蛋白，正确的亚细胞定位对其发挥生物学作用具有重要意义，而Ncl的异常定位则参与多种病理进程[18]。先前报道多聚焦于Ncl在肿瘤发生发展中的作用[29-30]，而近年来的研究发现Ncl也参与心血管疾病的发生发展，且主要围绕心肌梗死[31]、心力衰竭[32]、动脉粥样硬化[33](图1)。

2　核仁素与心肌梗死

心肌梗死(myocardial infarction, MI)是因冠状动脉持续性或急性缺氧缺血引发的心肌坏死，目前采用冠状动脉内血管术治疗能明显延长患者生命周期[34]，但手术并不是一劳永逸的，术后缺血再灌注不仅会对心脏造成进一步损伤，而且由于心脏再生能力弱，心脏梗死区的修复以瘢痕修复为主，所以易导致心室不良重构进而引发心力衰竭[35-36]。多项研究证实Ncl在梗死心肌组织中表达发生变化[37-39]，提示其在心肌梗死中可能发挥重要作用，但其作用机制尚未被完全阐明。

目前研究证实Ncl能通过心肌缺血预处理[31]、炎症反应[40]及自噬[38]等途径保护梗死心肌(图2)。心肌缺血预处理(ischemic preconditioning, IP)是一段短暂的心肌缺血再灌注(ischemic/perfusion, I/R)，可显著减轻随后较长期I/R造成的损伤，是一种强有力的内源性心脏保护机制[41-42]。JIANG等[43]研究者发现，Ncl是心肌IP过程中重要的内源性心肌保护因子，Ncl通过与热休克蛋白(heat shock protein, HSP)家族成员*HSPA1A* mRNA的3′UTR结合使其不易被降解，通过稳定*HSPA1A* mRNA来上调HSPA1A的表达，进而增强H_2O_2预处理(H_2O_2 preconditioning, H_2O_2-PC)介导的保护作用。该团队后续研究发现，长链非编码RNA(long noncoding RNA, lncRNA)和微小RNA(microRNA, miRNA)与Ncl的互作都能在心梗发生时保护心肌。在心肌IP条件下，lncRNA H19也可直接与Ncl的RNA结合域结合，在转录后修饰水平上稳定Ncl的表达，进而抑制caspase-3的表达来保护心肌细胞免受氧化应激诱导的凋亡[31]。Ncl作为一种磷酸化蛋白，磷酸化后可以参与核糖体RNA(rRNA)的合成、重组DNA的转录、细胞增殖



→: 激活; ⊣ : 抑制。
→: activation; ⊣ : inhibition.

图2 核仁素参与心肌修复的分子机制

Fig.2 Molecular mechanism of nucleolin involved in myocardial repair

和生长等多种生命进程[18]。TONG等[39]证实第76位和84位点的苏氨酸磷酸化是Ncl上调miR-21并抑制梗死心肌细胞凋亡必不可少的一步。该研究还发现在氧化应激下, Ncl从细胞核转移到细胞质后再发生磷酸化修饰, 一方面磷酸化的Ncl与miR-21结合, 另一方面直接与AGO2(Argonaute2蛋白)相互作用, 通过共同提高miR-21的表达来降低caspase-3活性, 以保护心肌细胞免受氧化应激造成的损伤。

MI后缺血心肌释放的损伤相关分子模式(damage-associated molecular patterns, DAMPs), 如腺嘌呤核苷酸三磷酸(adenosine-triphosphate, ATP)、线粒体DNA(mitochondrial DNA, mt-DNA)都可与模式识别受体(pattern recognition receptor, PRR)结合, 激活先天免疫系统[44-47]。研究证明, 线粒体在再灌注损伤中具有关键作用[48], 如经皮冠状动脉介入治疗后, mt-DNA从心肌梗死患者的心脏释放到循环中[49]。mt-DNA与细菌DNA类似, 含有促炎症的、未甲基化的CpG基序, 能够引起无菌性炎症[50]。MARIERO等[51]发现在缺氧/复氧条件下, 心肌细胞膜上表达的Ncl能够与mt-DNA结合, 从而促进原代心肌细胞对心脏细胞免疫原性DNA的摄取。mt-DNA的CpG通过Toll样受体-9激活心肌细胞中的NF-κB信号通路, 引发炎症反应, 而阻断Ncl可降低心肌细胞IL-1β和TNF-α的表达水平以及IL-6的释放水平。该研究首次报道了细胞外DNA能够与Ncl结合, 并通过Ncl吸收细胞外的DNA, 导致不良功能, 这也使其有望作为治疗急性心肌梗死后无菌炎症的新靶点。巨噬细胞的浸润在MI后炎症反应和增殖过程中表现出可塑性功能, 包括经典活化的巨噬细胞(M1, 促炎表型)和交替活化的巨噬细胞(M2, 抗炎表型)之间的转化[52]。TANG等[40]通过结扎冠状动脉左前降支建立小鼠MI模型, 检测心梗后第1、3、7、14、28天小鼠心肌Ncl的mRNA和蛋白质表达情况, 发现Ncl mRNA及蛋白表达从第3天开始逐渐下降, 然后逐渐上升, 在第7天时达到峰值。而心肌中的大部分巨噬细胞在心肌梗死2天后为M1表型, 5天后大部分为M2表型, 提示Ncl可能与巨噬细胞表型转换相关。机制上, Ncl通过结合*Notch3*和*STAT6* mRNA的5′UTR或翻译区, 上调Notch3和STAT6的表达促进M2巨噬细胞的极化, 进而减轻炎症反应, 促进心肌梗死后心肌细胞存活和组织修复。

在心肌缺血和心肌梗死小鼠模型中, 自噬相关基因缺失或药物抑制可加重心功能障碍和心肌重构[53]。DENG等[38]发现Ncl/自噬信号通路在缺血心肌中被激

活, 但单一的Ncl表达增加和自噬增强并不足以对抗缺血引起的心肌损伤。尼可地尔(Nicorandil)可通过上调Ncl/自噬轴影响TGF-β/Smad信号通路, 减轻心梗后心脏重构, 改善心功能。这些研究提示Ncl有望作为心血管药物的潜在作用靶点, 为治疗心肌梗死开辟新的途径。

3 核仁素与心力衰竭

高血压、瓣膜病、病理性心肌肥厚都会导致心力衰竭(heart failure, HF), 而高血压合并左心室肥厚和纤维化是导致HF的主要危险因素[54-55]。病理性心肌肥厚涉及到心肌细胞体积增大及胚胎基因的重新表达[56], MONTE等[57]发现在病理性心肌肥厚和HF小鼠模型中, 肥厚心肌细胞核中Ncl表达量增多, 但细胞核和细胞质的总Ncl减少, 并伴有核糖体中pre-rRNA和成熟rRNA(18S rRNA)的变化。使用siRNA敲低*Ncl*在新生大鼠心室肌细胞中的表达, 导致异染色质标志物H3K9Me3的增加, 同时pre-rRNA和18s rRNA的转录水平降低。这些研究提示Ncl参与异染色质向常染色质的转变过程, 并促进正常rRNA转录、加工及核糖体新生。研究还发现, Ncl的缺失促进了斑马鱼和小鼠心肌细胞中胚胎基因(斑马鱼中为*Bmp4*, 小鼠中为*ANF*、*β-MHC*)的表达, 并且*Bmp4*表达失调导致斑马鱼左右心室不对称和腹背轴形成缺陷[58], 表明Ncl可能通过*Bmp4*影响心肌细胞的可塑性, 进而影响心室形态, 参与病理性心肌肥厚和HF进程。另一项对38例缺血性心肌病(Ischemic cardiomyopathy, ICM)和27例扩张型心肌病(Dilated cardiomyopathy, DCM)临床样本的研究显示, 众多核仁蛋白中, 除Ncl在病理样本中表达水平升高外, 其余均无变化, 核仁中Ncl含量高于核质中, 且病理性心脏的核仁荧光强度高于对照组心肌细胞[32]。Ncl与自噬受体蛋白p62的表达呈剂量依赖性增加, 二者之间关系密切, 且支持核质转运过程[59]。以上研究证明, Ncl在细胞中的亚定位与其在心力衰竭中的作用密切相关。

4 核仁素与动脉粥样硬化

动脉粥样硬化的主要特征是在中、大型血管中形成富含脂肪的斑块[60]。病情发展与招募单核细胞向巨噬细胞分化有关, 随后巨噬细胞或平滑肌细胞吸收脂质成为影响炎症反应的泡沫细胞, 因此快速清除泡沫细胞能够抑制炎症反应, 最终延缓斑块的发展[61-62]。Ncl在调节动脉粥样硬化进展中具有重要作用[61]。LI等[63]观察到在巨噬细胞向泡沫细胞转变时, Ncl在蛋白水平上的表达逐渐降低, 并且Ncl能够与*ABCA1* mRNA结合, 增强*ABCA1*稳定性而上调其表达, 进而增强ABCA1促进胆固醇外排的功能, 抑制脂质积累和泡沫细胞形成。研究发现, 在正常情况下, Ncl与Dnm3os相互作用能阻止Dnm3os在促炎基因(如*IL6*基因)启动子组蛋白H3K9ac上的富集[33]。但是, 在糖尿病条件下, Dnm3os量的增加和Ncl水平的降低破坏了这种相互作用, 加剧了Dnm3os在H3K9ac上的富集, 从而导致了染色质松弛, 上调了*IL6*基因的表达, 引起了巨噬细胞功能紊乱。此外, SUN等[64]通过体内外实验证实, 动脉粥样硬化的诱因之一——氧化低密度脂蛋白(oxLDL)以剂量依赖的方式上调血管平滑肌中Ncl mRNA和蛋白质表达。血管平滑肌细胞的异常增殖是动脉粥样硬化发生发展的基本病理基础。在氧化低密度脂蛋白处理下, Ncl促进了血管平滑肌细胞的增殖和细胞周期变化, 增加了S期和G_2/M期群体, 降低了G_0/G_1期群体。正常情况下Aurora B主要分布在细胞核中, 在细胞周期中动态表达, 表达高峰位于G_2/M期, 提示Aurora B与Ncl可能存在某种关系。通过免疫共沉淀实验发现Aurora B与Ncl存在蛋白质相互作用, 推测二者结合可促进细胞增殖和细胞周期的改变。综上, Ncl在不同细胞、不同疾病中特异性的作用有待深入研究。

5 问题与展望

目前, 众多心血管疾病的治疗手段都不能有效修复受损心肌。Ncl是一类高度保守且广泛表达的核仁蛋白, 它在细胞增殖、分化、核糖体新生、细胞凋亡等方面发挥重要的调控功能。以往关于Ncl的研究多集中在肿瘤的发生发展中, 而在心血管疾病中的研究仍处于起步阶段。Ncl存在四个RNA结合位点, 能够调控众多下游基因的转录后表达, 但其具体分子机制尚未被完全阐明, 关于非编码RNA与Ncl之间的互作关系以及Ncl自身结构(如*Ncl* UTR等)和生物学功能的相关报道也寥寥无几, 亟需深入研究。同时, Ncl的不同表达量、在细胞的不同部位表达等都会发挥不同的功能, 因此明确心血管疾病中Ncl表达异常的细胞类型以及其与炎症反应、细胞死亡、增殖等信号通路的交互作用, 并在此基础上研发调节相关信号通路的小分子药物, 开展相关

的临床试验, 可为治疗心血管疾病提供新思路。因此深入研究Ncl在心血管疾病发生发展中的作用及调控机制, 对于心血管疾病的治疗具有重要意义。

作者贡献声明 涂均楚, 综述构思及撰写, 图表绘制。王燕丽, 综述构思及修订。陆琳、吴诚洁、张瑜, 综述修订。李杨欣, 综述构思, 图表设计及修订。

参考文献 (References)

[1] 国家心血管病中心. 中国心血管健康与疾病报告2020[J]. 心肺血管病杂志(NATIONAL CENTER FOR CARDIOVASCULAR DISEASE. Annual report of cardiovascular health and diseases 2020 [J]. Journal of Cardiovascular and Pulmonary Diseases), 2021, 40(9): 885-9.

[2] 方立, 王慷慨, 肖献忠. 细胞膜表面核仁素的功能[J]. 国际病理科学与临床杂志(FANG L, WANG K K, XIAO X Z. Function of nucleolin localized on the cell surface [J]. International Journal of Pathology and Clinical Medicine), 2007(5): 417-20.

[3] ORRICK L R, OLSON M O, BUSCH H. Comparison of nucleolar proteins of normal rat liver and Novikoff hepatoma ascites cells by two-dimensional polyacrylamide gel electrophoresis [J]. Proc Natl Acad Sci USA, 1973, 70(5): 1316-20.

[4] BIGGIOGERA M, BURKI K, KAUFMANN S H, et al. Nucleolar distribution of proteins B23 and nucleolin in mouse preimplantation embryos as visualized by immunoelectron microscopy [J]. Development, 1990, 110(4): 1263-70.

[5] LISCHWE M A, RICHARDS R L, BUSCH R K, et al. Localization of phosphoprotein C23 to nucleolar structures and to the nucleolus organizer regions [J]. Exp Cell Res, 1981, 136(1): 101-9.

[6] OCHS R, LISCHWE M, OLEARY P, et al. Localization of nucleolar phosphoprotein-B23 and phosphoprotein-C23 during mitosis [J]. Exp Cell Res, 1983, 146(1): 139-49.

[7] DURUT N, SAEZ-VASQUEZ J. Nucleolin: dual roles in rDNA chromatin transcription [J]. Gene, 2015, 556(1): 7-12.

[8] FAGERBERG L, HALLSTROM B M, OKSVOLD P, et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics [J]. Mol Cell Proteomics, 2014, 13(2): 397-406.

[9] GINISTY H, SICARD H, ROGER B, et al. Structure and functions of nucleolin [J]. J Cell Sci, 1999, 112(Pt6): 761-72.

[10] XIAO S, CAGLAR E, MALDONADO P, et al. Induced expression of nucleolin phosphorylation-deficient mutant confers dominant-negative effect on cell proliferation [J]. PLoS One, 2014, 9(10): e109858.

[11] PERCHARDE M, LIN C J, YIN Y, et al. A LINE1-nucleolin partnership regulates early development and ESC identity [J]. Cell, 2018, 174(2): 391-405.

[12] OKUWAKI M, SAOTOME-NAKAMURA A, YOSHIMURA M, et al. RNA-recognition motifs and glycine and arginine-rich region cooperatively regulate the nucleolar localization of nucleolin [J]. J Biochem, 2021, 169(1): 87-100.

[13] DORON-MANDEL E, KOPPEL I, ABRAHAM O, et al. The glycine arginine-rich domain of the RNA-binding protein nucleolin regulates its subcellular localization [J]. EMBO J, 2021, 40(20): e107158.

[14] ABDELMOHSEN K, GOROSPE M. RNA-binding protein nucleolin in disease [J]. Rna Biol, 2012, 9(6): 799-808.

[15] TUTEJA R, TUTEJA N. Nucleolin: a multifunctional major nucleolar phosphoprotein [J]. Crit Rev Biochem Mol, 1998, 33(6): 407-36.

[16] ROSU M C, MIHNEA P D, ARDELEAN A, et al. Clinical significance of tumor necrosis factor-alpha and carcinoembryonic antigen in gastric cancer [J]. J Med Life, 2022, 15(1): 4-6.

[17] TAGLIAFERRO M, ROSA P, BELLENCHI G C, et al. Nucleolar localization of the ErbB3 receptor as a new target in glioblastoma [J]. BMC Mol Cell Biol, 2022, 23(1): 13.

[18] JIA W, YAO Z, ZHAO J, et al. New perspectives of physiological and pathological functions of nucleolin (NCL) [J]. Life Sci, 2017, 186: 1-10.

[19] WU A, LIN L, LI X, et al. Overexpression of ARHGAP30 suppresses growth of cervical cancer cells by downregulating ribosome biogenesis [J]. Cancer Sci, 2021, 112(11): 4515-25.

[20] GABANELLA F, ONORI A, RALLI M, et al. SMN protein promotes membrane compartmentalization of ribosomal protein S6 transcript in human fibroblasts. [J]. Sci Rep, 2020, 10(1): 19000.

[21] BERNABÒ P, TEBALDI T, GROEN E J N, et al. *In vivo* translatome profiling in spinal muscular atrophy reveals a role for SMN protein in ribosome biology [J]. Cell Rep, 2017, 21(4): 953-65.

[22] GABANELLA F, BARBATO C, FIORE M, et al. Fine-tuning of mTOR mRNA and nucleolin complexes by SMN [J]. Cells, 2021, 10(11): 3015.

[23] THOREEN C C, CHANTRANUPONG L, KEYS H R, et al. A unifying model for mTORC1-mediated regulation of mRNA translation [J]. Nature, 2012, 485(7396): 109-13.

[24] GROW E J, WEAVER B D, SMITH C M, et al. p53 convergently activates Dux/DUX4 in embryonic stem cells and in facioscapulohumeral muscular dystrophy cell models [J]. Nat Genet, 2021, 53(8): 1207-20.

[25] SUN Z, YU H, ZHAO J, et al. LIN28 coordinately promotes nucleolar/ribosomal functions and represses the 2C-like transcriptional program in pluripotent stem cells [J]. Protein Cell, 2021, 13(7): 490-512.

[26] DAS S, DE S, SENGUPTA S. Post-transcriptional regulation of MMP2 mRNA by its interaction with miR-20a and Nucleolin in breast cancer cell lines [J]. Mol Biol Rep, 2021, 48(3): 2315-24.

[27] HUANG Y, LI Z, LIN E, et al. Oxidative damage-induced hyperactive ribosome biogenesis participates in tumorigenesis of offspring by cross-interacting with the Wnt and TGF-beta1 pathways in IVF embryos [J]. Exp Mol Med, 2021, 53(11): 1792-806.

[28] KIRMAN D C, RENGANATHAN B, CHUI W K, et al. Cell surface nucleolin is a novel ADAMTS5 receptor mediating endothelial cell apoptosis [J]. Cell Death Dis, 2022, 13(2): 172.

[29] SATOH M, CERIBELLI A, HASEGAWA T, et al. Clinical significance of antinucleolar antibodies: biomarkers for autoimmune diseases, malignancies, and others [J]. Clin Rev Allergy Immunol, 2022, 63(2): 210-39.

[30] THONGCHOT S, JIRAPONGWATTANA N, LUANGWATTANANUN P, et al. Adoptive transfer of anti-nucleolin T cells combined with PD-L1 inhibition against triple-negative breast cancer [J]. Mol Cancer Ther, 2022, 21(5): 727-39.

[31] CHEN C, LIU M, TANG Y, et al. LncRNA H19 is involved in

myocardial ischemic preconditioning via increasing the stability of nucleolin protein [J]. J Cell Physiol, 2020, 235(9): 5985-94.

[32] ROSELLO-LLETI E, RIVERA M, CORTES R, et al. Influence of heart failure on nucleolar organization and protein expression in human hearts [J]. Biochem Biophys Res Commun, 2012, 418(2): 222-8.

[33] DAS S, REDDY M A, SENAPATI P, et al. Diabetes mellitus-induced long noncoding RNA Dnm3os regulates macrophage functions and inflammation via nuclear mechanisms [J]. Arterioscler Thromb Vasc Biol, 2018, 38(8): 1806-20.

[34] DAGENAIS G R, LEONG D P, RANGARAJAN S, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study [J]. Lancet, 2020, 395(10226): 785-94.

[35] RIQUELME J A, CHAVEZ M N, MONDACA-RUFF D, et al. Therapeutic targeting of autophagy in myocardial infarction and heart failure [J]. Expert review of cardiovascular therapy, 2016, 14(9): 1007-19.

[36] LONBORG J T. Targeting reperfusion injury in the era of primary percutaneous coronary intervention: hope or hype [J]? Heart, 2015, 101(20): 1612-8.

[37] MAMAEV N N, KOVALYEVA O V, AMINEVA K K, et al. AgNORs in cardiomyocytes from surgical patients with coronary heart disease [J]. Mol Pathol, 1998, 51(4): 218-21.

[38] DENG H F, ZOU J, WANG N, et al. Nicorandil alleviates cardiac remodeling and dysfunction post-infarction by up-regulating the nucleolin/autophagy axis [J]. Cell Signal, 2022, 92: 110272.

[39] TONG Z, TANG Y, JIANG B, et al. Phosphorylation of nucleolin is indispensable to upregulate miR-21 and inhibit apoptosis in cardiomyocytes [J]. J Cell Physiol, 2019, 234(4): 4044-53.

[40] TANG Y, LIN X, CHEN C, et al. Nucleolin improves heart function during recovery from myocardial infarction by modulating macrophage polarization [J]. J Cardiovasc Pharmacol Ther, 2021, 26(4): 386-95.

[41] MURRY C E, JENNINGS R B, REIMER K A. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium [J]. Circulation, 1986, 74(5): 1124-36.

[42] SHI W, VINTEN-JOHANSEN J. Endogenous cardioprotection by ischaemic postconditioning and remote conditioning [J]. Cardiovasc Res, 2012, 94(2): 206-16.

[43] JIANG B, LIANG P, WANG K, et al. Nucleolin involved in myocardial ischaemic preconditioning via post-transcriptional control of HSPA1A expression [J]. Cardiovasc Res, 2014, 102(1): 56-67.

[44] FRANGOGIANNIS N G. The inflammatory response in myocardial injury, repair, and remodelling [J]. Nat Rev Cardiol, 2014, 11(5): 255-65.

[45] NAKAYAMA H, OTSU K. Mitochondrial DNA as an inflammatory mediator in cardiovascular diseases [J]. Biochem J, 2018, 475(5): 839-52.

[46] SHI Y, EVANS J E, ROCK K L. Molecular identification of a danger signal that alerts the immune system to dying cells [J]. Nature, 2003, 425(6957): 516-21.

[47] TIAN J, GUO X, LIU X M, et al. Extracellular HSP60 induces inflammation through activating and up-regulating TLRs in cardiomyocytes. [J]. Cardiovasc Res, 2013, 98(3): 391-401.

[48] KLONER R A, BROWN D A, CSETE M, et al. New and revisited approaches to preserving the reperfused myocardium [J]. Nat Rev Cardiol, 2017, 14(11): 679-93.

[49] BLIKSOEN M, MARIERO L H, OHM I K, et al. Increased circulating mitochondrial DNA after myocardial infarction [J]. Int J Cardiol, 2012, 158(1): 132-4.

[50] COLLINS L V, HAJIZADEH S, HOLME E, et al. Endogenously oxidized mitochondrial DNA induces *in vivo* and *in vitro* inflammatory responses [J]. J Leukoc Biol, 2004, 75(6): 995-1000.

[51] MARIERO L H, TORP M K, HEIESTAD C M, et al. Inhibiting nucleolin reduces inflammation induced by mitochondrial DNA in cardiomyocytes exposed to hypoxia and reoxygenation [J]. Br J Pharmacol, 2019, 176(22): 4360-72.

[52] MA Y, MOUTON A J, LINDSEY M L. Cardiac macrophage biology in the steady-state heart, the aging heart, and following myocardial infarction [J]. Transl Res, 2018, 191: 15-28.

[53] KANAMORI H, TAKEMURA G, GOTO K, et al. Autophagy limits acute myocardial infarction induced by permanent coronary artery occlusion [J]. Am J Physiol Heart Circ Physiol, 2011, 300(6): H2261-71.

[54] JIANG X, SHAO M, LIU X, et al. Reversible treatment of pressure overload-induced left ventricular hypertrophy through Drd5 nucleic acid delivery mediated by functional polyaminoglycoside [J]. Adv Sci, 2021, 8(5): 2003706.

[55] REN Z, YU P, LI D, et al. Single-cell reconstruction of progression trajectory reveals intervention principles in pathological cardiac hypertrophy [J]. Circulation, 2020, 141(21): 1704-19.

[56] 严思敏, 吴双, 孙丽, 等. 大鼠压力负荷增加心肌肥厚模型中核仁素的表达[J]. 中南大学学报(YAN S M, WU S, SUN L, et al. Expression of nucleolin in pressure overload-induced cardiac hypertrophy rats [J]. Journal of Central South University, Medical Science), 2014, 39(2): 124-8.

[57] MONTE E, MOUILLESSEAUX K, CHEN H, et al. Systems proteomics of cardiac chromatin identifies nucleolin as a regulator of growth and cellular plasticity in cardiomyocytes [J]. Am J Physiol Heart Circ Physiol, 2013, 305(11): H1624-38.

[58] JING Y, REN Y, WITZEL H R, et al. A BMP4-p38 MAPK signaling axis controls ISL1 protein stability and activity during cardiogenesis [J]. Stem Cell Rep, 2021, 16(8): 1894-905.

[59] CORTES R, ROSELLO-LLETI E, RIVERA M, et al. Influence of heart failure on nucleocytoplasmic transport in human cardiomyocytes [J]. Cardiovasc Res, 2010, 85(3): 464-72.

[60] LIBBY P, BURING J E, BADIMON L, et al. Atherosclerosis [J]. Nat Rev Dis Primers, 2019, 5(1): 56.

[61] CHEN W, LI L, WANG J, et al. Extracellular vesicle YRNA in atherosclerosis [J]. Clin Chim Acta, 2021, 517: 15-22.

[62] WOLF D, LEY K. Immunity and inflammation in atherosclerosis [J]. Circ Res, 2019, 124(2): 315-27.

[63] LI Y, JIANG B, LIANG P, et al. Nucleolin protects macrophages from oxLDL-induced foam cell formation through up-regulating ABCA1 expression [J]. Biochem Biophys Res Commun, 2017, 486(2): 364-71.

[64] SUN H, HUANG L, LIANG P, et al. Nucleolin regulates the proliferation of vascular smooth muscle cells in atherosclerotic via Aurora B [J]. J Cell Mol Med, 2021, 25(2): 751-62.