·综 述·

心血管衰老机制：蛋白稳态丧失、基因组不稳定性及炎症

郑 刚
（泰达国际心血管病医院互联网医院，天津 300457）

摘要：蛋白稳态丧失、基因组不稳定及炎症三者均参与心血管衰老，而心血管衰老与动脉粥样硬化（atherosclerosis）、心力衰竭（heart failure）及心肌病等多种心血管疾病的发生、发展密切相关。故蛋白稳态、基因组稳定性及炎症可能是衰老相关心血管疾病的治疗靶点。该文简要综述蛋白稳态丧失、基因组不稳定及炎症在心血管衰老中的作用机制，以期为今后心血管疾病的预防、诊断及新药研发提供新方向。

关键词：心血管系统；衰老；蛋白稳态丧失；基因组不稳定；炎症
中图分类号：R543 **文献标志码：**A **文章编号：**1672-9188(2024)10-1016-007
引用：郑刚. 心血管衰老机制: 蛋白稳态丧失、基因组不稳定性及炎症[J]. 世界临床药物, 2024, 45(10): 1016-1022. DOI：10.13683/j.wph.2024.10.003

Cardiovascular aging mechanism: loss of protein homeostasis, genomic instability and inflammation

ZHENG Gang
(*Internet Hospital, Teda Interational Cardiovascular Hospital , Tianjin 300457, China*)

Abstract: Loss of protein homeostasis, genomic instability and inflammation all involve in cardiovascular aging, and which is closely related to the occurrence and development of cardiovascular diseases, such as atherosclerosis, heart failure, cardiomyopathy and other. Therefore, protein homeostasis, genomic stability, and inflammation may be therapeutic targets for age-related cardiovascular diseases. This article reviewed the mechanisms of protein homeostasis loss, genomic instability, and inflammation in cardiovascular aging, in order to provide new directions for the prevention, diagnosis, and development of new drugs for cardiovascular diseases in the future.

Key words: cardiovascular system; aging; loss of protein homeostasis; genomic instability; inflammation

线粒体及肌节的密集包裹使得心血管系统获得独特功能（如心肌细胞的收缩功能），但这也限制了细胞的增殖能力。虽然人体所有细胞功能均会受年龄增长影响，但心肌及其他心血管细胞可能更易出现与年龄相关的功能障碍，甚至衰竭。随着年龄增长，心血管系统的细胞组成会发生改变，导致心脏、血管及微循环的结构和功能重塑。故年龄成为心血管健康的重要预测因子之一。本文就蛋白稳态丧失、基因组不稳定及炎症在心血管衰老中的作用机制作简要综述，以期为今后心血管疾病的预防、诊断及药物研发提供参考。

1 蛋白稳态丧失

蛋白稳态是机体健康和抗压能力的主要驱动因素[1]。蛋白质合成、折叠和降解之间的微妙平衡受分子伴侣及蛋白水解酶网络的严格调节[2]。蛋白质组的完整性通过对变性蛋白质进行重折叠或选择

收稿日期：2024-01-23
作者简介：郑刚，教授，研究方向：心力衰竭及高血压的诊断和治疗。

性降解来维持。当热休克蛋白（heat shock protein，HSP）和其他分子伴侣不能将蛋白质重折叠成正确的构象时，功能失调的蛋白质必须被泛素 - 蛋白酶体系统（ubiquitin-proteasome system，UPS）或分子伴侣介导的自噬（chaperone-mediated autophagy，CMA）破坏。CMA 是蛋白质降解形式之一，其中热休克同源蛋白与指定用于降解特定蛋白的 KFERQ 基序结合[1]，促进二者结合物通过受体 - 溶酶体相关膜糖蛋白（lysosomal associated membrane glycoprotein，LAMP）2A 易位到溶酶体中[3]。但上述稳态维持效率会随年龄增长而下降，导致蛋白质错误折叠以及受损蛋白质的积累，并可能形成非功能性蛋白聚集物[4]。这些非功能性蛋白聚集物与心血管疾病，如动脉粥样硬化（atherosclerosis）、心房颤动（atrial fibrillation）、心力衰竭（heart failure，HF）及各类心肌病的发生相关[5—6]。

蛋白稳态与心肌细胞结构及功能息息相关[7—9]。蛋白酶体及 HSP 参与蛋白稳态的调节，二者活性及表达水平随年龄增长而降低，故而导致氧化及泛素化蛋白质在心脏积累，从而导致心血管疾病的发生[10—11]。在脉管系统中亦能观察到类似作用机制。研究表明，在主动脉巨噬细胞和平滑肌细胞中，CMA 活性及相关基因表达水平随年龄增长而降低，从而影响动脉粥样硬化的发生[12—13]；此外，蛋白酶体活性降低也会通过促进细胞衰老，导致动脉粥样硬化的发生[14]。有学者发现，在老化的主动脉中存在淀粉样蛋白积累[15—16]，可为上述机制提供佐证。

目前蛋白稳态丧失在心血管疾病中的重要作用已明确，其或能为心血管疾病的治疗提供新靶点。晶状体蛋白 αB（crystalline αB，CryAB）错义突变会导致错误折叠的蛋白质积聚，引发蛋白稳态丧失，进而导致心肌重塑、心肌疾病，甚至心力衰竭[17—19]。现有证据表明，心脏 CryAB 过表达以及激活泛素缀合酶 9 诱导的 UPS 可改善心肌病中的蛋白稳态，或有潜力治疗相关疾病。动物试验表明，香叶基丙酮可减少 *CryAB* 突变小鼠心肌中蛋白聚集体，并改善心功能、提升存活率[22]；此外，香叶基丙酮还可改善心肌缺血模型大鼠的再灌注损伤[23]。在脉管系统中，促 LAMP2A 过表达能提高 CMA 活性以减轻模型小鼠动脉粥样硬化严重程度，并减缓其进展[12]。值得注意的是，限制热量摄入也能通过提升蛋白稳态以延缓心血管衰老[24—25]。

2 基因组不稳定

基因组不稳定是器官及物种衰老的常见特征，其在不同组织间存在较大差异。在心血管系统中，基因组稳定性随年龄增长而降低[26—27]，且存在性别差异[28]。动物试验显示，在老年小鼠中，小鼠基因突变主要形式为基因重排，但这并非衰老的诱因，而是心脏衰老的特征[27,29]。此外，虽然端粒与基因组稳定性直接相关，其消耗会导致心血管衰老，且与小鼠心血管风险有关[30]，但在人类中与端粒缩短相关的心脏病一般与心血管衰老无关[31—32]。

与平滑肌细胞相比，血管内皮细胞更易发生 DNA 损伤、端粒功能障碍[33]，且在人类动脉粥样硬化斑块中发现 DNA 损伤[34—35]。近来有学者发现，一些基因位点的突变或缺失导致 DNA 完整性受损或修复缺陷，从而引发心血管疾病。例如：核苷酸切除修复交错互补基因 1 表达或功能缺陷会影响 DNA 修复，导致内皮功能障碍、血管硬化加重，进而导致心血管疾病的发生[36—38]。*BUBR1* 突变也被证实会导致模型小鼠动脉弹性减低、硬化加重、舒张功能受损[39]。但相关研究具有一定的局限性，需进行全面、系统的基因组分析，以更全面了解与 DNA 损伤和心血管衰老之间的相关性。

现有证据表明，未定潜能的克隆性造血（clonal hematopoiesis of indeterminate potential，CHIP）与动脉粥样硬化及缺血性心肌病 HF 等心血管疾病的发生有关[40—42]。既往研究也已证实，*CHIP* 突变会导致动脉粥样硬化性心血管疾病发生风险增高[43]。现

有证据表明，向心性肥胖（central obesity）及代谢综合征（metabolic syndrome）相关心血管风险与骨髓造血增加和高循环白细胞计数有关，后者会加剧心血管系统 CHIP 及免疫细胞积聚，从而加剧慢性炎症[44—45]。多项研究验证 *CHIP* 突变会促进动脉粥样硬化、病理性心脏重塑及 HF，并尝试探索具体作用机制[40,46—49]，结果发现，*CHIP* 突变的人类和模型动物其免疫细胞均有促炎症表型，提示炎症或是 *CHIP* 突变致心血管疾病的重要机制之一[40,46—48,50]。

3 炎症

炎症会加快衰老进程，且其与年龄相关心血管疾病（如动脉粥样硬化）的发生密切相关[51]。现有证据表明，动脉粥样硬化的发生与炎症性病变有关，涉及多种免疫细胞及细胞因子[52—53]。炎症性病变在心脏衰老过程中亦十分明显。心肌免疫细胞浸润的丰度、亚型组成、功能和激活状态会随时间推移而变化，且具有性别差异[54—56]。此外，心肌 T 细胞亚群也会随年龄增长而变化，转化为促炎性更强的表型[57]。动物试验表明，$CD4^+$ T 细胞分化会促进小鼠心肌炎症转变[58]，且 T 细胞的促炎作用会损害新生小鼠的心肌再生能力，使其心脏结构及功能发生异常[59]。Desdin-Mico 等[60] 研究发现，线粒体转录因子 A 缺乏会影响 T 细胞线粒体功能，进而加速心血管系统衰老，通过阻断肿瘤坏死因子（tumor necrosis factor，TNF）-α 信号转导则可逆转上述作用。另有研究表明，IκB 激酶（IκB kinase，Ikk）及其下游靶点核因子（nuclear factor，NF）-κB 诱导的过度炎症反应会引起心肌病及 HF[61]，阻断 Ikk/NF-κB 通路可延缓心血管衰老，延长寿命[62]。

除动脉粥样硬化及其相关冠状动脉疾病外，射血分数保留的 HF（HF with ejection fraction preservation，HFpEF）也被认为是一种炎症性多器官综合征[63—64]，主要由衰老引起，常见于老年人[65]。有证据表明，钠-葡萄糖协同转运蛋白 2 抑制剂具有心脏保护作用[66—67]，其作用机制涉及抑制炎症及抗衰老等[68—72]。Deng 等[73] 发现，β- 羟基丁酸可通过作用于核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体 3 炎症小体，抑制白介素（interleukin，IL）-1β 成熟以及促炎细胞因子诱导的线粒体功能障碍，从而延缓 HFpEF 进展[73]。多项研究显示，靶向炎症机制能有效延缓衰老进展，治疗心血管疾病，为炎症参与心血管衰老提供佐证[74—77]。

环状鸟苷一磷酸 - 腺苷一磷酸合成酶（cyclic guanosine monophosphate and adenosine monophosphate synthase，cGAS）- 干扰素基因刺激蛋白（stimulator of interferon genes，STING）通路是慢性炎症及衰老的关键驱动因素，其与内皮功能障碍相关[78—79]，并参与早老症（progeria）的发生[80]。而学者发现，早老症患者的心血管病变在多方面与老年人群一致[81]。此外，动物试验提示抑制 cGAS-STING 可改善动脉粥样硬化及心肌梗死（myocardial infarct）后的心肌重构[82—83]。

虽然现有证据已证实炎症是年龄相关心血管疾病的重要发病机制之一[84]，但尚缺乏证据支持抗炎药物用于相关疾病的预防。阿司匹林（aspirin）作为一种非甾体抗炎药物，低剂量应用能抑制血小板聚集并诱导自噬[85]，但多项大型临床研究均未能证实其可预防初始心血管事件[86—88]。新近研究表明，阿司匹林联合用药方案可用于心血管疾病的二级预防[89]，但其一级预防作用尚待验证。此外，对于抗炎药物预防心血管衰老的适宜人群仍未明确。现有证据表明，*CHIP* 突变的老年人以及有全身炎症症状的患者对卡那单抗（canakinumab）较为敏感[90—91]。

4 结语

心血管衰老有多种机制参与。蛋白稳态丧失与年龄相关心血管功能下降有关，维持蛋白稳定能延缓心血管衰老。基因组稳定性虽已被证实参与心血管衰老，且其作用与炎症等其他机制交叉，但以心血管细胞本身的基因组不稳定为靶点是否能发挥心血管抗衰老作用尚不清楚。炎症是心血管疾病及心

血管衰老的共同机制，但对于可通过抗炎治疗以延缓心血管衰老的适宜人群仍未明确，具体干预方案亦尚待完善。

参考文献：

[1] López-Otín C, Kroemer G. Hallmarks of health[J]. Cell, 2021, 184(1): 33-63.

[2] Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing[J]. Nat Rev Mol Cell Biol, 2019, 20(7): 421-435.

[3] Kaushik S, Cuervo AM. The coming of age of chaperone-mediated autophagy[J]. Nat Rev Mol Cell Biol, 2018, 19(6): 365-381.

[4] Alberti S, Hyman AA. Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing[J]. Nat Rev Mol Cell Biol, 2021, 22(3): 196-213.

[5] Gouveia M, Xia K, Colón W, *et al*. Protein aggregation, cardiovascular diseases, and exercise training: where do we stand?[J]. Ageing Res Rev, 2017, 40: 1-10.

[6] Henning RH, Brundel BJJM. Proteostasis in cardiac health and disease[J]. Nat Rev Cardiol, 2017, 14(11): 637-653.

[7] Hofmann C, Katus HA, Doroudgar S. Protein misfolding in cardiac disease[J]. Circulation, 2019, 139(18): 2085-2088.

[8] McLendon PM, Robbins J. Proteotoxicity and cardiac dysfunction[J]. Circ Res, 2015, 116(11): 1863-1882.

[9] Martin TG, Myers VD, Dubey P, *et al*. Cardiomyocyte contractile impairment in heart failure results from reduced BAG3-mediated sarcomeric protein turnover[J]. Nat Commun, 2021, 12(1): 2942.

[10] Bulteau AL, Szweda LI, Friguet B. Age-dependent declines in proteasome activity in the heart[J]. Arch Biochem Biophys, 2002, 397(2): 298-304.

[11] Colotti C, Cavallini G, Vitale RL, *et al*. Effects of aging and anti-aging caloric restrictions on carbonyl and heat shock protein levels and expression[J]. Biogerontology, 2005, 6(6): 397-406.

[12] Madrigal-Matute J, de Bruijn J, van Kuijk K, *et al*. Protective role of chaperone-mediated autophagy against atherosclerosis[J]. Proc Natl Acad Sci USA, 2022, 119(14): e2121133119.

[13] Jones RC, Karkanias J, Krasnow MA, *et al*. The Tabula Sapiens: a multiple-organ, single-cell transcriptomic atlas of humans[J]. Science, 2022, 376(6594): eabl4896.

[14] Marfella R, Di Filippo C, Laieta MR, *et al*. Effects of ubiquitin-proteasome system deregulation on the vascular senescence and atherosclerosis process in elderly patients[J]. J Gerontol A Biol Sci Med Sci, 2008, 63(2): 200-203.

[15] Degenhardt K, Wagner J, Skodras A, *et al*. Medin aggregation causes cerebrovascular dysfunction in aging wild-type mice[J]. Proc Natl Acad Sci USA, 2020, 117(38): 23925-23931.

[16] Mucchiano G, Cornwell GG, Westermark P. Senile aortic amyloid. Evidence for two distinct forms of localized deposits[J]. Am J Pathol, 1992, 140(4): 871-877.

[17] Rajasekaran NS, Connell P, Christians ES, *et al*. Human αB-crystallin mutation causes oxido-reductive stress and protein aggregation cardiomyopathy in mice[J]. Cell, 2007, 130(3): 427-439.

[18] Tannous P, Zhu HX, Johnstone JL, *et al*. Autophagy is an adaptive response in desmin-related cardiomyopathy[J]. Proc Natl Acad Sci USA, 2008, 105(28): 9745-9750.

[19] Ma XC, Mani K, Liu HY, *et al*. Transcription factor EB activation rescues advanced αB-crystallin mutation induced cardiomyopathy by normalizing desmin localization[J]. J Am Heart Assoc, 2019, 8(4): e010866.

[20] Galata Z, Kloukina I, Kostavasili I, *et al*. Amelioration of desmin network defects by αB-crystallin overexpression confers cardioprotection in a mouse model of dilated cardiomyopathy caused by *LMNA* gene mutation[J]. J Mol Cell Cardiol, 2018, 125: 73-86.

[21] Gupta MK, Gulick J, Liu RJ, *et al*. Sumo E2 enzyme UBC9 is required for eficient protein quality control in cardiomyocytes[J]. Circ Res, 2014, 115(8): 721-729.

[22] Sanbe A, Daicho T, Mizutani R, *et al*. Protective effect of geranylgeranylacetone via enhancement of HSPB8 induction in desmin-related cardiomyopathy[J]. PLoS One, 2009, 4(4): e5351.

[23] Ooie T, Takahashi N, Saikawa T, *et al*. Single oral dose of geranylgeranylacetone induces heat-shock protein 72 and renders protection against ischemia/reperfusion injury in rat heart[J]. Circulation, 2001, 104(15): 1837-1843.

[24] Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing[J]. Nat Rev Cardiol, 2018,

15(9): 566-577.

[25] Yang L, Licastro D, Cava E, *et al*. Long-term calorie restriction enhances cellular quality-control processes in human skeletal muscle[J]. Cell Rep, 2016, 14(3): 422-428.

[26] De Majo F, Martens L, Hegenbarth JC, *et al*. Genomic instability in the naturally and prematurely aged myocardium[J]. Proc Natl Acad Sci USA, 2021, 118(36): e2022974118.

[27] Dollé ME, Snyder WK, Gossen JA, *et al*. Distinct spectra of somatic mutations accumulated with age in mouse heart and small intestine[J]. Proc Natl Acad Sci USA, 2000, 97(15): 8403-8408.

[28] Ji HW, Kwan AC, Chen MT, *et al*. Sex diferences in myocardial and vascular aging[J]. Circ Res, 2022, 130(4): 566-577.

[29] Busuttil RA, Dollé M, Campisi J, *et al*. Genomic instability, aging, and cellular senescence[J]. Ann NY Acad Sci, 2004, 1019: 245-255.

[30] Munoz-Lorente MA, Cano-Martin AC, Blasco MA. Mice with hyper-long telomeres show less metabolic aging and longer lifespans[J]. Nat Commun, 2019, 10(1): 4723.

[31] Sharifi-Sanjani M, Oyster NM, Tichy ED, *et al*. Cardiomyocyte-specific telomere shortening is a distinct signature of heart failure in humans[J]. J Am Heart Assoc, 2017, 6(9): e005086.

[32] Chang ACY, Chang ACH, Kirillova A, *et al*. Telomere shortening is a hallmark of genetic cardiomyopathies[J]. Proc Natl Acad Sci USA, 2018, 115(37): 9276-9281.

[33] Bloom SI, Tucker JR, Lim J, *et al*. Aging results in DNA damage and telomere dysfunction that is greater in endothelial versus vascular smooth muscle cells and is exacerbated in atheroprone regions[J]. Geroscience, 2022, 44(6): 2741-2755.

[34] Martinet W, Knaapen MWM, de Meyer GRY, *et al*. Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques[J]. Circulation, 2002, 106(8): 927-932.

[35] Gray K, Kumar S, Figg N, *et al*. Effects of DNA damage in smooth muscle cells in atherosclerosis[J]. Circ Res, 2015, 116(5): 816-826.

[36] Durik M, Kavousi M, van der Pluijm I, *et al*. Nucleotide excision DNA repair is associated with age-related vascular dysfunction[J]. Circulation, 2012, 126(4): 468-478.

[37] Ataei Ataabadi E, Golshiri K, van der Linden J, *et al*. Vascular ageing features caused by selective DNA damage in smooth muscle cell[J]. Oxid Med Cell Longev, 2021, 2021: 2308317.

[38] Bautista-Nino PK, Portilla-Fernandez E, Rubio-Beltran E, *et al*. Local endothelial DNA repair deficiency causes aging-resembling endothelial-specific dysfunction[J]. Clin Sci (Lond), 2020, 134(7): 727-746.

[39] Matsumoto T, Baker DJ, d'Uscio LV, *et al*. Aging-associated vascular phenotype in mutant mice with low levels of BubR1[J]. Stroke, 2007, 38(3): 1050-1056.

[40] Jaiswal S, Natarajan P, Silver AJ, *et al*. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease[J]. N Engl J Med, 2017, 377(2): 111-121.

[41] Dorsheimer L, Assmus B, Rasper T, *et al*. Association of mutations contributing to clonal hematopoiesis with prognosis in chronic ischemic heart failure[J]. J Am Med Assoc Cardiol, 2019, 4(1): 25-33.

[42] Shi CX, Aboumsallem JP, Suthahar N, *et al*. Clonal haematopoiesis of indeterminate potential: associations with heart failure incidence, clinical parameters and biomarkers[J]. Eur J Heart Fail, 2023, 25(1): 4-13.

[43] Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease[J]. Nat Rev Cardiol, 2020, 17(3): 137-144.

[44] Devesa A, Lobo-Gonzalez M, Martinez-Milla J, *et al*. Bone marrow activation in response to metabolic syndrome and early atherosclerosis[J]. Eur Heart J, 2022, 43(19): 1809-1828.

[45] Schloss MJ, Swirski FK, Nahrendorf M. Modifiable cardiovascular risk, hematopoiesis, and innate immunity[J]. Circ Res, 2020, 126(9): 1242-1259.

[46] Fuster JJ, MacLauchlan S, Zuriaga MA, *et al*. Clonal hematopoiesis associated with *TET2* deficiency accelerates atherosclerosis development in mice[J]. Science, 2017, 355(6327): 842-847.

[47] Sano S, Oshima K, Wang Y, *et al*. TET2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome[J]. J Am Coll Cardiol, 2018, 71(8): 875-886.

[48] Sano S, Oshima K, Wang Y, *et al*. CRISPR-mediated gene editing to assess the roles of TET2 and Dnmt3a in clonal

hematopoiesis and cardiovascular disease[J]. Circ Res, 2018, 123(3): 335-341.

[49] Zekavat SM, Viana-Huete V, Matesanz N, *et al*. TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease[J]. Nat Cardiovasc Res, 2023, 2: 144-158.

[50] Abplanalp WT, Cremer S, John D, *et al*. Clonal hematopoiesis-driver DNMT3A mutations alter immune cells in heart failure[J]. Circ Res, 2021, 128(2): 216-228.

[51] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty[J]. Nat Rev Cardiol, 2018, 15(9): 505-522.

[52] Conti S, Cassis P, Benigni A. Aging and the renin-angiotensin system[J]. Hypertension, 2012, 60(9): 878-883.

[53] Engelen SE, Robinson AJB, Zurke YX, *et al*. Therapeutic strategies targeting inflammation and immunity in atherosclerosis: how to proceed?[J]. Nat Rev Cardiol, 2022, 19(8): 522-542.

[54] Esfahani NS, Wu Q, Kumar N, *et al*. Aging influences the cardiac macrophage phenotype and function during steady state and during inflammation[J]. Aging Cell, 2021, 20(8): e13438.

[55] Koenig AL, Shchukina I, Amrute J, *et al*. Single-cell transcriptomics reveals cell-type-specific diversification in human heart failure[J]. Nat Cardiovasc Res, 2022, 1(3): 263-280.

[56] De Arellano MLB, Pozdniakova S, Kühl AA, *et al*. Sex diferences in the aging human heart: decreased sirtuins, pro-inflammatory shift and reduced anti-oxidative defense[J]. Aging(Albany NY), 2019, 11(7): 1918-1933.

[57] Ramos GC, van den Berg A, Nunes-Silva V, *et al*. Myocardial aging as a T-cell-mediated phenomenon[J]. Proc Natl Acad Sci U S A, 2017, 114(12): E2420-E2429.

[58] Delgobo M, Heinrichs M, Hapke N, *et al*. Terminally diferentiated $CD4^{+}$T cells promote myocardial inflammaging[J]. Front Immunol, 2021, 12: 584538.

[59] Dolejsi T, Delgobo M, Schuetz T, *et al*. Adult T-cells impair neonatal cardiac regeneration[J]. Eur Heart J, 2022, 43(28): 2698-2709.

[60] Desdin-Mico G, Soto-Heredero G, Aranda JF, *et al*. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence[J]. Science, 2020, 368(6497): 1371-1376.

[61] Maier HJ, Schips TG, Wietelmann A, *et al*. Cardiomyocyte-specific IκB kinase (IKK)/NF-κB activation induces reversible inflammatory cardiomyopathy and heart failure[J]. Proc Natl Acad Sci U S A, 2012, 109(29): 11794-11799.

[62] Hasegawa Y, Saito T, Ogihara T, *et al*. Blockade of the nuclear factor-κB pathway in the endothelium prevents insulin resistance and prolongs life spans[J]. Circulation, 2012, 125(9): 1122-1133.

[63] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction[J]. Nat Rev Cardiol, 2017, 14(10): 591-602.

[64] Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation[J]. J Am Coll Cardiol, 2013, 62(4): 263-271.

[65] Withaar C, Li SH, Meems LMG, *et al*. Aging and HFpEF: are we running out of time?[J]. J Mol Cell Cardiol, 2022, 168: 33-34.

[66] Solomon SD, McMurray JJV, Claggett B, *et al*. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction[J]. N Engl J Med, 2022, 387(12): 1089-1098.

[67] Anker SD, Butler J, Filippatos G, *et al*. Empagliflozin in heart failure with a preserved ejection fraction[J]. N Engl J Med, 2021, 385(16): 1451-1461.

[68] Elrakaybi A, Laubner K, Zhou Q, *et al*. Cardiovascular protection by SGLT2 inhibitors – Do anti-inflammatory mechanisms play a role?[J]. Mol Metab, 2022, 64: 101549.

[69] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control[J]. Nat Rev Cardiol, 2020, 17(12): 761-772.

[70] Zannad F, Ferreira JP, Butler J, *et al*. Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme[J]. Eur Heart J, 2022, 43(48): 4991-5002.

[71] Hoong CWS, Chua MWJ. SGLT2 inhibitors as calorie restriction mimetics: insights on longevity pathways and age-related diseases[J]. Endocrinology, 2021, 162(8): bqab079.

[72] Packer M. SGLT2 inhibitors: role in protective reprogramming of cardiac nutrient transport and metabolism[J]. Nat Rev Cardiol, 2023, 20(7): 443-462.

[73] Deng Y, Xie MD, Li Q, *et al*. Targeting mitochondria-inflammation circuit by β-hydroxybutyrate mitigates HFpEF[J]. Circ Res, 2021, 128(2): 232-245.

[74] Marín-Aguilar F, Lechuga-Vieco AV, Alcocer-Gomez E, *et al*. NLRP3 inflammasome suppression improves longevity and prevents cardiac aging in male mice[J]. Aging Cell, 2020, 19(1): e13050.

[75] Tardif JC, Kouz S, Waters DD, *et al*. Efficacy and safety of low-dose colchicine after myocardial infarction[J]. N Engl J Med, 2019, 381(26): 2497-2505.

[76] Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease[J]. N Engl J Med, 2017, 377(12): 1119-1131.

[77] Everett BM, Cornel JH, Lainscak M, *et al*. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure[J]. Circulation, 2019, 139(10): 1289-1299.

[78] Yu HL, Liao K, Hu Y, *et al*. Role of the cGAS-STING pathway in aging-related endothelial dysfunction[J]. Aging Dis, 2022, 13(6): 1901-1918.

[79] Sladitschek-Martens HL, Guarnieri A, Brumana G, *et al*. YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS-STING[J]. Nature, 2022, 607(7920): 790-798.

[80] Kreienkamp R, Graziano S, Coll-Bonfill N, *et al*. A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin[J]. Cell Rep, 2018, 22(8): 2006-2015.

[81] Olive M, Harten I, Mitchell R, *et al*. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging[J]. Arterioscler Thromb Vasc Biol, 2010, 30(11): 2301-2309.

[82] Pham PT, Fukuda D, Nishimoto S, *et al*. STING, a cytosolic DNA sensor, plays a critical role in atherogenesis: a link between innate immunity and chronic inflammation caused by lifestyle-related diseases[J]. Eur Heart J, 2021, 42(42): 4336-4348.

[83] Rech L, Abdellatif M, Pöttler M, *et al*. Small molecule STING inhibition improves myocardial infarction remodeling[J]. Life Sci, 2022, 291: 120263.

[84] Lopez-Otin C, Blasco MA, Partridge L, *et al*. Hallmarks of aging: an expanding universe[J]. Cell, 2023, 186(2): 243-278.

[85] Castoldi F, Humeau J, Martins I, *et al*. Autophagy-mediated metabolic effects of aspirin[J]. Cell Death Discov, 2020, 6(1): 129.

[86] McNeil JJ, Wolfe R, Woods RL, *et al*. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly[J]. N Engl J Med, 2018, 379(16): 1509-1518.

[87] Gaziano JM, Brotons C, Coppolecchia R, *et al*. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease(ARRIVE): a randomised, double-blind, placebo-controlled trial[J]. Lancet, 2018, 392(10152): 1036-1046.

[88] Bowman L, Mafham M, Wallendszus K, *et al*. Effects of aspirin for primary prevention in persons with diabetes mellitus[J]. N Engl J Med, 2018, 379(16): 1529-1539.

[89] Castellano JM, Pocock SJ, Bhatt DL, *et al*. Polypill strategy in secondary cardiovascular prevention[J]. N Engl J Med, 2022, 387(11): 967-977.

[90] Svensson EC, Madar A, Campbell CD, *et al*. TET2-Driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial[J]. J Am Med Assoc Cardiol, 2022, 7(5): 521-528.

[91] Ridker PM, MacFadyen JG, Everett BM, *et al*. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial[J]. Lancet, 2018, 391(10118): 319-328.

（编辑：王 佳）