

血管紧张素转换酶 2 与心血管疾病研究进展

焦晓璐, 秦彦文*

(首都医科大学附属北京安贞医院 北京市心肺血管疾病研究所 上气道功能障碍相关心血管疾病
北京市重点实验室, 北京 100029)

摘要: 血管紧张素转换酶 2(ACE2)是 SARS 病毒(SARS-CoV)、新型冠状病毒(SARS-CoV-2)感染机体的主要受体,也是肾素-血管紧张素-醛固酮系统的主要成员之一。ACE2 对多种心血管疾病具有保护作用,SARS-CoV-2 可以降低机体 ACE2 的表达,这可能是新型冠状病毒肺炎(COVID-19)后期产生心血管并发症的原因之一。本文总结了 ACE2 在多种心血管疾病发病过程中的作用及其机制,希望为新型冠状病毒肺炎(COVID-19)的治疗提供新的思路。

关键词: 血管紧张素转换酶 2;心血管疾病;肾素-血管紧张素-醛固酮系统

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Progress of angiotensin converting enzyme 2 in cardiovascular diseases

JIAO Xiao-lu, QIN Yan-wen*

(the Key Laboratory of Upper Airway Dysfunction-related Cardiovascular Diseases, Beijing Anzhen Hospital, Capital Medical University,
Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing 100029, China)

Abstract: Angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV and SARS-CoV-2(severe acute respiratory syndrome coronavirus 2) viruses, and it is also one of the main family members of renin-angiotensin-aldosterone system. ACE2 has a protective effect on cardiovascular diseases and inhibits the development of cardiovascular diseases. SARS-CoV-2 reduces the expression of ACE2 of host, which may be one of the reasons for cardiovascular complications in the later stage of coronavirus disease 2019(COVID-19). Thus, the role and mechanism of ACE2 in the development of cardiovascular diseases were summarized in this article in order to provide potential strategy development for the treatment of COVID-19.

Key words: angiotensin-converting enzyme 2; cardiovascular diseases; renin-angiotensin-aldosterone system

血管紧张素转换酶 2(angiotensin-converting enzyme 2, ACE2)是一种 805 个氨基酸的 1 型跨膜蛋白,分子量约为 120 ku,其基因由 18 个外显子组成,并定位到 X 染色体(Xp22)^[1]。ACE2 几乎存在于所有器官中,在气道、肺、心、肾、肠、膀胱和睾丸中高表达,同时其存在于几乎所有器官的动静脉内皮细胞和动脉平滑肌细胞中。研究表明,ACE2 是 SARS 病毒(severe acute respiratory syndrome coronavirus,

SARS-CoV)、新型冠状病毒(SARS-CoV-2)感染机体的主要受体^[2],也是肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)的主要成员之一。在 RAAS 激活后,ACE 可切割血管紧张素 I(Ang I)的 C 端,产生血管紧张素 II(Ang II)。ACE2 是 ACE 的同源物,其氨基末端结构与 ACE 具有大约 42%的序列同一性^[1]。ACE2 是 RAAS 的负性调节剂,在 RAAS 中,ACE2 将 Ang I 转换为功能

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* 通信作者(corresponding author):qinyanwen@126.com

未知的 Ang-(1-9), 将 Ang II 转换为 Ang-(1-7)^[3]。但是, 与 ACE 相比, ACE2 对 Ang I 的亲合力相对较弱, ACE2 对 Ang II 的催化效率是对 Ang I 的 400 倍^[4]。这表明 ACE2 主要是抑制 AngII 的作用。ACE2 对多种心血管疾病具有保护作用, SARS-CoV-2 可以降低机体 ACE2 的表达, 这可能是新型冠状病毒肺炎 (coronavirus disease 2019, 简称“新冠肺炎”, COVID-19) 后期产生心血管并发症的原因之一。本文总结了 ACE2 在多种心血管疾病发病过程中的作用及其机制, 希望为新型冠状病毒肺炎的治疗提供新的思路。

1 ACE2 与高血压

高血压是我国最常见的慢性病之一, ACE2 在高血压发生发展过程中扮演重要角色。有研究表明, ACE2 启动子的高甲基化与原发性高血压的发病相关^[5]。在中国新疆人群中, ACE2 (rs4646188) 基因多态性与原发性高血压有关^[6]。ACE2 (rs2074192) 和 (rs2106809) 基因多态性与血压相关, 在女性中, CCGC 单倍型携带者的平均收缩压比非携带者低 3.4 mmHg (1 mmHg = 0.133 kPa); 在男性中, CCGC 单倍型携带者的平均收缩压比非携带者低 2.4 mmHg^[7]。高血压患者脑脊液中 ACE2 活性增加, 且与收缩压相关^[8]。

ACE2 是 RAAS 系统的关键成员之一, RAAS 系统在调节血压和体液平衡中发挥重要作用。RAAS 系统存在两个主轴, 血管收缩轴 [肾素/ACE/AngII/血管紧张素 II 受体 1 型 (AT1R)] 以及血管舒张轴 [ACE2/Ang(1-7)/Mas 受体 (MasR)]。正常生理情况下, 这两个主轴相互作用, 相互抵消, 共同控制血压的稳定^[9]。ACE2 可将 Ang II 转换为 Ang-(1-7), 发挥心血管保护作用, Ang II-Ang(1-7) 之间的失衡与糖尿病患者的炎症反应增加和血管功能障碍有关, 并可能导致这些患者发生高血压^[10]。蛋清衍生物 IRW 可通过 ACE2/Ang-(1-7)/MasR 轴, 降低高血压大鼠的血压^[11]。异丙酚可以通过上调 ACE2-Ang-(1-7)-MasR 轴, 增加磷酸化内皮型一氧化氮合酶表达, 减弱 Ang II 诱导的血管内皮细胞凋亡, 改善内皮功能, 降低血压^[12]。FGF21 可以通过激活 ACE2-Ang-(1-7)-MasR 轴, 降低 Ang II 诱导的高血压及血管重塑^[13]。新型降压药物 LCZ696 可以抑制

高血压大鼠心脏中的 ACE 和 AT1 R 蛋白表达, 上调 ACE2, MasR 和 AT2 R 的表达, 发挥降低血压, 减缓心肌重塑的作用^[14]。Nrf2 缺乏可以上调肾内 ACE2 和 Ang(1-7) 受体的表达, 减轻糖尿病小鼠的高血压和肾病^[15]。

除在 RAAS 系统中发挥作用外, ACE2 还可以直接参与高血压的发病过程。与野生型大鼠相比, 高血压大鼠下丘脑 ACE2 水平明显降低, 这表明 ACE2 缺乏与大鼠高血压有关^[16]。脑 ACE2 过表达可以通过抑制环氧合酶介导的炎症反应而抑制神经源性高血压的发生^[17]。神经元 ACE2 缺失可减少与血压调节有关的 AC-N 交感神经元的抑制性输入, 从而导致血压的升高^[18]。脂肪细胞 ACE2 缺乏促进了雌性小鼠肥胖症高血压的形成, 使其收缩压增加^[19]。B38-CAP (一种 ACE2 样酶) 处理可抑制 AngII 诱导的小鼠高血压^[20]。ACE2 在高血压与高血压血管重塑中发挥重要作用, 有望成为改善高血压血管重塑, 减轻高血压靶器官损害的关键治疗靶点。

2 ACE2 与主动脉瘤

主动脉瘤是一种风险极高的心脏大血管疾病。在血流剪切力的作用下, 受损的升主动脉管壁呈现扩张或隆起, 最终薄弱的主动脉管壁会因无法承受持续的血流冲击而破裂, 造成患者大出血而猝死。高血压是主动脉瘤形成、破裂的关键危险因素, 而 ACE2 在高血压发生发展过程中发挥着重要作用, 因此, ACE2 在主动瘤中的作用也值得关注。据了解, 血浆与主动脉组织 ACE2 水平的降低, 可能在胸主动脉瘤扩张和随后夹层的发展中起重要作用^[21]。开放式手术修复破裂腹主动脉瘤 (abdominal aortic aneurysm, AAA) 术前第 1 天的血清 ACE2 水平与术后院内死亡率呈显著负相关, 血清 ACE2 水平降低是开放手术修复破裂 AAA 患者住院死亡的独立危险因素^[22]。在小鼠模型中, 白藜芦醇可以通过上调 ACE2 抑制 AAA 生长^[23]。ACE2 缺乏会促进 Ang II 诱导的 AAA 的发生, 而 ACE2 激活会抑制 AAA 的形成^[24]。ACE2 基因过表达通过抑制炎症反应和金属蛋白酶的激活而显著减少 *ApoE*^{-/-} 小鼠中 AAA 的发生并抑制 AAA 的形成^[25]。这些研究结果可以进一步证明, ACE2 在腹主动脉瘤的发生发展过程中发挥重要作用。

3 ACE2与动脉粥样硬化性心血管疾病

动脉粥样硬化性心血管疾病是威胁人类健康、造成人类死亡最主要的原因之一,其全球罹患率与致死率均名列前茅。越来越多的证据表明,ACE2在动脉粥样硬化性心血管疾病发生发展过程中扮演重要角色。ACE2(rs4646188)基因多态性与血脂紊乱及其发生的缺血性卒中有关^[6]。在女性中,冠心病患者的循环ACE2水平显著升高;循环ACE2水平与冠心病发病独立相关,ACE2可能作为一种代偿机制参与冠心病的发生发展^[26]。慢性肾衰竭患者中,循环ACE2活性与动脉粥样硬化风险有关,ACE2可作为预测动脉粥样硬化风险的生物标志物^[27]。

ACE2可以将Ang II转化为Ang(1-7)从而对抗ACE与Ang II的作用。ACE2与Ang(1-7)可以通过保护内皮功能、抑制炎症反应,从而显著抑制早期动脉粥样硬化病变的形成^[28]。ACE2缺乏可增强高胆固醇血症小鼠Ang II诱导动脉粥样硬化和AAA的形成,这种影响可能是由于Ang II浓度增加而Ang(1-7)浓度降低所引起的^[29]。NaHS(HS供体)通过上调颈动脉ACE2的表达,促进Ang II转化为抗动脉粥样硬化的Ang-(1-7),大大减轻了动脉粥样硬化的严重程度^[30]。坎地沙坦通过抑制促炎性氧化还原AT1,恢复ACE2-Ang-(1-7)-MasR轴的功能,发挥保护血管和抑制动脉粥样硬化发生的作用^[31]。

除在RAAS系统中的作用以外,ACE2还可以直接调控动脉粥样硬化的形成。ACE2缺乏可以促进巨噬细胞聚集、血管平滑肌细胞增殖、血管炎性反应相关基因表达增强,从而促进动脉粥样硬化斑块和动脉新生内膜的形成^[32]。神经肽类通过ACE2依赖机制抑制炎症反应和EC-白细胞的相互作用,抑制动脉粥样硬化的形成^[33]。氯沙坦可以调节动脉粥样硬化斑块中的ACE2活性,在动脉粥样硬化的治疗中发挥重要作用^[34]。ACE2活化剂diminazene处理ApoE^{-/-}小鼠,虽然并未改变动脉粥样硬化病变的大小,但可以通过增加胶原蛋白含量、减少金属蛋白酶-9的表达和巨噬细胞浸润,改善斑块的稳定性。

4 ACE2与心肌重塑

心肌重塑是多种心血管疾病发生发展的病理生理基础,主要包括心肌肥大、心肌纤维化等关键环

节。研究表明,高血压患者循环ACE2水平与心脏重塑有关^[35]。血浆ACE2活性与严重的心肌纤维化有关^[36]。在射血分数降低的心衰患者中,血清ACE2活性与左心室收缩功能呈负相关,而在射血分数正常的心衰患者中,血清ACE2活性与左心室收缩功能无相关性,血清ACE2活性具有区分心衰患者射血分数是否正常的诊断价值^[37]。

有证据表明RAAS系统中的ACE2/Ang-(1-7)/MasR轴,除了降血压的作用,还有利于改变压力反射敏感性和去甲肾上腺素能神经传递,因此,该途径在心血管疾病中可以产生心脏保护作用^[38]。ACE2过表达可激活ACE2/Ang-(1-7)/MasR轴,减弱MKP-1上调和MAPKs活性降低,抑制心脏纤维化重塑^[39]。Apelin可拮抗心脏中肾素-血管紧张素系统的过度活化,诱导衰竭心脏中ACE2的表达,以Ang-(1-7)依赖性方式改善心脏功能和病理性重塑^[40]。高强度间歇训练可以调节ACE2/Ang-(1-7)/MasR轴,提高胰岛素敏感性,减轻左心室肥大^[41]。Azilsartan通过调节ACE2/Ang-(1-7)/MasR通路可显著减少心脏纤维化与肥大,逆转异常的心脏结构重塑,并部分改善db/db小鼠的葡萄糖代谢^[42]。醋酸地米那嗪(diminazene aceturate, DIZE)可增ACE2的活性,从而增加Ang-(1-7)的产生,保护心肌梗后心脏功能,抑制心脏结构重塑,改善心肌功能,减少心肌梗后心脏后间质纤维化和舒张功能障碍^[43-45]。在小鼠体内增加ACE2的水平可以防止并逆转心衰,ACE2和Ang-(1-7)已成为针对心衰治疗的关键保护途径,重组人ACE2已通过I和II期临床试验,证明了其没有不良反应^[46]。

ACE2还可以直接在心肌重塑中发挥作用。ACE2样酶B38-CAP可抑制AngII诱发的小鼠心脏肥大和纤维化;还可抑制小鼠压力超负荷引起的病理性肥大,心肌纤维化和心脏功能障碍^[20]。DKK3可以通过调节ADAM17/ACE2途径的活性,同时抑制GSK-3 β / β -catenin途径,减轻AngII引起的心肌肥大和纤维化^[47]。SIRT6通过激活AMPK-ACE2信号传导,抑制心脏病理性重塑、纤维化和心肌损伤,发挥心脏保护作用^[48]。miR-30e介导的ACE2通路,通过抑制心肌细胞自噬,在阿霉素诱导的心力衰竭大鼠中发挥心脏保护作用^[49]。ACE2的激活可以阻止缺氧诱导的细胞凋亡,促进成年心肌细胞中HMGB1的表达,从而

减轻心肌缺血后的心脏功能障碍^[50]。ACE2 可以负性调节肥胖引起的心外膜炎性反应和心脏的胰岛素抵抗,从而抑制心功能障碍的发生^[51]。

5 ACE2 与其他心血管疾病

ACE2 除了在高血压、动脉粥样硬化、动脉瘤、心肌重塑等心血管疾病中发挥保护作用以外,还在多种其他心血管疾病中发挥重要的保护作用。有证据表明,血浆 ACE2 活性可以预测主动脉狭窄的死亡率^[36]。房颤患者血清 ACE2 活性显著升高,且血浆 ACE2 升高与晚期的左心房结构重塑显著相关^[52];ACE2 过表达可激活 ACE2/Ang-(1-7)/MasR 轴,调节速激肽诱导的离子通道和连接蛋白重塑,降低房颤的持续时间^[39]。ACE2 的激活可改善高血糖大鼠心脏电功能,引起心室复极的心脏电变化,表现出较短的 QT 和 QTc 间隔,ACE2 有望成为治疗高血

糖引起的室性心律失常的新治疗剂^[53]。ACE2 可将 Ang II 转化为 Ang-(1-7),导致 Mas1 活化,改善肺血流动力学以及减少氧化剂和炎症介质标志物,从而改善肺动脉高压^[54]。

由上可知,ACE2 在心血管系统中发挥重要的保护作用,主要是在 RAAS 系统中,通过 ACE2/Ang-(1-7)/MasR 轴,平衡 ACE/Ang II/ATR1 轴的作用,发挥心血管保护作用;其次,ACE2 本身可以通过抑制炎症反应、调控内皮细胞功能、抑制平滑肌细胞增殖等作用,发挥其对心血管系统的保护作用,ACE2 有望成为心血管疾病一个新的治疗靶点。同时,ACE2 对与多种心血管疾病也具有一定诊断与预测价值,有望开发新的诊断、预测试剂盒,简化心血管疾病的诊断。SARS-CoV-2 可使机体 ACE2 水平降低,这可能是新型冠状病毒肺炎(COVID-19)后期极易产生心血管并发症的原因之一。

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