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评 述 血管稳态与重构的调控机制专辑

补体介导的炎症免疫功能紊乱在高血压及其靶器官损伤中的作用

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摘要 高血压是导致心脑血管疾病的首要危险因素, 但其发病机制尚不清楚. 近年来研究表明, 大量的炎症免疫细胞激活参与高血压发生发展的全过程, 提示慢性低度的炎症免疫诱导了血管损伤及其并发症的发生. 补体途径作为免疫系统的重要调节因子, 其在调节炎症反应, 招募免疫细胞, 分泌调节因子等过程中都起着重要的调控作用. 补体途径的异常激活和补体分子的过量表达参与高血压相关心血管疾病的调控过程. 本文综述了补体途径激活参与高血压靶器官损伤调节的研究进展, 以期为心血管免疫学研究走向临床拓展思路.

关键词 高血压, 补体途径, 炎症免疫

补体是存在于人和动物血清及组织液中的一类蛋白质, 其发现至今已有一百多年的历史. 19世纪比利时细菌学家Bordet发现血清被加热到一定程度, 虽然抗体并未失活(仍保持与抗原相互作用的效应), 但却失去摧毁细菌的能力, 由此推测血清中存在一种辅助抗体发挥作用的物质, 之后该物质被命名为补体. 补体介导的免疫应答及炎症反应是体内重要的效应放大系统, 在非特异及特异性免疫中都起了重要的生物学作用. 近年来大量的研究证实, 高血压的本质是一种慢性低度的炎症免疫反应过程, 而补体作为一重要介质在血管损伤中起到至关重要的作用. 本文简述补体介导的炎症免疫功能紊乱在血压调节及靶器官损伤中的作用.

1 补体系统及其生物学作用

补体系统由体液补体成分、可溶性和膜型补体调节蛋白、补体受体等30余种糖蛋白组成. 补体系统的基本组成包括9种血清蛋白成分, 按发现的先后顺序分别命名为C1~C9, 是补体活化的经典途径(classical pathway), 即抗原抗体复合物刺激上述补体固有成分, 产生一系列生物学效应的过程. 补体还可通过旁路途径(alternative pathway)活化, 即不经过C1, C4, C2, C3b与Cfb形成C3bBb这一C3转化酶, 在D因子和P因子的辅助下启动后续的酶促级联反应. 补体激活的第三条途径是凝集素途径(MBL pathway), 即MBL与细菌表面的还甘露醇残基结合后水解C4和C2, 从而启动后序的酶促级联反应. 补体经过这三条既独立又交叉的

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途径被激活, 不同补体途径激活后, 形成C3转换酶, 导致主要补体成分C3分解为补体3a(C3a)和补体3b(C3b), C3b和C3转化酶进一步结合形成C5转化酶, 导致补体成分C5分解为补体C5a和补体C5b, 最终经过级联反应形成膜攻击复合物(membrane attack complex, MAC). 补体激活后产生的C3a和C5a会分别与细胞表面的C3aR和C5aR结合进一步引发免疫反应[1,2].

补体系统的主要生物学作用是识别和破坏侵入机体的病原体, 肝脏来源的血浆补体是病原体的首要防线, 免疫细胞包括T细胞和抗原递呈细胞也产生补体成分, 是连接先天免疫和适应性免疫的桥梁. 补体激活过程中产生一系列炎症介质, 如C3a, C4a, C5a, 与细胞表面的相应受体结合, 释放组胺等血管活性物质, 增加组织通透性促进炎症反应. 此外, 补体激活还可以产生一些调理素(如C3b, C4b等), 结合免疫细胞(中性粒细胞及巨噬细胞)表面相应抗体, 促进病原体被吞噬及杀伤, 也称补体的调理作用. 补体在清除免疫复合物方面也有其特殊作用[3,4].

2　补体诱导的免疫细胞激活

近年来随着高血压机制研究的深入, 人们逐渐认识到高血压的发生发展是一慢性的低度免疫炎症反应过程. 传统意义上的免疫包括固有免疫(innate immunity)和适应性免疫(adaptive immunity), 前者又称天然免疫, 由单核/巨噬细胞、中性粒细胞及NK细胞介导; 适应性免疫又称获得性免疫, 主要由淋巴细胞包括T细胞和B细胞介导[5]. 各种遗传或环境因素导致的血压上升会激活多种心血管活性物质, 如血管紧张素Ⅱ(angiotensin Ⅱ, AngⅡ)、内皮素(endothelin, ET)、活性氧(reactive oxygen species, ROS)等首先激活炎症反应, 诱导炎症因子如单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)、白介素6(interleukin 6, IL-6)和肿瘤细胞坏死因子α(tumor necrosis factorα,TNFα)的表达, 从而促进大量的免疫细胞, 如单核/巨噬细胞、树突状细胞和淋巴细胞的募集与激活, 参与血压调节和靶器官损伤过程的调控[6,7].

巨噬细胞是人体免疫系统吞噬作用最强的免疫细胞. 多种高血压动物模型包括AngⅡ灌注、DOCA(desoxycorticosterone acetate)-盐敏感性高血压小鼠均证实, 补体分子C3和C5在巨噬细胞中大量表达, 并通过C3a和C5a受体(C3aR和C5aR)参与巨噬细胞极化调控[8~10]. 巨噬细胞依据其功能可以分为M1促炎性巨噬细胞和M2抗炎性巨噬细胞, 补体通路的激活导致C3a和C5a大量产生, 诱导M1性巨噬细胞极化, 促进炎症因子的表达与释放[11,12]. 血压的上升促进巨噬细胞表达补体分子C1q, 后者进一步参与血管平滑肌细胞生物学功能的调控[13]. 临床数据证实, 高血压肾病患者肾脏组织补体C3表达增加伴随有肾组织内大量巨噬细胞的浸润[14]. 这些结果都表明, 巨噬细胞是介导补体与血压调节和高血压靶器官损伤的关键效应细胞. 天然免疫系统的另一主要成员树突状细胞近年来已经被证实广泛参与血压调节及高血压靶器官损伤的调控. 树突状细胞主要标志分子CD11b和CD11c分别是补体受体3(CR3)和补体受体4(CR4)的主要组成部分, 补体分子C1q促进树突状细胞的成熟与活化, 介导其抗原递呈作用, 并参与炎症因子的表达调控[15]. 补体受体C5aR表达于肾脏树突状细胞, 促进AngⅡ诱导的高血压肾损伤[16]. 中性粒细胞是另一诱导补体活化的主要天然免疫细胞, 已有研究报道多种高血压动物模型中均检测到嗜中性粒细胞的过度激活[17]. 补体C5a能促进嗜中性粒细胞外杀菌网络(neutrophil extracellular traps)的形成, 进而促进炎症小体的活化, 加剧动脉瘤的进程[18].

适应性免疫系统包括T淋巴细胞和B淋巴细胞同样参与血压调节. T细胞在高血压中的作用已经受到国内外学者的广泛关注. 利用免疫缺陷小鼠, 证实T/B细胞缺陷小鼠($Rag1^{-/-}$)抑制AngⅡ或DOCA-盐诱导的高血压, 而过继转移T细胞用以回复高血压表型, 进一步研究发现与正常对照T细胞相比, 过继转移高血压患者T细胞显著促进AngⅡ诱导的$Rag1^{-/-}$小鼠的血压增加[19]. T细胞依据其功能可以分为促进免疫炎症反应的Th1、Th17细胞和发挥抗炎效应的Th2、调节性T细胞(regulatory T cell, Treg)细胞等. 补体对T细胞的调控可以分为直接和间接两种形式. 间接形式主要是指补体分子通过激活前述天然免疫细胞包括巨噬细胞、树突状细胞等释放炎症因子, 进而参与T细胞生物学活性的调控. C3a/C5a通过促进树突状细胞释放IL-23, 进而参与Th17细胞的活化, 分泌IL-17加剧炎症反应[20]. 已有大量研究报道, T细胞合成释放的IL-17参与高血压靶器官损伤过程的调控, 因此通过靶向补体干预IL-17的合成释放是一种潜在具有转化价值的防治高血压发

生发展的研究策略[21,22]. 另一方面, 补体受体C3aR/C5aR大量表达于T细胞, 干预C3aR/C5aR活性能诱导T细胞向免疫抑制性Treg细胞的分化[23,24]. 已有研究报道, 激活Treg细胞能通过抑制免疫炎症反应降低血压, 多次过继转移Treg细胞抑制AngⅡ诱导的高血压[25,26]. 与正常Treg细胞相比, C3aR/C5aR敲除的Treg细胞能够长期维持免疫抑制活性, 因此单次过继转移C3aR/C5aR敲除的Treg能够显著降低血压以及高血压引起的靶器官损伤[27]. B细胞通过产生自身抗体激活AT1受体和α肾上腺素能受体参与血压调节, 新进研究证实, B细胞缺失拮抗AngⅡ诱导的高血压及血管损伤[28]. 补体受体分子同样在B细胞中大量表达分布, 但目前其是否参与高血压及靶器官损伤的调控仍不清楚.

3 补体与血管损伤及血压调节

血管损伤是高血压发生发展的病理学基础, 其病理过程涉及血管内膜、中膜、外膜以及外周脂肪组织, 补体途径的活化参与血管各组分生物学功能的调节. 由于血清中存在大量的补体分子, 并且血管内皮细胞中大量表达补体分子受体, 因此补体途径的活化在血管功能调节中发挥着重要作用. C1q促进内皮细胞的增殖和迁移, 诱导血管环出芽的形成, C1抑制因子C1INH抑制免疫细胞的浸润和补体C3的沉积, 阻止血管损伤后新生内膜的形成[29~31]. C3及其水解产物C3a通过p38 MAPK(mitogen-activated protein kinase)和NF-κB(nuclear factor kappa B)通路的激活诱导血管内皮细胞ICAM-1(intercellular adhesion molecule 1)和VCAM-1(vascular cell adhesion molecule 1)的表达, 募集巨噬细胞向损伤部位聚集[32,33]. C5a通过其受体介导的信号通路促进内皮细胞ICAM-1和PAI-1(plasminogen activator inhibitor-1)的表达, 加剧血管损伤后新生内膜的形成[34]. 补体途径抑制因子CD59和DAF等则能够阻断补体途径的活化, 抑制内皮细胞炎症的表达和免疫细胞的募集, 改善血管损伤后的修复过程[35,36]. 近年来的研究表明, 内皮细胞间质化(endothelial-to-mesenchymal transition, EndoMT)在高血压导致的心脏和肾脏靶器官损伤过程中起着关键性的作用. C3a和C5a可以通过激活AKT通路, 诱导内皮细胞表型的改变, 促进纤维化分子的表达, 抑制内皮细胞标志分子的表达. C3a和C5a受体拮抗剂通过抑制Wnt/β-catenin通路抑制血管活性物质诱导的内皮间质化[37,38]. 血管平滑肌细胞对维持血管张力及在血管重构过程中是最关键的细胞组分, 补体C3和C3a能够直接参与自发性高血压大鼠(spontaneous hypertension rat, SHR)平滑肌细胞的表型转化、增殖和迁移, 分泌趋化因子MCP1等募集巨噬细胞[39,40]. AngⅡ促进巨噬细胞分泌补体C1q, 后者通过激活β-catenin通路促进平滑肌细胞的增殖, 加剧高血压诱导的血管重构[13]. 管周脂肪来源的补体C3和C5促进外膜成纤维细胞的增殖和肌成纤维化, 诱导巨噬细胞向M1型促炎性转化, 促进炎症因子的表达, 而C5a受体拮抗剂诱导巨噬细胞向M2型抗炎性转化, 抑制高血压诱导的血管纤维化和血管外膜胶原的沉积[10,11].

补体分子可以直接参与调节心血管活性物质. SHR肾脏补体C3的表达显著强于对照WKY(Wistar-Kyoto)大鼠, C3表达上调促进肾组织内部肾素-血管紧张素系统的活化[41]. C3敲除小鼠可抑制输尿管结扎诱导的血压升高, 降低肾脏组织内的AngⅡ水平, 抑制肾脏上皮细胞间质化[42]. C3能够促进SHR来源的血管平滑肌细胞由收缩型表型向增殖型表型转化, 促进平滑肌细胞的增殖[39]. 高盐饮食诱导Dahl盐敏感性(Dahl-salt sensitive, Dahl-SS)高血压大鼠补体途径的活化, 然而利用可溶性补体受体1(soluble complement receptor1, sCR1)处理Dahl-SS大鼠, 阻断C3和C5水解酶介导的补体途径的活化并不能阻止血压的升高和蛋白尿的生成. 与之类似的实验结果显示, 敲除补体C3或补体途径抑制因子CD59并不影响AngⅡ诱导的高血压, 这提示血压调节是一种复杂的病理生理过程, 单一阻断补体途径并不能有效地控制血压[43~45].

然而, 多种高血压动物模型均证实, 补体途径活化与血压调节密切相关, 最常见的为AngⅡ诱导模型. 活化的补体分子包括C1q, C3和C5等, 但直接阻断这些补体分子并不能够抑制血管活性物质诱导的血压升高, 提示补体系统对血压的调节并不是直接作用. 由于补体分子可以参与调控免疫细胞的活性, 而且多种免疫细胞参与血压调节, 表明补体分子可能通过调控免疫细胞的活性间接参与血压调节. 研究证实一次性过继转移C3aR和C5aR联合敲除的Treg细胞, 可以显著降低AngⅡ诱导的高血压, 而转移野生型的Treg细胞则不能维持血压水平, 必须多次注射Treg才能抑制血压的升高[25,26]. 机制研究提示, 敲除C3aR和C5aR维持Treg

细胞特征转录因子Foxp3(forkhead box protein P3)的表达，促进其免疫抑制活性和抗炎因子的表达. 野生型Treg细胞在AngⅡ和C3a/C5a刺激下，很快丢失特征转录因子Foxp3的表达，抑制其抗炎活性，导致免疫炎症反应的放大，加剧AngⅡ诱导的高血压[27]. 新近研究证实，IL-17阳性的γδT细胞和Th17细胞参与高血压动物模型的血压调节，IL-17通过抑制内皮细胞NO的产生，促进ROS的生成，进而通过加剧血管纤维化和促进肾脏钠的重吸收等潜在的分子机制促进血压的升高[46]. C3a/C5a信号通路的阻断可抑制T细胞合成释放IL-17，因此是否可以通过干预补体途径，进而抑制AngⅡ，高盐等高血压危险因素诱导的IL-17阳性T细胞的活化值得进一步深入研究[47].

4　补体与高血压靶器官损伤

高血压导致的靶器官损伤主要包括心、脑、肾等组织器官，特别是补体途径的活化在高血压肾损害和心脏重构中的作用近年来受到广泛关注. 高血压模型的肾脏组织中能检测到大量补体分子的表达，包括C1q，C3，C3c，C5和C5b-9等，这些补体分子通过补体级联反应，产生大量炎症介质，如C3a和C5a等，介导高血压靶器官的损伤[8]. C1q和C3大量表达于肾脏周细胞和免疫细胞，尽管C1q的具体肾脏病理学作用仍有待阐明，但敲除C3能够抑制巨噬细胞浸润，改善肾纤维化，利用脂质体清除巨噬细胞能够抑制补体的活化和肾脏纤维化的进展[48]. C3a可以促进肾小管上皮细胞间质化和纤维化细胞的形成，诱导肾素的表达，C3敲除可以抑制肾脏RAAS系统的激活，机制研究证实，C3a通过激活转录因子LXRα(liver X receptor α)和KLF5(Krüppel-like factor 5)发挥这一关键性的调控作用[41,49]. C5敲除抑制DOCA-盐敏感性高血压诱导的肾小球硬化和蛋白尿，C5的水解产物C5a及其受体C5aR在高血压模型的肾脏组织中高表达，特别是C5aR集中表达于肾脏中的树突状细胞和巨噬细胞. C5aR敲除能够抑制AngⅡ诱导的肾小球损伤和蛋白尿，降低肾脏炎症因子的表达，但没有降低血压水平[16,50]. 与之不同的是，本团队[27]的研究工作证实，C3aR和C5aR联合敲除小鼠不仅能抑制AngⅡ诱导的高血压肾损伤和炎症因子的表达，还能显著抑制血压的升高，并且发现C3aR和C5aR大量表达于T细胞，通过促进炎症反应加剧肾纤维化，而抑制C3aR和C5aR能显著促进Treg细胞活化，抑制炎症反应和肾损伤的进展. 这些研究结果提示，补体分子广泛表达于肾脏组织中，包括肾脏实质细胞和浸润的免疫细胞，从而调节高血压肾损伤的各个环节，包括早期的免疫细胞浸润和炎症反应，以及随后的肾纤维化过程，因此深入阐明补体作用的分子机制将为今后选择合适的干预靶点开发新的药物提供理论基础.

多种不同的高血压动物模型均证实补体分子在心脏内广泛分布，AngⅡ诱导的高血压心脏重构过程中伴随有C3和CD59分子的表达，但是C3敲除、C3aR敲除和CD59敲除并没有显著改变AngⅡ诱导的心脏重构，然而心肌活检显示，C3aR阳性的免疫细胞大量存在于非缺血性心脏病患者心肌组织中，并能预测心衰的发展进程，因此C3aR在高血压心脏重构中的具体作用仍有待深入研究[9,16,51]. 与之相反，补体下游分子C5则在高血压心脏重构过程中发挥至关重要的调控作用，C5aR敲除，抗C5中和抗体和C5a受体拮抗剂均能显著抑制AngⅡ诱导的心脏重构，抑制巨噬细胞在心脏中的浸润，随后的骨髓重建实验证实C5aR主要表达于单核/巨噬细胞，介导炎症因子的表达释放[9,52,53]. 本团队[11]的研究也进一步证实，C5a而非C3a参与高血压模型中巨噬细胞的M1/M2极化过程的调控，进而参与炎症反应的调节，延缓高血压靶器官损伤. 最近的研究发现在心肌细胞衰老过程中，C5a/C5aR的表达水平明显增加，利用C5aR拮抗剂可以明显延缓心肌细胞的衰老，抑制TNFα和IFNγ等炎症因子的表达[54]. 另外，在新生小鼠的心尖切除实验中，C5aR大量表达于损伤部位的心肌细胞中，敲除C5aR或利用C5aR的拮抗剂能显著抑制心肌细胞的再生能力[55]. 这些研究研究提示，C5aR可独立于免疫调控，在心肌细胞的增殖与衰老过程中发挥重要调控作用.

5　总结与展望

总之，补体途径激活介导一系列级联反应能够放大炎症反应，同时促进RAAS系统激活，诱导血压水平的升高. 同时高血压动物模型亦证实，血压升高可以促进补体分子在靶器官的表达，诱导补体级联反应，加剧高血压靶器官损伤. 然而迄今为止，补体在高血压相关心血管疾病中的临床研究仍十分有限，尽管当年

Mathis[56]曾经评论“补充调节T细胞可以对抗高血压”; 甚至有学者提出靶向调节T细胞的C3aR和C5aR可能成为治疗高血压的新靶点[57], 但是距离真正走向临床应用还非常遥远. 一项中国人群的研究证实, C3的水平与高血压前期呈正相关性, 尽管其与高血压的相关性不明显, 可能与样本量及异质性有关[58]. 高血压肾病患者的组织活检标本证实, 相对于正常对照, 高血压肾病患者的肾脏间质有更多的补体C3沉积, 并且C3水平与巨噬细胞浸润呈正相关性, 这些临床研究提示, 补体特别是C3可能通过炎症反应参与高血压患者靶器官损伤过程[14]. 值得注意的是, 目前已有很多靶向补体系统的药物进入临床, 用于治疗免疫和炎症相关疾病. 靶向补体C5的抑制剂ravulizumab已经用于治疗溶血性尿毒症综合症, C3抑制剂pegcetacoplan已经被批准用于治疗阵发性夜间血红蛋白尿[59~62]. 然而值得关注是, 补体系统成分复杂, 涉及到炎症反应的各个方面, 目前尚不清楚哪些补体分子可以作为防治高血压靶器官损伤的干预靶点. 后续研究需要更多地关注高血压发生发展的不同阶段补体分子活化的机制及异同点, 寻找其共性的关键靶点. 同时值得关注是, 高血压是和衰老密切相关的, 而补体途径的异常活化也是衰老的典型特征之一, 阐明衰老对补体系统的影响及其在增龄相关的高血压发生发展中的关系也值得进一步研究.

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The role of complement pathway-mediated inflammation and immune regulation in the development of hypertension and related target organ damage

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Hypertension is one of the major risk factors for cardiovascular and cerebrovascular diseases. However, the molecular and pathological mechanism of hypertension remains unclear. Recent studies suggest that immune cell activation is involved in the development of hypertension, and chronic low-grade inflammation induces vascular dysfunction and related diseases. The complement pathway, as an important regulator of the immune system, plays a critical role in recruiting immune cells, regulating inflammation and inflammatory factors release. Abnormal activation of complement pathway and up-regulation of complement molecules are involved in the process of hypertension-related cardiovascular diseases. We herein mainly review the role of complement pathway in hypertension and related target organ damage, and propose a potential target for translational research in cardiovascular immunology.

hypertension, complement pathway, inflammation and immunity

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