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综 述

AMPK激活剂抗炎保护效应研究进展

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摘 要：腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)是细胞能量调节的关键激酶，近期研究表明AMPK也在炎症这一高耗能分子反应中发挥重要调控作用。目前常用的AMPK激活剂有5-氨基咪唑-4-甲酰胺核苷酸(5-aminoimidazole-4-carboxamide ribonucleotide, AICAR)和A-769662，此外二甲双胍及脂联素发挥生物活性也与激活AMPK密切相关。大量研究表明，这些激活剂可在急性肺损伤、哮喘、结肠s炎、肝炎、动脉粥样硬化等多种炎症相关性疾病动物模型中发挥有效的保护作用。因而，AMPK激活剂在炎症相关性疾病的防治中具有广阔的研发和应用前景。

关键词：腺苷酸活化蛋白激酶；AICAR；A-769662；二甲双胍；脂联素
中图分类号：R332；R363.2；R329.2

Advances on the anti-inflammatory and protective effect of AMPK activators

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Abstract: AMP-activated protein kinase (AMPK) is a key enzyme in the regulation of cellular energy homeostasis. Recent studies demonstrated that AMPK also plays an important role in the modulation of inflammation, an energy-intensive molecular response. The commonly used AMPK activators include 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and A-769662. In addition, the biological activities of metformin and adiponectin are closely related to activation of AMPK. Numerous studies have shown that these AMPK activators play an effectively protective role in animal models of acute lung injury, asthma, colitis, hepatitis, atherosclerosis and other inflammatory diseases. Therefore, AMPK activators may have promising potential for the prevention and treatment of inflammation related diseases.

Key words: AMP-activated protein kinase; AICAR; A-769662; metformin; adiponectin

腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) 是维持细胞能量稳态的关键激酶，而炎症的发生和发展与细胞能量代谢状态密切关联，因而，AMPK 在炎症反应中具有极其重要的调节功能[1]。越来越多的资料表明，采用 AMPK 激活剂可在多种炎症损伤中发挥抗炎保护效应[2]；此外，有研究表明二甲双胍以及脂联素的抗炎效应也与 AMPK 的激活密切相关[3]。本文综述常用 AMPK 激活剂抗炎保护效应的最新研究进展，以期为炎症损伤的防治提供新思路。

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1 AMPK简介

1.1 AMPK的结构和代谢调节

人类AMPK由1号、2号、5号、7号及12号共5条染色体基因编码，是异源三聚体复合物，由具有催化活性的α亚基和有调节作用的β、γ亚基构成[4]，其中α亚基和β亚基各有2个亚型、γ亚基有3个亚型[5]（图1）。AMPK是细胞内最重要的能量感受器，在细胞内ATP减少而AMP或ADP增多，即AMP/ATP、ADP/ATP比值增高时，γ亚基结合AMP或ADP，AMPK被激活，AMPK在α亚基上的Thr^{172}磷酸化为其激活标志。活化的AMPK降低耗能的合成代谢，增强产能的分解代谢以提升细胞内的ATP水平，维持细胞能量平衡[6]。此外，由于细胞的增殖、凋亡、炎症细胞活化等生理及病理生理反应均为高耗能的分子反应，AMPK在这些过程中也发挥重要调控作用[7]。

1.2 AMPK的抗炎保护作用

AMPK除了维持能量平衡外，也在炎症反应中发挥着重要的调控作用[2, 7]。有研究表明，过表达组成性激活的AMPKα (constitutively-activated AMPKα, caAMPKα)可抑制脂多糖(lipopolysaccharide, LPS)诱导的THP-1人急性单核细胞白血病细胞株和U-937人淋巴瘤细胞株分泌TNF-α；而采用shRNA敲低AMPKα表达或过表达显型失活突变AMPKα (dominant negative mutant AMPKα, dnAMPKα)可增强LPS诱导的THP-1及U-937细胞中TNF-α的分泌[8]。此外，用siRNA干扰AMPKα表达可促进巨噬细胞分化为经典活化的M1型巨噬细胞、增强TNF-α及IL-6分泌并促进炎症发生[9]。此外，在高脂饮食引起血管周围脂肪组织炎症的研究中，AMPK敲除的小鼠血管周围脂肪组织有更多的巨噬细胞浸润[10]。

1.3 AMPK的抗炎机制

沉默信息调节因子1 (Sirtuin 1, SIRT1)广泛存在于真核生物，通过调节多种蛋白质的去乙酰化修饰参与多种生理、病理过程[11]。SIRT1受烟酰胺腺嘌呤二核苷酸氧化态与还原态比值(NAD^+/NADH)的调节，当NAD^+含量增加或者NAD^+/NADH比值

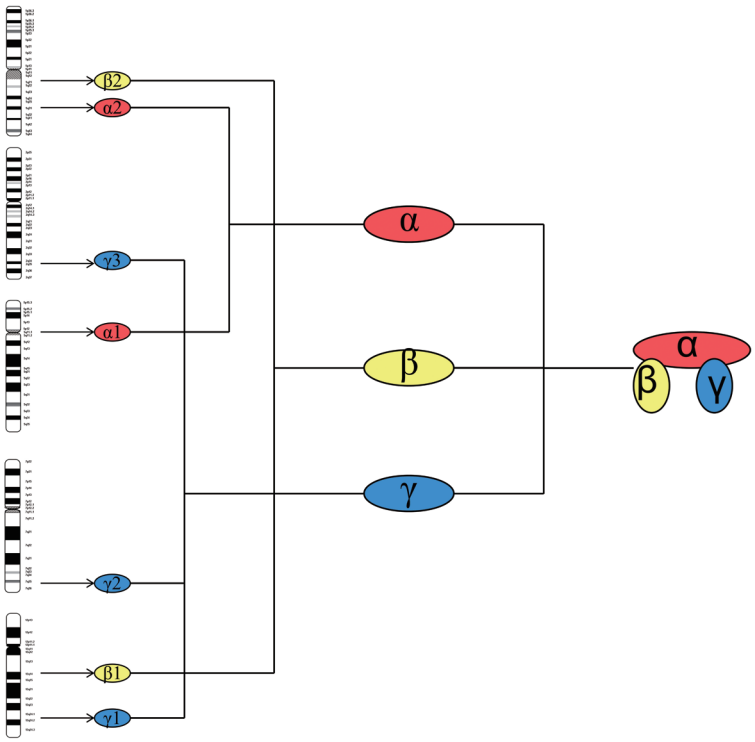

图 1. AMPK表达结构模式图

Fig. 1. Human AMPK consists of three subunits of α, β and γ, including two subtypes of the α and β subunits, and three subtypes of the γ subunit. Human AMPK is encoded by chromosomes 1, 2, 5, 7 and 12. Chromosome 1 encodes α2 (1q31) and β2 (1q21.1), chromosome 2 encodes γ3 (2q35), chromosome 5 encodes α1 (5p12), chromosome 7 encodes γ2 (7q35-36), and chromosome 12 encodes β1 (12q24.1) and γ1 (12q12-14).

升高时，SIRT1 被激活[12]。AMPK 可通过上调烟酰胺磷酸核糖转移酶 (nicotinamide phosphoribosyltransferase, NAMPT) 增加 NAD^+ 含量而增强 SIRT1 的活性[13, 14]。SIRT1 可通过对组蛋白的去乙酰化修饰抑制炎性基因的表达[15]，此外，SIRT1 可使核因子 κB (nuclear factor κB, NF-κB) 发生去乙酰化而限制 NF-κB 的激活，这也参与抑制炎性基因的表达[16]。因此，AMPK 可通过增强 SIRT1 活性抑制炎症反应。转录共激活因子 P300 是一种组蛋白乙酰化酶，其通过对 NF-κB 亚基 P65 乙酰化修饰而使得 NF-κB 向细胞核转位，进而促进炎性相关基因表达，AMPK 可通过对 P300 磷酸化修饰以及促进 SIRT1 对 P65 的去乙酰化修饰，而抑制 NF-κB 向细胞核转位过程，从而抑制炎症反应的发生[17]。

生物活性氧 (reactive oxygen species, ROS) 是线粒体氧化代谢的产物[18]，当其积累过多时可导致内质网应激 (endoplasmic reticulum stress, ERS)，ERS 一方面增加蛋白质折叠进一步促进 ROS 的产生，过量的 ROS 反过来导致线粒体内钙沉积而损伤线粒体膜，进而导致线粒体发生裂变；另一方面，ERS 诱导硫氧还蛋白互作蛋白 (thioredoxin-interacting protein, TXNIP) 启动 NLRP3 炎性体，后者增加 caspase-1 的表达从而促进成熟 IL-1β 的加工，进而促进其下游炎性因子 IL-6 的分泌，最终导致炎症反应及细胞凋亡，AMPK 可通过调节动力相关蛋白 1 (dynamin-related protein 1, Drp1) 活化而抑制该过程，进而减少 IL-1β、IL-6 及 caspase-1 等的产生，最终抑制炎症反应和细胞凋亡[19]，此外，AMPK 还可通过抑制 NADPH 氧化酶活性以减少 NADPH 的消耗，从而减少 ROS 积累，也可抑制该过程[20]。

此外，AMPK 可通过磷脂酰肌醇 3- 激酶 (phosphoinositide-3-kinase, PI3K) 间接活化丝氨酸 / 苏氨酸激酶 Akt (蛋白激酶 B，protein kinase B)，活化的 Akt 使糖原合成酶激酶 3β (glycogen synthase kinase 3β, GSK3β) Ser^9 磷酸化而失活，GSK3β 的失活抑制 Toll 样受体介导的促炎细胞因子的释放[21]，同时 GSK3β 对环磷酸腺苷效应元件结合蛋白 (cyclic AMP responsive element binding protein, CREB) 起负性调节作用[22]，CREB 为抗炎因子 IL-10 产生所必需，所以 GSK3β 的失活也促进了抗炎细胞因子 IL-10 的产生[23]。因此，AMPK 可能通过 PI3K/Akt/GSK3β/CREB 抑制炎症反应的发生。

2 AMPK激活剂及其作用机理(图2)

2.1 AMPK激活剂5-氨基咪唑-4-甲酰胺核苷酸(AICAR)

AICAR 激活 AMPK 主要是通过代谢转化为 ZMP，ZMP 的化学结构与 AMP 类似，可以在不改变 AMP/ATP 比值情况下，既可以直接变构激活 AMPK，也可以通过激活 AMPK 激酶 (AMPKK) 活化 AMPK[24]。

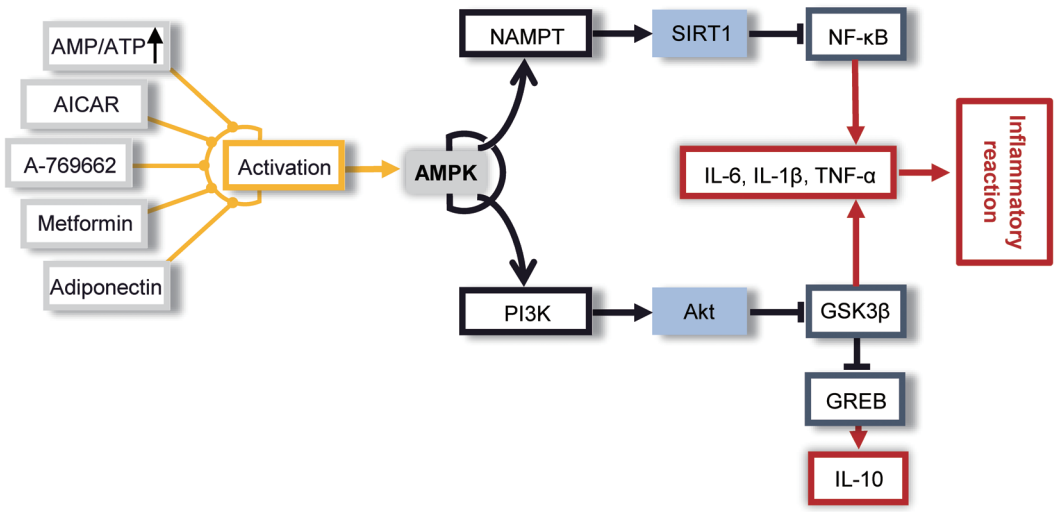

图 2. AMPK激活及其抗炎机制

Fig. 2. AMPK activation and it's anti-inflammatory mechanism. When cellular AMP/ATP ratio decreased or AMPK activators AICAR, A-769662, metformin and adiponectin were used, AMPK was activated. Activated AMPK inhibits inflammatory reaction through Sirtuin 1 (SIRT1) or PI3K/Akt/GSK3β/CREB pathway. NAMPT: nicotinamide phosphoribosyltransferase; PI3K: phosphoinositide-3-kinase; CREB: cyclic AMP responsive element binding protein.

2.2 AMPK激活剂A-769662

A-769662 为噻吩并吡啶酮衍生物，是唯一的 AMPK 特异性激活剂，能够选择性结合 AMPKβ1 调节亚基，使 AMPKα 亚基异位并提升其活性 [25, 26]，A-769662 与 AMPKβ1 亚基相互作用还能够防止 AMPKα Thr^{172} 的去磷酸化 [27]。

2.3 二甲双胍及脂联素

近期的一系列研究表明，二甲双胍抗糖尿病及抑制炎症反应的药理作用与 AMPK 的活化密切相关 [28]。相关研究提示，二甲双胍可抑制线粒体氧化呼吸链的复合体 I、阻断线粒体氧化呼吸链的电子传递，这使得 AMP、ADP 不能转化为 ATP，AMP 和 ADP 积累而 ATP 减少，从而增加了 AMP/ATP 比值，间接激活 AMPK [29]。

在对 2 型糖尿病的研究中发现脂联素能减轻高血糖诱导的氧化应激和炎症反应，而这一作用也与 AMPK 密切相关 [30]。此外，脂联素还可使巨噬细胞向抗炎型 M2 巨噬细胞分化，这一作用也与激活 AMPK 密切相关 [31]。脂联素激活 AMPK 的机制十分复杂，但有研究表明脂联素是通过与其 I 型受体结合而激活 AMPK [32]。

3 AMPK激活剂的抗炎保护效应

3.1 呼吸系统

在 LPS 诱导的急性肺损伤中，AMPK 激活剂 AICAR 处理可减少中性粒细胞浸润、下调炎性细胞因子 TNF-α，IL-1β 及 IL-6 的产生、抑制肺泡上皮细胞凋亡，减轻肺组织损伤 [33]。与此类似，用二甲双胍处理，也可明显减轻肺泡和呼吸性细支气管的损伤、减少中性粒细胞和巨噬细胞的浸润、减轻肺水肿；通过 Western blot 分析发现，在二甲双胍处理组 AMPK 磷酸化明显增强，提示二甲双胍减轻肺损伤可能与激活 AMPK 密切关联 [34, 35]。Piao 等人将脂联素基因转染到急性肺损伤小鼠进行基因治疗，发现治疗组肺组织和肺泡液中 TNF-α 和 IL-1β 含量明显低于对照组，而 AMPK 磷酸化水平则比对照组高，因此，脂联素可能也通过激活 AMPK 减轻急性肺损伤 [36]。

Park 等人的研究显示，二甲双胍可抑制哮喘动物气道内的嗜酸性粒细胞浸润，降低支气管的纤维化，在二甲双胍组中 AMPK 的磷酸化明显增强，采用 AMPK 激活剂 AICAR 处理，同样可减轻哮喘 [37]，二甲双胍通过活化 AMPK 使 mTOR 磷酸化失活，这可抑制 S 期激酶相关蛋白 2 (S-phase kinase-associated protein 2, Skp2) 的表达，使得细胞周期素依耐性激酶抑制蛋白 27 (cyclin dependent kinase inhibitor protein 27, p27) 不被 Skp2 降解，p27 抑制呼吸道平滑肌细胞的增殖，从而抑制呼吸道重塑，阻止其发展为不可逆转的气流阻塞 [38]，因此二甲双胍和 AICAR 激活 AMPK 对减轻哮喘有重要作用。脂联素也可通过激活 AMPK 抑制促炎性细胞因子如 TNF-α、IL-6 等的表达、促进抗炎性因子 IL-10 的表达而抑制呼吸道的炎症反应，在哮喘中发挥抗炎保护作用 [39]。

3.2 消化系统

AMPK 的活化在结肠炎中也发挥保护作用，AICAR 激活 AMPK 可促进肠特异性转录因子 CDX-2 (caudal type homeobox-2) 的表达，这可增加细胞跨膜电阻、降低细胞通透性，改善肠道 Caco-2 细胞的屏障功能，用 AMPK 质粒转染肠道 Caco-2 细胞，可改善肠道上皮细胞的屏障功能 [40]。二甲双胍通过降低促炎性细胞因子 TNF-α、IL-1β 及 IL-6 水平、增强肠道屏障功能、抑制细菌的易位，显著减轻结肠炎症反应，其抗炎保护作用也与激活 AMPK 密切相关 [41]。脂联素在结肠炎中的保护作用也得到了证实，脂联素与其受体结合可调节适应性免疫以维持肠道稳态，而脂联素基因敲除的小鼠结肠炎明显加重，脂联素的抗炎保护效应也与激活 AMPK 密切相关 [42]。

肝缺血 - 再灌注损伤的研究显示，在再灌注开始时用 AICAR 激活 AMPK，发现巨噬细胞及中性粒细胞浸润减少，炎性细胞因子 IL-1β、TNF-α 和 IL-6 以及趋化因子 ICAM-1、CCL-2 和 CXCL-10 均明显降低，此外，AICAR 降低了乳酸等糖酵解代谢产物的浓度，同时也降低了 ATP 的消耗，与对照组相比，AICAR 处理组小鼠的肝脏损伤明显减轻 [43]。

AMPK 激活剂 AICAR 在四氯化碳诱导的急性肝损伤中具有抗炎保护作用，这种保护作用得益于 AMPK 的激活，抑制炎性细胞因子 TNF-α、IL-6 等释放，以及抑制诱导性一氧化氮合酶、基质金属蛋白酶的上调 [44]。二甲双胍在丙型肝炎中有着保护作用，二甲双胍激活 AMPK，增强 I 型干扰素信号通路，影响丙型肝炎病毒的复制 [45]，此外，在慢性丙型肝炎中，脂联素激活 AMPK 可以抑制肝星状细胞释放 NO，并可阻断 TGF-β 信号通路，从而抑制肝星状细胞增殖及迁移，进而抑制肝纤维化的形成 [46]。

3.3 循环系统

亲环素 (cyclophilin) 在动脉粥样硬化形成中具有关键作用，它能增加血管壁细胞清道夫受体表达，提高血管壁细胞对脂质的吸收，促进巨噬细胞的迁移和形成泡沫细胞 [47]；研究表明二甲双胍能够减少亲环素的表达，从而减少血管壁细胞清道夫受体，减少低密度脂蛋白的吸收，减少泡沫细胞形成，并抑制血管壁 ROS 及炎性因子产生，而发挥这些作用与激活 AMPK 密切相关 [48]，AMPK 激活剂 AICAR 也具有类似效应，通过 SIRT1/DOT1L 信号轴改善线粒体功能，延迟血管内皮细胞衰老，从而抑制动脉粥样硬化的形成 [49]。Ma 等人的研究显示，AICAR、A-769662 及二甲双胍可增强高密度胆固醇的抗动脉粥样硬化的作用，AMPK 的激活增强逆向转运胆固醇、增加肝脏对胆固醇的摄取和排泄、降低高密度脂蛋白炎症指数、并诱导巨噬细胞向抗炎型 M2 巨噬细胞分化 [50]。脂联素也可通过激活 AMPK 发挥抗动脉粥样硬化的作用 [51]。然而，Zhang 等人通过敲除或转染 AMPKα 技术，发现 AMPK 激活介导单核细胞向巨噬细胞转化，促进动脉粥样硬化的发生和发展 [52]，这一研究结果与上述二甲双胍、AICAR 及 A-769662 激活 AMPK 在动脉粥样硬化发生和发展研究中的结果相矛盾，提示 AMPK 激活剂发挥抗动脉粥样硬化的作用可能还与其非 AMPK 依赖的作用有关，同样也提示 AMPK 在动脉粥样硬化发生和发展中的角色仍不明确，还需要大量研究。

心肌缺血 - 再灌注损伤的研究显示，在心肌再灌注的前 15 min 用二甲双胍或 AICAR 激活 AMPK，心肌梗死面积明显减小，而用 AMPK 抑制剂 compound C 处理可消除二甲双胍或 AICAR 的保护作用，这表明二甲双胍或 AICAR 激活 AMPK 在心肌缺血 - 再灌注损伤中也具有保护作用 [53]。

3.4 其他

在肾缺血 - 再灌注损伤的研究中，在小鼠肾缺血前 24 h 用二甲双胍或者 AICAR 处理，肾小管坏死程度和上皮细胞脱落明显减轻，因此二甲双胍、AICAR 可在肾缺血 - 再灌注损伤中发挥保护效应 [54]。Xu 等人对脑缺血 - 再灌注损伤的研究表明，在小鼠颈动脉结扎后施以脂联素处理，脂联素处理组细胞凋亡标记分子激活型 caspase-3 染色阳性的细胞数明显减少，组织学分析也发现神经细胞的变性、坏死程度明显减轻，而用 siRNA 干扰脂联素表达后，神经细胞激活型 caspase-3 染色阳性细胞明显增多，组织学分析也发现神经细胞坏死程度更严重且范围更大，这提示脂联素可在脑缺血 - 再灌注损伤中发挥保护效应 [55]。

4 结语

AMPK 与机体多种生理、病理状态有关，对维持能量平衡、抑制炎症反应、维持氧化还原平衡、生长发育与衰老等均有着重要意义，目前常用的 AMPK 激活剂有 AICAR、A-769662，此外，大量研究表示二甲双胍、脂联素等发挥相应药理作用与激活 AMPK 密切相关。但是，这些 AMPK 激活剂发挥抗炎保护效应仍不能排除其非 AMPK 依赖的方式。炎症是众多临床疾病发生和发展的基础性发病机制，现有研究表明，上述 AMPK 激活剂可通过复杂的机制抑制炎症相关基因的表达、减轻组织的炎症损伤，因而，AMPK 激活剂在炎症相关性疾病中具有重要的潜在价值以及广阔的研发和应用前景。

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