AMPK在转化医学研究中的意义与展望

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摘要 单磷酸腺苷活化蛋白激酶(AMPK)是一个调控能量稳态的重要激酶, 也是一个参与许多细胞信号传导通路的关键蛋白。目前认为, AMPK不仅在代谢障碍而且在心血管疾病及生殖障碍等许多病理状态中都具有重要的调节作用。此外, 它在人类恶性肿瘤中也扮演着重要的角色。然而, 有关AMPK在临床上的作用及其重要意义尚未完全阐明。该文从分子生物学基础到临床应用等多个方面详细综述了AMPK的研究进展, 指出AMPK是转化医学研究的热点, 围绕AMPK的研究及其结果将作为未来多种疾病的分子治疗手段应用于个体化医疗中。

关键词 单磷酸腺苷活化蛋白激酶; 癌症; 心血管疾病; 细胞信号; 代谢障碍; 个体化医疗; 生殖障碍; 转化医学

Implication and Prospect of AMPK in Translational Medical Research

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Abstract 5′-Adenosine monophosphate-activated protein kinase (AMPK) is an important enzyme in energy homeostasis. It is also a pivotal protein involved in many cellular signaling cascades. It is now considered as a key regulator not only in metabolic disorders but also in many other pathological conditions including cardiovascular disease and reproductive disorders. In addition, it plays a significant role in human malignancy. However, the property of AMPK in terms of clinical significance is not yet fully characterised. In this review, we covered current advances in AMPK research from the molecular basis to its clinical relevance. We also concluded that AMPK is a hot research spot in translational medicine. As a consequence, the outcome of AMPK research could be used as molecular therapeutic target in personalised medicine.

Key words AMPK; cancer; cardiovascular disease; cell signaling; metabolic disorder; personalised medicine; reproductive disorder; translational medicine

单磷酸腺苷活化蛋白激酶(5′-adenosine monophosphate-activated protein kinase, AMPK)是广泛存在于动植物体内的重要蛋白激酶。当前对AMPK的研究日益深入, 其生物学作用及其在临床靶向治疗中的应用也越来越受到关注。因此, AMPK已成为生物化学与细胞生物学等多学科的研究热点。据统计, 自1988年AMPK首次出现在文献中以来, 对该激酶的研究进展迅速, 至2012年, 平均一天就有两篇相关论文发表[1]。本文将就目前对AMPK的研究状况作一个系统的回顾, 并着重探讨AMPK在转化医学中的意义及应用。

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1 AMPK的分子生物学基础

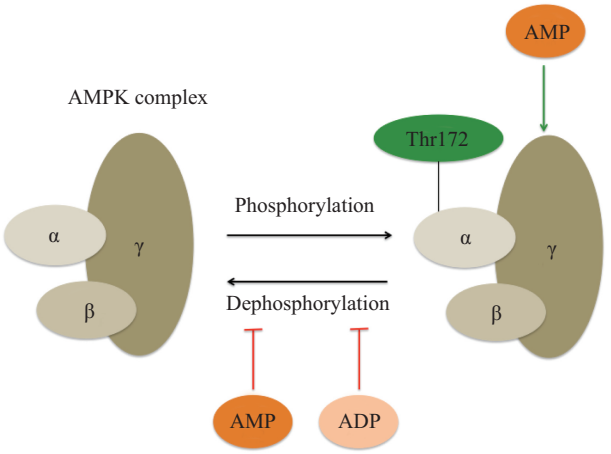
1.1 AMPK的结构与表达

AMPK由α、β、γ三个亚单位组成, 这三个亚单位由7个基因编码的蛋白质亚型(protein isoforms)组成, 分别是α1、α2、β1、β2、γ1、γ2和γ3[2]。其中, α亚单位包含了一个具有催化作用的丝氨酸/苏氨酸蛋白激酶结构域, β和γ亚单位则起调节作用[2-3], 不同亚型在不同组织中的分布与表达也不尽相同[4-5]。

1.2 AMPK的调节

在细胞水平, 单磷酸腺苷(adenosine monophosphate, AMP)与AMPK的γ亚单位结合可以激活AMPK的别构调节[6], AMP或者二磷酸腺苷(adenosine diphosphate, ADP)与γ亚单位的结合也可以阻止AMPK的去磷酸化, 从而阻止AMPK的失活, 而三磷酸腺苷(adenosine triphosphate, ATP)则可以拮抗该作用[1]。

目前认为, α亚单位172位苏氨酸(Thr172)的磷酸化是AMPK激活的主要机制[7-8](图1)。虽然AMPK的激活可能由多个激酶调控[9], 但主要的激酶有两个, 即肝激酶B1(liver kinase B1, LKB1)和钙/钙调蛋白激酶激酶β(calcium/calmodulin-dependent protein kinase kinase beta, CaMKKβ)[1]。Thr172的磷酸化由这两个激酶的活性决定, 其中LKB1表现为持续激活状态[10], 而CaMKKβ则由钙及钙调蛋白激活[11]。虽



AMPK是一个异源三聚体复合物, 它在α亚单位被Thr172磷酸化而激活, AMP与γ亚单位结合而引起别构激活, AMP或者ADP与γ亚单位结合同时能抑制AMPK的去磷酸化。

AMPK is a heterotrimeric complex. It is activated at the alpha subunit by phosphorylation of Thr172. Binding of AMP to the γ subunit initiates allosteric activation. Binding of AMP or ADP to the γ subunit also inhibits the dephosphorylation of AMPK.

图1 单磷酸腺苷活化蛋白激酶(AMPK)的结构与调节

Fig.1 Structure and regulation of AMPK

然AMPK的去磷酸化机制还未完全阐明, 但目前的研究表明, 金属依赖蛋白磷酸酯酶(metal-dependent protein phosphatase, PPM)家族在催化AMPK的去磷酸化过程中起主导作用[1]。

1.3 AMPK的激活剂

任何能够导致AMP:ATP比值改变的状态, 如缺氧、缺血、运动、葡萄糖缺乏等均可以激活AMPK[12]。

5-氨基咪唑-4-甲酰胺核苷酸(5-amino-4-imidazolecarboxamide-riboside, AICAR)是一个广泛使用的AMPK激活剂, 能在细胞内转换为AMP类似物环腺苷–磷酸衍生物5-aminoimidazole-4-carboxamide-1-β-D-ribofuranosyl-5-monophate(ZMP), 从而激活AMPK[13]。其他AMP类似物如WS070117也具有激活AMPK的作用[14]。据报道, 炎症介质白介素-6(interleukin-6, IL-6)也可以增加AMP的浓度, 从而升高AMP:ATP比值以激活AMPK[15]。

另一个重要的AMPK激活剂是A769662, 它具有与AICAR完全不同的作用机制。A769662是一个高选择性的AMPK激活剂, 在直接激活AMPK的同时还能抑制Thr172的去磷酸化, 且该作用不受AMPK上游激酶的限制[16]。特别值得一提的是, A769662仅作用于β1亚型, 因此只含有β2亚型的AMPK不能被其激活[17], 而且由于其较低的50%有效浓度(half maximal effect concentration, EC_{50}), A769662可以在相对于其它激活剂较低的浓度下激活AMPK[18]。

PT1, 一个我国学者首先发现的小分子激活物, 可以通过抑制AMPK α亚单位的自抑制(auto-inhibition)而直接激活AMPK[19]。临床常用于治疗2型糖尿病的两种药物二甲双胍(双胍类)和罗格列酮(噻唑烷二酮类)也可以激活AMPK, 虽然它们的药理学作用并不完全是由AMPK介导的[20-21]。最新的研究证实, 水杨酸类药物有激活AMPK的作用, 其机制和A769662类似[22]。此外, 另一类广泛使用的他汀类药物也能激活AMPK[23]。有趣的是, 传统中药黄连素也有激活AMPK的作用[24]。一些蛋白质也可以激活AMPK, 如一种可以介导严重厌食的睫状神经营养因子(ciliary neurotrophic factor, CNTF)就具有该作用[25]。

1.4 生物学作用

作为能量感受器, AMPK通过感知细胞内AMP:ATP比值的变化来调控线粒体的功能, 从而维持能量稳态[26]。升高的AMP:ATP或ADP:ATP比值都会

使AMPK激活, 从而启动分解代谢的信号通路, 同时抑制合成代谢的信号通路, 提高细胞ATP水平[26]。AMPK的激活不但可以增强线粒体的生物合成、细胞自噬及线粒体自噬[27], 而且能通过磷酸化多个代谢酶的方式抑制对细胞生长和增殖极其重要的脂肪酸合成、类异戊二烯合成、甘油三酯及磷脂合成、糖原合成及核糖体RNA合成[12], 这些代谢酶包括乙酰辅酶A羧化酶1(acetyl-CoA carboxylase 1, ACC1)、HMG-CoA还原酶(HMG-CoA reductase, HMGCR)、糖原磷酸酰基转移酶、糖原合成酶及RNA聚合酶I转录因子[12]。AMPK还可以通过调控磷酸化酶的方式, 直接控制蛋白的磷酸化[28-29], 例如, AMPK可以磷酸化肿瘤抑制基因*p53*而中止细胞周期[30]。另一个抑癌基因*p27*也可以被AMPK激活而启动, 进而抑制细胞生长[31]。此外, AMPK还与细胞极性(polarity)的维持和细胞周期的调控有关[27]。

PI3K/Akt/mTOR信号通路在mRNA翻译及核糖体生物合成中具有重要作用[32], 而AMPK通过磷酸化结节性硬化复合物2(tuberous sclerosis complex 2, TSC2)和雷帕霉素靶目标复合物1(target of rapamycin complex 1, TORC1)的Raptor亚单位, 能够抑制该信号通路[33-34], 从而抑制蛋白质合成[26]。通过Unc-51-类激酶1(Unc-51-like kinase 1, ULK1)的磷酸化, AMPK与mTOR共同参与细胞自噬的调控[35]。有研究表明[36], AMPK可以在血管平滑肌细胞中启动同源性磷酸酶–张力蛋白(phosphatase and tensin homolog, PTEN)的表达, 这对AMPK在PI3K/Akt/mTOR通路中的作用有了新的启示。

有研究指出, AMPK还能调控生物钟周期[37]。在中枢神经系统, AMPK也具有重要的生理意义, 如在下丘脑水平激活AMPK有刺激进食和调节体重的作用[38-39]。除下丘脑外, 位于后脑的孤束核(nucleus tractus solitaries, NTS)同样有调节食欲的作用, AMPK在NTS的激活也可以促进食欲[40]。使用基因技术已经成功建立了不同的动物模型, 这为研究不同组织、不同生理或病理状态下AMPK缺失或过度表达的表型, 并进一步阐明AMPK的生物学作用提供了新的手段。Viollet等[41]对不同的AMPK动物模型作了详细的综述。

1.5 与AMPK有关的细胞信号调控

与AMPK存在相互作用(crosstalk)的信号通路不但包括了上述的PI3K/AKT/mTOR通路, 而且通过磷酸化β-连环蛋白(β-catenin), AMPK可以调控激活Wnt通路, 进而调控脂肪生成[42]。

有研究指出, 转化生长因子-β(transforming growth factor beta, TGF-β)激活的激酶-l(TGF-β-activated kinase-1, TAK-1)与AMPK的磷酸化也有联系[43], 但TAK-1是否是AMPK的上游激酶还未确定[26]。蛋白激酶A(protein kinase A, PKA)也被证实可以在丝氨酸173(Ser173)位点磷酸化AMPK α1亚型, 从而阻止AMPK α在Thr172的磷酸化, 这个crosstalk被认为是AMPK负反馈调节的机制[44]。

AMPK的激活可以抑制肿瘤坏死因子-α(tumour necrosis factor-alpha, TNF-α)介导的白细胞黏附(leukocyte adhesion)[45]。内皮一氧化氮合成酶(endothelial NO synthase, eNOS), 这个对维持心血管内稳态极其重要的信号蛋白也是一个可以被AMPK激活的酶[46]。

有报道指出, AMPK还参与了促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)家族信号通路的调控(图 2), 但其相关机制尚未阐明[47-50]。

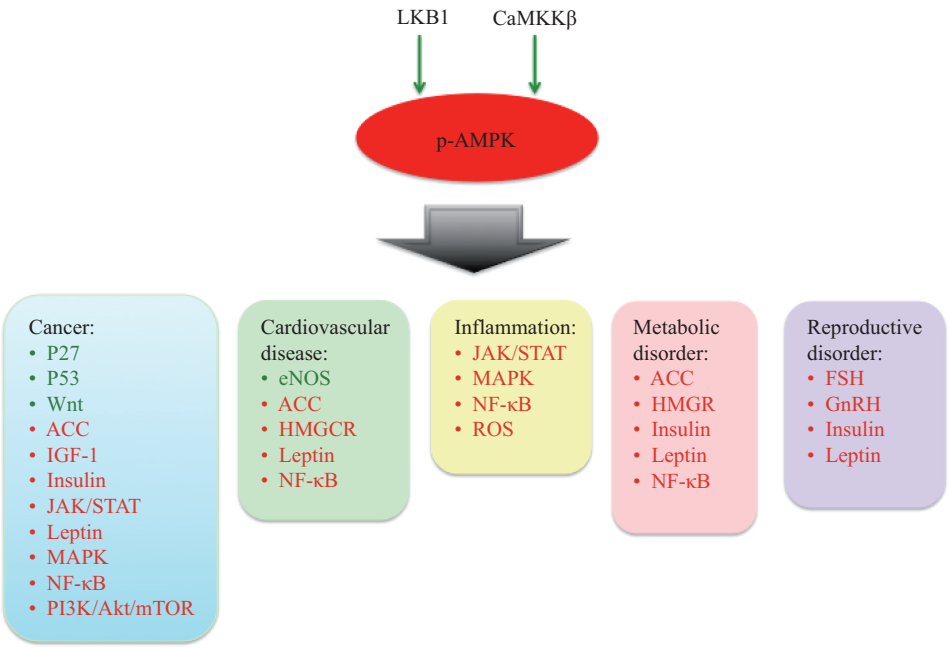
2 AMPK在转化医学中的意义

转化医学的定义是把基础科学研究中得到的新知识、新机制、新技术有效地转化到疾病预防、诊断与治疗的各个阶段, 从而提高健康质量[51]。其目的是要实现“从实验室到床旁(bench-to-bedside)”的跨学科研究, 进而为不同的病人提供不同的治疗方案[52]。此外, 利用临床中的观察和发现使用“事实引导的研究(facts-driven research)”的概念, 反推疾病的发病机制也是转化医学的重要研究方法[53]。

AMPK与基础和临床医学的密切联系奠定了其在转化医学中的重要意义及应用基础, 它不但有可能作为代谢异常和细胞增殖失调疾病(包括2型糖尿病、代谢综合征、动脉粥样硬化)及癌症的治疗靶点[54-57], 其所具有的抗炎作用也有助于慢性炎性疾病的治疗[58]。

2.1 AMPK与代谢障碍

由于AMPK具有调控细胞代谢的作用, 因此它在糖尿病、代谢综合征及肥胖等代谢障碍疾病中具有重要的意义。Zhang等[59]对不同的AMPK激活剂在代谢异常中的作用作了深入的综述。AMPK不仅通过前述多种途径参与糖尿病的病理生理过程, 其激活还可以促进葡萄糖转运蛋白4(glucose



AMPK的磷酸化激活是由两个上游激酶LKB1和CaMKKβ催化的。磷酸化后的的AMPK(p-AMPK)可以上调(绿色)或者下调(红色)存在于癌症、心血管疾病、炎症、代谢障碍和生殖障碍中的各种细胞信号。

Activation of AMPK is catalyzed by two upstream kinases: LKB1 and CaMKKβ. Upon activation, p-AMPK could either up-regulate (green) or down-regulate (red) those cell signals involved in cancer, cardiovascular disease, inflammation, metabolic disorder and reproductive disorder.

图2 AMPK激活的信号调节意义

Fig.2 Implication of signals regulated by activation of AMPK

transporter type 4, GLUT4)的移位及转录[60]。研究表明, 使用二甲双胍可以激活2型糖尿病患者脂肪组织内的AMPK[61], 也有证据指出, AMPK通路的调控异常与代谢综合征密切相关[62]。通过胰岛素/mTOR/AMPK通路的介导, AMPK与胰岛素受体底物(insulin receptor substrate, IRS)之间还存在反馈调节机制[63]。值得一提的是, 内皮细胞中AMPK的选择性激活在糖尿病性血管病变中具有血管保护作用[64]。使用AMPK α1基因敲除(gene knockout)小鼠的研究发现, 降低AMPK活性可以导致脂肪细胞变小和脂解作用(lipolysis)的增加[65]。

与代谢异常密切相关的肥胖也和AMPK有密切联系, 而且许多药物的抗肥胖效果都是通过AMPK信号通路介导的[66-67]。由于肥胖同时是慢性肾脏疾病(chronic kidney disease, CKD)的高危因素, 因此CKD与AMPK也有密切联系[68]。

值得注意的是, 很多重要的激素都与组织中AMPK活性的调控有关, 但在不同组织中其调控作用不同, 甚至有相反的作用[69]。这些激素包括瘦素(leptin)、脂联素(adiponectin)、抵抗素(resistin)、脑肠肽(ghrelin)、大麻素(cannabinoids)、胰岛素、胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)和糖皮质激素。Lim等[69]对这些激素在下丘脑组织、脂肪组织、肝组织和心脏中对AMPK的调控作了全面综述。最新研究指出, 性激素在能量稳态中也发挥着重要作用, 在脂肪细胞中, 雄激素可以抑制LKB1的转录从而抑制AMPK的磷酸化, 而雌激素却具有相反的作用[70]。这提示我们去重新理解能量稳态与性激素的调控及其相互作用。可以预见, 随着对AMPK作用机制的深入了解, 诸如二甲双胍等激活AMPK的药物可以在治疗包括2型糖尿病及肥胖等代谢障碍性疾病中发挥重要作用。

2.2 AMPK与生殖障碍

多囊卵巢综合征(polycystic ovarian syndrome, PCOS)是较常见的引起生殖障碍的原因之一[71], PCOS病人除了不孕外还经常合并肥胖及胰岛素抵

抗[72]。与PCOS有关的生化改变包括升高的黄体生成素与促卵泡激素比值、睾酮水平及其生物利用度, 以及升高的胰岛素水平合并胰岛素抵抗[71]。垂体水平的能量稳态与生殖功能的调控有重要联系[73]。临床证据也指出[74], 同时使用二甲双胍治疗PCOS(尤其是在肥胖及糖耐量异常和/或胰岛素抵抗的患者中)提高了排卵的可能性及怀孕的成功率。二甲双胍对AMPK的激活作用抑制了激活素(activin)和促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)介导的促性腺激素细胞(gonadotroph)信号通路[71], 在垂体细胞中使用二甲双胍激活AMPK不但抑制了GnRH诱导的黄体生成素(luteinizing hormone, LH)及促卵泡激素(follicle-stimulating hormone, FSH)分泌, 而且抑制了激活素诱导的FSH释放及FSH的β亚单位mRNA表达[73]。使用二甲双胍治疗PCOS也能使患者的血清LH浓度下降[75-77]。动物实验同样证实通过激活AMPK, 二甲双胍和AICAR具有直接抑制下丘脑水平的GnRH分泌从而缩短发情周期(oestrous cycle)的作用[78]。这些发现为生殖障碍的病因及其治疗提供了新的认识, 结合AMPK在性激素调控中的作用, 可以预见AMPK将是生殖障碍转化研究的热点。

2.3 AMPK与炎症和心血管疾病

鉴于炎症和心血管疾病的密切联系, 本文在此一并讨论。AMPK与多种炎症介质的关系如IL-6激活AMPK的作用及AMPK抑制TNF-α的作用, 使其在此类疾病中的应用非常广泛。有AMPK激活作用的CNTF在肝及骨骼肌组织中也有抑制炎症信号通路的作用[79]。另一个炎症的上游调控物——巨噬细胞抑制因子(macrophage inhibitory factor, MIF)同样可以在心肌缺血的时候经CD74激活AMPK[80], 而MIF在保护心肌缺血再灌注损伤中的作用也为炎症与代谢的联系提供了线索[80]。Salt等[58]对AMPK的抗炎(anti-inflammatory)机制及作用进行了综述, 并指出可能的机制包括抑制核转录因子-κB(nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB)信号、抑制MAPK通路、调控活性氧类(reactive oxygen species, ROS)、抑制JAK-信号转导转录激活因子(Janus kinase and signal transducer and activator of transcription, JAK-STAT)通路、抑制白细胞浸润(leukocyte infiltration)、调控细胞因子合成(cytokine synthesis)以及调控脂类代谢等。AMPK抑制脂肪酸合成和胆固醇合成的作用在治疗动脉粥样硬化中亦具有重要意义[55]。在心肌梗死中使用二甲双胍治疗有明显的心肌保护作用, 而该作用是通过AMPK-eNOS信号通路介导的[81]。尤其值得一提的是, 在缺血再灌注(ischemia-reperfusion)损伤中, 激活AMPK对心肌有保护作用[82-83]。动物实验也证实在缺血再灌注模型中, AMPK α2基因抑制(gene knockdown)的小鼠与正常小鼠相比有更严重的心肌损伤[84]。

AMPK对遗传性心脏病也有重要影响: 已经在家族性预激综合征(Wolff-Parkinson-White syndrome)患者[85]及家族性肥厚性心肌病的患者中发现AMPK的基因突变[86-87], 这为针对此类疾病开发新的基因治疗提供了可能性。

AMPK与心功能不全的联系尚待阐明: 研究发现, AMPK的磷酸化水平随着纽约心脏病学会(New York Heart Association, NYHA)对心功能分级的增加而增加[88], 该结论提示: 左室心功能不全与AMPK/ACC信号通路介导的脂肪酸氧化有密切关系, 为今后改善心肌细胞的代谢进而治疗心衰提供了新的思路。AMPK在心肌肥厚(cardiac hypertrophy)及左心室重构(LV remodelling)中也有重要作用, Zaha等[89]对上述AMPK在心脏病中的调控作用作了详尽的综述。利用基因抑制的小鼠模型研究发现, AMPK的缺陷可以加剧高脂饮食诱导肥胖所致的糖耐量异常、心肌肥厚、心肌收缩功能不全及胞内钙离子调控障碍[90]。

需要注意的是, 在脑血管疾病中AMPK所起到的作用却相反。有研究指出, 在中风模型中, 抑制AMPK有神经保护作用, 利用AMPK α1及AMPK α2敲除的小鼠进一步证实了AMPK的激活对急性中风造成的不利影响是由α2亚型引起的[91]。

相同AMPK亚型在不同组织中截然不同的作用可能与不同的细胞类型有关, 不同疾病状态中的细胞信号通路异常也可能引起不同的作用。由于AMPK在炎症与心血管系统疾病中的广泛联系与不同作用, 更需要阐明AMPK与其它细胞信号通路的相互作用机制及其分子病理学基础, 从而使相关研究结果能够尽快转化为临床服务。

2.4 AMPK与癌症

AMPK的激活与降低增殖的联系在很多不同的细胞株(cell line)中得到了证实, 研究不仅包括了诸如肺癌、乳腺癌、膀胱癌、卵巢癌、肾癌、恶性黑

素瘤、胰腺癌、甲状腺癌、恶性胶质瘤、结肠癌和前列腺癌等实体肿瘤(solid tumor)细胞, 也包括一些血液系统恶性疾病的细胞, 如急性淋巴细胞性白血病、套细胞淋巴瘤(mantle cell lymphoma, MCL)以及急性粒细胞性白血病[92-94]。目前所知, AMPK信号通路至少与两个肿瘤抑制物LKB1和TSC2有关[95-96]。有学者指出, 多种不同机制参与了AMPK介导的抑癌作用[26]。使用不同的AMPK激活剂被证明有降低癌细胞生长的作用, 如AICAR可以明显降低HeLa、Du145及HepG2等癌细胞增殖却不影响正常细胞[97], 但由于AICAR的毒性作用限制了其临床应用[98]。体外实验证明, 二甲双胍可以明显抑制乳腺癌细胞的增殖[99]; 临床研究也发现, 使用二甲双胍治疗的糖尿病患者与使用其它降糖药的患者相比有较低的癌症发生率[100]。使用电离辐射(ionizing radiation, IR)激活AMPK也被证明可以增加癌细胞的放疗敏感性[101]。有研究指出, 通过激活AMPK, 黄连素能起到抑制大肠癌细胞迁移的作用[102]。

然而激活AMPK在癌症治疗中的作用仍然有争议, 并需要进一步的研究[27]。尽管不少研究指出激活AMPK有抑制癌细胞生长及增殖的作用, 但另一些研究却得出相反的结论[103], 例如最新报道指出, 在能量缺乏的情况下, AMPK可以通过调控烟酰胺腺嘌呤二核苷酸磷酸(NADPH)而促进肿瘤细胞的存活[104]。另外, 血管新生(angiogenesis)在肿瘤扩张及转移中具有重要作用, 而在内皮细胞中血管新生需要AMPK的激活, 下调AMPK可以抑制内皮细胞的迁移和增殖[105-106]。例如, 激活AMPK虽然可以在体外实验中有效抑制乳腺癌细胞生长, 但却可能因为其促进血管新生的作用而导致肿瘤进展[99]。

目前争议最多的是前列腺癌。研究指出, AMPK的上游激酶CaMKKβ在前列腺癌细胞中升高, 特别是在雄激素受体(androgen receptor, AR)的作用下。因此, 抑制CaMKKβ/AMPK通路可以抑制前列腺癌细胞的生长(growth)、迁移(migration)及侵袭(invasion)[107]。有证据表明, 在前列腺癌的发展过程中, AR及CaMKKβ之间存在的反馈调节是前列腺癌生长的重要机制[108-109]。由于AR信号通路在前列腺肿瘤生成及发展中具有举足轻重的作用, 进一步阐明AMPK通路与AR通路的crosstalk具有重要意义。

近期研究指出, 不同的AMPK亚型与卵巢癌的分级有关, 而且其在肿瘤发展各阶段中的表达也不一样, 更为重要的是这种不同的表达与卵巢癌的预后有联系[110], 这些证据提示, 不同亚型的AMPK在肿瘤发展中可能起着不一样的作用。特别需要指出的是, 在正常细胞中, AMPK通路的调控通常有降低细胞生长的作用, 而癌细胞却有减弱这种作用的倾向[1]。因此, 有必要在不同的肿瘤以及肿瘤不同的发展阶段中研究AMPK通路的上游和下游激酶, 才能进一步阐明其作用。

如果AMPK的激活确实有益于癌症的话, 那么二甲双胍和水杨酸等药物除了原有药效外是否还适用于癌症患者？如果这样, 不仅降低了新药研发的成本、提高了速度, 还将使更多的病人获益, 也使现有药物的对症治疗发展为分子水平的对因治疗, 充分体现了转化医学研究的优势。此外, 由于现有证据指出AMPK的激活可能具有肿瘤自我保护作用, 因此AMPK抑制剂的研究、开发与应用也同样重要。进一步阐明AMPK在不同肿瘤及同一肿瘤不同发展阶段中的作用也将为研究成果转化提供支持。 而AMPK与包括放疗及化疗在内的肿瘤全身治疗的相互作用机制尚需要进一步探讨, 进而开发出个体化、高效、特异的肿瘤综合治疗方案。

3 AMPK在转化医学中的展望

转化医学的发展使传统的研究方式朝着多学科、多领域、多系统的方向迈进, 基础研究和临床研究的界限越来越模糊。这不仅更新了对原有疾病的认识, 而且使得最新的基础研究成果可以尽快地转化运用于临床实践。当前医学正在朝着个体化医疗(personalised medicine)的方向发展, 而转化医学正是个体化医疗的基石与手段[111]。同样, 对于临床研究及医疗实践来说, 传统的内、外、妇、儿的分科界限也越来越模糊, 未来的医学发展将会是以结合生物化学、分子生物学、生物信息学、基因组学、生理学、病理学、药理学、流行病学、临床医学等多个学科的跨学科、跨专业、跨部门合作的转化医学为主导(图3)。

由于AMPK在细胞代谢活动中的重要调控作用, 使其在临床各个学科中都受到了高度关注, 尤其在心血管疾病、代谢障碍和肿瘤等疾病中的重要性更是不言而喻。 体外实验及临床证据已经证明AMPK在上述疾病中都可以作为治疗靶点, 这就需要在阐明疾病分子病理学的基础上, 开发出能够在

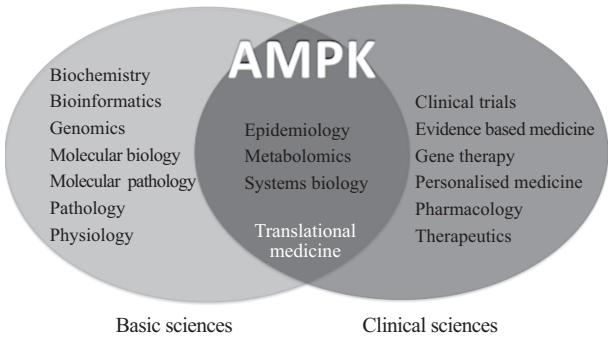


图3 AMPK在转化医学多学科中的意义

Fig.3 Implication of AMPK in multidiscipline of translational medicine

靶组织中激活或抑制AMPK活性的高选择性、高特异性药物, 并应用于临床, 从而达到基础研究向临床治疗的转化。必须指出的是, 上述研究与应用并不是相互独立的, 而是彼此联系、相互支撑的。在治疗阶段还应该根据疾病和/或病人状态的不同而选择不同的治疗方案, 并根据治疗目标选择单用或联用其它药物, 从而实现个体化医疗。特别需要指出的是, 多部门、跨学科的合作在实现研究成果向临床实践快速、有效的转化中将起到举足轻重的作用。

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