

综述

乳酸化修饰在疾病中的作用及机制研究进展

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[摘要] 乳酸是细胞呼吸的产物。葡萄糖进入细胞后, 在己糖激酶等的催化作用下通过糖酵解代谢成丙酮酸。当细胞氧供充足时, 丙酮酸通过线粒体基质中的丙酮酸脱氢酶转化为乙酰辅酶A参与三羧酸循环, 为细胞提供必需的能量。当细胞缺氧时, 丙酮酸由胞质中的乳酸脱氢酶催化生成乳酸。乳酸不仅为线粒体呼吸提供能量源, 还通过自分泌、旁分泌和内分泌等形式在炎症反应、创伤修复、记忆形成和神经保护以及肿瘤生长和转移等病理生理过程中发挥重要作用, 影响疾病发展和预后。表观遗传修饰是通过修饰酶共价添加或水解组蛋白和DNA结构中的功能基团以调节基因复制、转录和翻译等过程, 影响细胞生物学效应。组蛋白是真核生物染色体的基本结构蛋白, 其翻译后修饰诸如甲基化、乙酰化等影响其与DNA双链的亲合性, 改变染色质结构, 广泛参与基因的表达调控。最新研究发现组蛋白上可以发生乳酸化修饰, 即通过对组蛋白上的赖氨酸残基添加乳酸基团, 使其作为一种全新的表观遗传修饰发挥作用。随着研究的深入, 乳酸化修饰也被证明广泛发生在非组蛋白上。乳酸化修饰的发现扩大了对乳酸参与疾病病理机制的认识。该文主要综述了乳酸化修饰在肿瘤、炎症疾病和神经系统疾病中的作用和机制, 以期对相关疾病的研究与诊疗提供新思路。

[关键词] 乳酸; 乳酸化修饰; 肿瘤; 炎症疾病; 神经系统疾病

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Research progress in the role and mechanism of lactylation in diseases

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[Abstract] Lactic acid is a product of cell respiration. After entering into cells, glucose is metabolized to pyruvate by glycolysis. When the oxygen supply is sufficient, pyruvate is converted to acetyl coenzyme A through pyruvate dehydrogenase in the mitochondrial matrix to participate in the tricarboxylic acid cycle and provide necessary energy for cells. Pyruvate is catalysed by lactate dehydrogenase in the cytoplasm to produce lactate while cells are grown under hypoxic conditions. Lactate not only provides energy for mitochondrial respiration, but also plays important roles in inflammatory responder, wound repair, memory formation and neuroprotection as well as tumor growth and metastasis and other pathophysiological processes through autocrine, paracrine, and endocrine forms, which affects the development and prognosis of diseases. Epigenetic modification regulates gene replication, transcription and translation by covalently adding or hydrolyzing functional groups on histones and DNA through related enzymes and affects the biological effects of cells. Histones are the major structural proteins of eukaryotic chromosomes. Their post-translational modifications, such as methylation and acetylation, affect their affinity with DNA, change chromatin structures, and are widely involved in regulation of gene expression. Recent studies have found that histones can undergo lactylation, which is a new epigenetic modification by adding lactate to lysine residues on histones. As the research deepens, numerous evidences reveal that lactylation also occurs on non-histone proteins. The discovery of lactylation has expanded our understanding of lactate functions in the pathogenesis of diseases. In this review, we summarize the roles and mechanisms of lactylation in tumor, inflammatory and neural system diseases, in order to provide new ideas for the research, diagnosis and treatment of these diseases.

[Key words] lactic acid; lactylation; tumor; inflammatory disease; neural system disease

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糖代谢是细胞内能量代谢的最主要方式,乳酸是细胞无氧糖酵解的代谢产物。葡萄糖进入细胞后,在己糖激酶等的催化作用下通过糖酵解代谢成丙酮酸。丙酮酸既可以进入线粒体参与三羧酸循环和氧化磷酸化,亦可在无氧条件下由乳酸脱氢酶催化产生乳酸。乳酸通常以3种异构体形式存在,即L-乳酸、D-乳酸及外消旋体DL-乳酸^[1]。其中,L-乳酸是大多数哺乳动物糖酵解的主要代谢产物,在肿瘤、脓毒症及自身免疫性疾病中发挥重要作用^[2]。20世纪初,德国生物化学家在肝癌细胞观察到其糖酵解活性比正常肝细胞活跃,进而提出瓦博格效应,即肝癌细胞在有氧的条件下表现为高摄取葡萄糖,糖酵解活跃,从而使肿瘤微环境(tumor microenvironment, TME)中乳酸含量显著增高^[3]。科学家后续发现瓦博格效应也存在于免疫细胞中,即当免疫细胞受到外界刺激时,其代谢就会向有氧糖酵解转变。真核生物染色体由DNA和组蛋白构成,组蛋白通过胞内修饰酶添加甲基、乙酰基等基团,影响基因表达、DNA复制和修复等过程。最近研究^[4]发现组蛋白的一种新的翻译后修饰——乳酰化修饰,即组蛋白的赖氨酸残基上被添加了一个乳酸基团,是糖酵解开关键的表现遗传学标记^[5]。乳酰化的发现表明乳酸对细胞功能具有多重影响,扩大了人们对乳酸及相关疾病机制的认识。本文对乳酰化修饰与相关疾病的关系进行综述。

1 乳酰化与肿瘤

在TME中,乳酸呈高水平状态,胞外酸性环境可促进癌细胞增殖特性。不同部位的肿瘤中乳酸浓度水平与肿瘤转移皆具有强相关性,即乳酸浓度越高,肿瘤越倾向于转移,患者总生存期和无病生存期越短^[6]。乳酸通过作用于多种免疫细胞,使TME处于免疫抑制状态,以利于肿瘤细胞增殖和转移。例如,肿瘤相关巨噬细胞表面CD206、CD301和CD163等抑制免疫型M2样巨噬细胞标志物表达增加,使癌细胞更容易黏附、侵袭和迁移;抑制糖酵解可降低上述抑制免疫型M2样巨噬细胞标志物表达^[7]。外源给以抑制性自然杀伤T细胞乳酸,其过氧化物酶增殖物激活受体 γ 2(peroxisome proliferator activated receptor- γ 2, PPAR γ 2)表达显著降低,导致胆固醇合成和 γ 干扰素(interferon- γ , IFN- γ)产生均降低^[8]。乳酸

通过作用于树突状细胞表面G蛋白偶联受体81(G-protein coupled receptor 81, GPR81),减弱IFN- α 的产生^[9]。缺乏GPR81的树突状细胞高表达白介素-12(interleukin-12, IL-12)和IL-6,以及恢复产生IFN- α 的能力^[10]。由于乳酸在肿瘤中的重要作用,乳酰化修饰在肿瘤中的作用也备受学者关注。

1.1 乳酰化与结肠癌

甲基转移酶3(methyltransferase-like protein 3, METTL3)在结肠癌小鼠肿瘤浸润髓样细胞中表达上调,并与肿瘤进展呈正相关,条件敲除Mettl3基因后,具有抗肿瘤功能的免疫细胞数量明显增加;进一步研究发现,Mettl3启动子区域的组蛋白H3K18发生乳酰化修饰,致使METTL3表达增加;同时METTL3自身的锌指结构域也发生乳酰化,使编码JAK1的mRNA m⁶A甲基化修饰增加,激活JAK1-STAT3通路,启动下游免疫抑制分子的表达,有利于肿瘤细胞逃逸^[11]。根据癌症基因组图谱(The Cancer Genome Atlas, TCGA)分析,结肠腺癌患者结肠组织中前蛋白转化酶枯草溶菌素转化酶9(proprotein convertase subtilisin/kexin 9, PCSK9)表达水平明显高于正常组织,且与肿瘤病理分级密切相关;体外敲低HT29和HCT116细胞中PCSK9基因后,结肠癌细胞生存、迁移和侵袭能力均降低;同时,其上清中乳酸浓度降低,胞内蛋白泛乳酰化水平降低,所以研究者推测PCSK9可能通过调节胞内蛋白乳酰化水平调节癌细胞生存、迁移和侵袭^[12]。因此,乳酰化可能促进结肠癌的发生发展。

1.2 乳酰化与前列腺癌

较健康人群而言,前列腺癌患者的前列腺细胞中KIAA1199表达显著增加,与缺氧诱导因子-1 α (hypoxia inducible factor-1 α , HIF-1 α)、血管内皮生长因子A(vascular endothelial growth factor A, VEGFA)和CD34的表达呈正相关^[13];常氧条件下,用乳酸处理PC3和DU145细胞,HIF-1 α 显著乳酰化,同时毛细血管样结构形成增加,且上述现象可通过沉默单羧酸转运蛋白1(monocarboxylate transporter 1, MCT1)来逆转。因此,在常氧条件下,MCT1可介导HIF-1 α 发生乳酰化修饰,引发KIAA1199的促血管生成作用,促进前列腺癌细胞的扩散。

1.3 乳酰化与胃癌

研究^[14]显示,用质谱法对AGS细胞中乳酰化蛋白进行筛选,在1 014种蛋白质中发现2 375个乳酰化位点。此外,与邻近健康组织相比,胃肿瘤组织中乳酰化水平更丰富,使用TNM分期和Kaplan-Meier分析结果说明高水平的乳酰化与胃肿瘤预后不良相关。因此,乳酰化可能是胃癌不良预后的一个标志。

2 乳酰化与炎症疾病

2.1 乳酰化与脓毒症

脓毒症是机体遭受病原体感染所发生的炎症级联放大反应,可进展为机体多器官功能衰竭甚至死亡;血清中乳酸升高与脓症患者死亡率增加具有显著相关性^[15]。在脓毒症初期,为抵抗病原微生物及毒素入侵,体内将产生高水平炎症反应,而过度炎症会损害自身组织;乳酸可通过抑制炎症因子的产生缓解自身组织损伤;但脓毒症晚期,因免疫系统过度消耗使机体呈免疫抑制状态,乳酸的此种作用可能会损害机体^[16]。乳酸通过小鼠巨噬细胞表面GPR81介导的信号抑制促炎因子的表达,并诱导巨噬细胞向M2型极化^[17]。此外,乳酸钠处理可抑制脓毒症大鼠模型血清中IL-1 β 等促炎因子产生,改善脓毒症微循环障碍以及心脏和肾脏损伤^[18]。因此,乳酸在脓毒症中发挥了抑制促炎因子产生的作用。高迁移率族蛋白B1(high mobility group box-1 protein, HMGB1)是一种高度保守且普遍存在的蛋白质,在脓毒症后期高表达并影响脓毒症的发展和预后^[19]。与脓毒症对照小鼠相比,给予乳酸的脓毒症小鼠血清中乳酸水平和HMGB1水平显著升高,而存活率则显著降低;抑制乳酸生成可逆转上述现象,表明乳酸与脓毒症血清中HMGB1水平以及死亡率密切相关^[20];该研究还显示,给予巨噬细胞乳酸可促进HMGB1胞质转移、溶酶体定位和外泌体形式释放;进一步研究证实,乳酸可通过乙酰化酶P300/CBP使HMGB1发生乳酰化;同时,乳酸可通过激活大肿瘤抑制激酶1(large tumor suppressor kinase 1, LATS1)介导Yes相关蛋白(Yes associated protein, YAP)磷酸化和降解,抑制YAP依赖的沉默调节蛋白1(sirtuin 1, SIRT1)的表达和核转位,使HMGB1乙酰化水平显著增加。一项临床前瞻性研究^[21]显示,在健康志愿者和危重患

者的外周血单核细胞中均检测到乳酰化,而休克患者乳酰化水平较高。H3K18乳酰化表达与急性生理与慢性健康评估(acute physiology and chronic health evaluation, APACHE II)评分、第1天序贯器官衰竭估计(Sequential Organ Failure Assessment, SOFA)评分、ICU住院时间、机械通气时间和血清乳酸水平呈正相关;与非脓毒症休克患者相比,脓毒症休克患者H3K18乳酰化水平更高,表明H3K18乳酰化可能反映危重症的严重程度。因此,乳酰化在脓毒症后期可能是有害因素。

2.2 乳酰化与结肠炎

中度和重度溃疡性结肠炎患者结肠黏膜细胞因炎症而产生大量乳酸,导致粪便pH值较低^[22]。给予乳酸处理的结肠炎小鼠血清中IL-6水平产生减少,组织炎症状况缓解^[23]。敲除*Gpr81*会增加小鼠肠道树突状细胞和巨噬细胞的炎症因子生成,并加剧结肠炎症^[24]。说明乳酸在溃疡性结肠炎中通过GPR81进入细胞起到抑制炎症因子分泌、缓解结肠炎病情作用。在右旋糖酐硫酸钠诱导的结肠炎中,野生型小鼠骨髓源性巨噬细胞比B细胞受体关联蛋白(B-cell receptor-associated protein, *Bcap*)基因缺陷小鼠产生更多的乳酸;缺乏*Bcap*会阻碍叉头框蛋白O1(forkhead box protein O1, FOXO1)和糖原合成酶激酶-3 β (glycogen synthase kinase-3 β , GSK-3 β)的失活,有助于*Bcap*缺陷小鼠持续增强炎症状态,导致小鼠组织修复受损和长期肠道炎症;外源添加乳酸可逆转*Bcap*缺陷,且对照骨髓源性巨噬细胞组蛋白的乳酰化水平增强并向修复表型转变^[25]。最新研究^[26]发现,乳酸可通过降低致病性辅助性T细胞17(T helper cell 17, Th17)淋巴细胞数量改善结肠炎病程;乳酸钠导致极化的Th17细胞编码促进调节性T细胞(regulatory cells, Tregs)表型发育和功能的主要转录因子叉头框P3(forkhead box P3, FOXP3)表达上调,细胞致病性所需的基因显著下调,使致病性Th17细胞向Tregs表型转变;进一步研究发现,乳酸处理的CD4⁺T淋巴细胞中H3K18乳酰化增加,且*Foxp3*近端启动子区H3K18乳酰化富集。因此,乳酸促进Th17细胞*Foxp3*启动子区H3K18乳酰化增加,使细胞表型向Tregs转变,从而降低致病性Th17细胞数量,改善结肠炎病情。

3 乳酰化与神经系统疾病

星形胶质细胞产生的乳酸可为神经元提供燃料,也可通过激活神经元表面乳酸受体传递胞外信号。多项临床研究^[27-28]表明,神经系统疾病患者脑组织中乳酸含量较健康人高。因此,乳酸水平变化与神经系统疾病密切相关。

3.1 乳酰化与阿尔茨海默病

研究^[29]发现,在阿尔茨海默病小鼠脑内A β 斑块处,M2型丙酮酸激酶(pyruvate kinase M2, PKM2)表达增加,使糖酵解产生乳酸增加,增加的乳酸进一步使处于糖酵解相关基因启动子附近的组蛋白H4K12乳酰化增加,进而促进了糖酵解过程。这种正反馈环路使小胶质细胞代谢和功能紊乱,影响神经元的功能,导致认知能力下降;通过阻断PKM2阻断该循环会降低H4K12乳酰化水平,抑制糖酵解基因转录,降低乳酸水平,缓解认知能力减弱。因此,组蛋白H4K12的乳酰化促进阿尔茨海默病的进展。

3.2 乳酰化与抑郁症

在慢性应激诱导的抑郁症小鼠模型^[30]中,外周给予乳酸可增加大脑乳酸水平,减少焦虑和抑郁样行为。在挫败应激抑郁模型的小鼠前额叶皮质中,乳酸和乳酰化水平都显著增加,且与焦虑程度呈正相关;进一步质谱鉴定结果显示,小鼠前额叶皮质中有63种蛋白的赖氨酸发生乳酰化,且主要富集在核小体中^[31]。在抑郁症等精神类疾病中,乳酰化可能促进疾病的发生发展。

4 乳酰化与其他疾病

4.1 乳酰化与肺纤维化

肺纤维化是间质性肺疾病典型病理特征,非重复性损伤修复过程导致正常的肺部结构破坏,肺部瘢痕,最终器官衰竭^[32]。肺肌成纤维细胞代谢紊乱和肺泡巨噬细胞粗纤维化表型在肺纤维化的病理进展中起主要作用^[33]。肺肌成纤维细胞有氧糖酵解增强,使肺组织乳酸含量显著增加^[34]。研究^[35]发现,乳酸可促进未成熟肺泡巨噬细胞中促纤维化

介质的表达,对乳酸处理的小鼠肺泡巨噬细胞进行染色质免疫沉淀技术(chromatin immunoprecipitation, CHIP)分析显示,修复基因如精氨酸酶1(arginase 1, *Arg1*)、血小板衍生生长因子(platelet-derived growth factor, *Pdgf*)、血小板反应蛋白1(thrombospondin 1, *Thbs1*)和血管内皮生长因子(vascular endothelial growth factor, *Vegf*)启动子近端区域的组蛋白乳酰化显著增加;该研究还证明P300介导组蛋白乳酰化和促纤维化基因的表达,若敲低巨噬细胞中的P300,组蛋白乳酰化水平及促纤维化基因表达则降低。因此,乳酰化促进促纤维化基因的表达,对肺纤维化的发展和预后会产生不良影响。

4.2 乳酰化与寄生虫病

有研究^[36]报道,在弓形虫的955种蛋白质上鉴定出1964个乳酰化位点,分布在多个亚细胞区室中,其中组蛋白H4K12乳酰化和H3K14乳酰化富集在与基于运动和细胞侵袭相关的微管蛋白基因的启动子和外显子区域中。此外,组蛋白乳酰化也存在于疟原虫中,它可能是疟原虫表观遗传库的关键参与者^[37]。因此,乳酰化也可能会参与这些寄生虫对机体的感染,更多的细节还有待于进一步研究。

5 乳酰转移酶和去乳酰化酶

与其他蛋白翻译后修饰类似,乳酰化是一种酶促反应,需要相应的乳酰转移酶和去乳酰化酶催化。研究发现,L-乳酸形成相应的乳酰辅酶A,为乳酰化提供乳酸基团,使组蛋白发生乳酰化^[4]。体外研究^[38]证明,去乙酰化酶家族成员HDAC1~3和SIRT1~3是赖氨酸去乳酰化酶,其中HDAC3的去乳酰化能力最强。在小鼠心梗模型单核细胞中的最新研究^[39]发现,组蛋白乙酰转移酶GCN5可作为乳酰转移酶发挥作用。此外,有研究^[40]在大肠埃希菌中鉴定出YiaC作为乳酰转移酶,CobB作为去乳酰化酶,调控细菌的乳酰化网,进而调节细菌代谢和生长。尽管乳酰化相关修饰酶的鉴定取得了一定进展,但组蛋白的乳酰基如何转移以及对基因表达的影响,包括非组蛋白的乳酰化及其作用机制依然不够清楚,仍需大量研究探索。

6 总结与展望

细胞应对环境刺激时做出适应性改变, 如癌细胞改变糖代谢方向, 促进葡萄糖摄取和分解, 以满足细胞对能量和生物合成的快速需求。由于酶或代谢产物的移位, 许多代谢产物可作为染色质修饰酶的底物或辅因子发挥表观遗传修饰作用。作为糖酵解产物, 乳酸可在相关修饰酶的催化作用下使组蛋白和非组蛋白发生乙酰化修饰。乙酰化在促进肿瘤进展、脓毒症不良预后、加重神经系统疾病和肺纤维化中起重要作用, 但其对结肠炎可能起到有益作用。此外, 乙酰化也存在于寄生虫中并可能参与其对机体的感染。除上述描述的与乙酰化相关的疾病外, 在其他有乳酸增加的疾病中是否存在乙酰化需要进一步研究。糖酵解产生的乙酰辅酶A和三羧酸循环产生的乙酰辅酶A的水平协同决定细胞命运, 并在不同细胞和种属中对多种蛋白进行修饰, 相关修饰的作用、修饰酶的鉴定以及乙酰化和乙酰化等

翻译后修饰的关系仍不十分清楚。目前非组蛋白的乙酰化研究较少, 值得更多关注。深入探索组蛋白和非组蛋白的乙酰化修饰及其生物学效应将扩大我们对乳酸及相关疾病治疗的视野。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

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