

doi: 10.13241/j.cnki.pmb.2019.14.016

苹果酸 - 天冬氨酸穿梭关键酶和肺腺癌临床特征的相关性 *

辛向兵¹ 熊延路¹ 思 越² 潘明宏^{1,2} 石明延^{1,2} 卢 强¹ 李小飞¹ 韩 勇^{1Δ}

(1 空军军医大学唐都医院胸外科 陕西 西安 710038; 2 空军军医大学基础医学院学员队 陕西 西安 710032)

摘要 目的:探讨苹果酸 - 天冬氨酸穿梭途径中的关键酶和肺腺癌临床特征的相关性。**方法:**首先从 GEO 数据库、TCGA 平台中获取肺腺癌的转录组数据和相应的临床信息, 通过非参数检验分析苹果酸脱氢酶 1/2 和天冬氨酸氨基转移酶 1/2 这四种关键酶在肿瘤组织和正常组织之间的表达差别, 再进一步分析其与肺腺癌患者总生存期、人口学特征、TNM 参数以及肿瘤恶性生物学标志物之间的关系。**结果:**肺腺癌中苹果酸脱氢酶 1/2 和天冬氨酸氨基转移酶 1/2 均呈高表达; 天冬氨酸氨基转移酶 2 (Glutamic-oxaloacetic transaminase 2, GOT2) 和肺腺癌的生存概率有关, 高表达 GOT2 的病人往往具有较短的总生存期; GOT2 的表达和肺腺癌的人口学特征、TNM 参数、临床分期均无明显统计学关联, 与肿瘤恶性标志物 PCNA 呈显著正相关($r=0.2, P<0.05$)。**结论:**肺腺癌组织中苹果酸 - 天冬氨酸穿梭途径中关键酶 GOT2 呈高表达, 并可能促进肺腺癌的发生和恶性进展。

关键词:有氧糖酵解; 苹果酸 - 天冬氨酸穿梭; 肺腺癌; 生存分析; 天冬氨酸氨基转移酶 2

中图分类号: R734.2 文献标识码: A 文章编号: 1673-6273(2019)14-2683-04

Association between the Key Enzymes in Malate-aspartic Acid Shuttle and Clinical Features of Lung Adenocarcinoma*

XIN Xiang-bing¹, XIONG Yan-lu¹, SI Yue², PAN Ming-hong^{1,2}, SHI Ming-yan^{1,2}, LU Qiang¹, LI Xiao-fei¹, HAN Yong^{1Δ}

(1 Department of Thoracic Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, Shaanxi, 710038, China;

2 School of Basic Medicine, Air Force Medical University, Xi'an, Shaanxi, 710032, China)

ABSTRACT Objective: To investigate the correlation between the key enzymes in the malate-aspartate shuttle pathway and clinical features of lung adenocarcinoma. **Methods:** Firstly, the transcriptome data and corresponding clinical information of lung adenocarcinoma were obtained from GEO database and TCGA platform. Then nonparametric analysis was applied to evaluate expression difference of key enzymes (malate dehydrogenase 1/2 and aspartate aminotransferase 1/2) between the tumor tissue and the normal tissue. Furthermore, relationships between enzymes and clinical features like overall survival rate, demographic characteristics, TNM parameters and malignant biomarkers were investigated. **Results:** Malate dehydrogenase 1/2 and aspartate aminotransferase 1/2 were highly expressed in lung adenocarcinoma; Glutamic-oxaloacetic transaminase 2 (GOT2) was tightly correlated to survival probability of lung adenocarcinoma, where patients with high expression of GOT2 tended to have shorter overall survival time; There is no statistically significant association between GOT2 expression and demographic characteristics, TNM parameters, and clinical stage of lung adenocarcinoma; But correlation analysis exhibited positive correlation between GOT2 and the tumor malignant marker PCNA ($r=0.2, P<0.05$). **Conclusion:** GOT2, a key enzyme in the malate-aspartate shuttle pathway, was highly expressed in lung adenocarcinoma and may contribute to the initiation and malignant progression of lung adenocarcinoma.

Key words: Aerobic glycolysis; Malic acid-aspartate shuttle; Lung adenocarcinoma; Survival analysis; Aspartate aminotransferase 2

Chinese Library Classification (CLC): R734.2 **Document code:** A

Article ID: 1673-6273(2019)14-2683-04

前言

肺癌是危害人类健康的头号癌症杀手, 每年全球范围内肺癌致死病例约一百多万, 肺腺癌(Lung adenocarcinoma, LUAD)是肺癌的主要亚型^[1-4]。虽然基于驱动基因的分子靶向治疗在肺腺癌中取得突破性进展^[5], 如表皮生长因子受体(Epidermal growth factor receptor, EGFR)、间变性淋巴瘤激酶(Anaplastic

lymphoma kinase, ALK) 等驱动突变的靶向治疗取得不错的效果, 但是仍然存在严重的耐药现象和不敏感问题, 且临床上还存在着大量缺乏阳性突变的患者^[6-8]。因此, 肺腺癌的致病机理仍需要进一步研究明确。

肿瘤的代谢异常或者代谢重编程与其发生发展密切相关^[9-12]。有氧糖酵解是最典型的肿瘤代谢特点, 即肿瘤细胞即使在氧气充足的条件下也采用糖酵解的方式, 大量摄入葡萄糖,

* 基金项目: 国家自然科学基金项目(81772462)

作者简介: 辛向兵(1979-), 硕士研究生, 主治医师, 主要研究方向: 胸部疾病的基础及临床研究, E-mail: 429392090@qq.com

Δ 通讯作者: 韩勇(1970-), 博士生导师, 教授, 主要研究方向: 胸部疾病的基础及临床研究,

E-mail: hanyong_td@163.com, 电话: 029-84777437

(收稿日期: 2019-01-26 接受日期: 2019-02-21)

生成乳酸^[13,14]。有氧糖酵解为肿瘤细胞的快速增殖提供了大量的生物大分子合成原料,同时也显著影响肿瘤存活、浸润转移等其他恶性生物学特征^[9,13,15]。糖酵解的循环运行依赖于氧化型烟酰胺腺嘌呤二核苷酸 (Nicotinamide adenine dinucleotide, NAD⁺)的不断补充,而真核生物内最主要的补充途径就是苹果酸-天冬氨酸穿梭。苹果酸脱氢酶 1/2 (Malate dehydrogenase1/2,MDH1/2) 和天冬氨酸氨基转移酶 1/2 (Glutamic-oxaloacetic transaminase 1/2,GOT1/2) 是介导该穿梭途径的关键酶。以往的研究显示这些关键酶和胰腺癌、子宫癌以及神经系统肿瘤的恶性进展有关^[16-18],但其在肺癌尤其是肺腺癌中的功能尚缺乏充分的研究。本研究通过 TCGA、GEO 数据库探索了这四种关键酶的表达量,并分析了其和肺腺癌临床病理特征的关联,以期对肺腺癌的临床诊断和治疗提供更多的参考依据。

1 材料与方法

1.1 材料

GEO 数据库和 TCGA 平台提供了肺腺癌的基因表达数据和对应的临床数据。其中,GEO 数据库提供了肺腺癌的基因芯片结果:GSE32863 数据集 (58 例肺腺癌和 58 例正常肺组织),和 GSE10072 数据集 (58 例肺腺癌和 49 例正常肺组织)^[19,20]。TCGA-LUAD 提供了肺腺癌的转录组测序数据,包括用于基因表达量差异分析的 58 例肺组织和 58 例肺腺癌的转录谱以及

用于临床指标统计学分析的具有完整临床资料的 253 例肺腺癌测序结果^[21]。

1.2 统计学分析

全文所需的统计分析和图形绘制均使用 R 语言。采用 wilcoxon 秩和检验分析关键酶 MDH1、MDH2、GOT1、GOT2 在肺腺癌组织和正常组织中的表达差异;随后绘制了这四种酶的表达量和肺腺癌总生存概率的 Kaplan-Meier 生存曲线,并采用 log-rank 检验来进行统计学分析 (依据表达量的中位数为高低表达组);采用卡方检验探讨生存相关酶和人口学特征、TNM 参数、分期等肺腺癌临床特征的关系;Z 分数将测序表达量标准化,并使用 Pearson 积差相关系数分析了生存相关酶和肺腺癌恶性生物学标志物增殖细胞核抗原 (Proliferating cell nuclear antigen,PCNA)、增殖标记 Ki-67(Marker of proliferation Ki-67, MKI67)的关系。以 $P<0.05$ (双侧)为差异具有统计学意义。

2 结果

2.1 肺腺癌中四种关键酶的表达情况

在基因芯片 GSE32863 中,MDH2、GOT1、GOT2 在肺腺癌组织中高表达,而 MDH1 在肺腺癌组织中低表达;在基因芯片 GSE10072 中,MDH1、MDH2、GOT1、GOT2 都在肺腺癌组织中高表达;在 TCGA-LUAD 测序结果中,MDH1、MDH2、GOT1、GOT2 都在肺腺癌组织中高表达。见图 1。

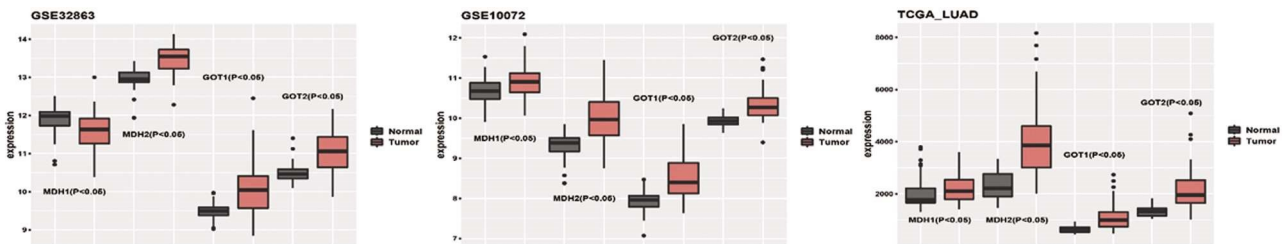


图 1 肺腺癌中四种关键酶的表达情况

Fig.1 Expression of four key enzymes in the lung adenocarcinoma

2.2 肺腺癌中四种关键酶表达量和总生存期的关系

我们使用中位数,分别将这四种酶分为高低表达两组人群,然后绘制了 Kaplan-Meier 生存概率曲线并使用 log-rank 检验比较差异。结果显示 MDH1、MDH2、GOT1 的表达都和肺腺

癌患者的总生存期无关,而 GOT2 的表达量和肺腺癌患者的总生存期明显相关,高表达 GOT2 的肺腺癌患者的具有较差的预后。见图 2。

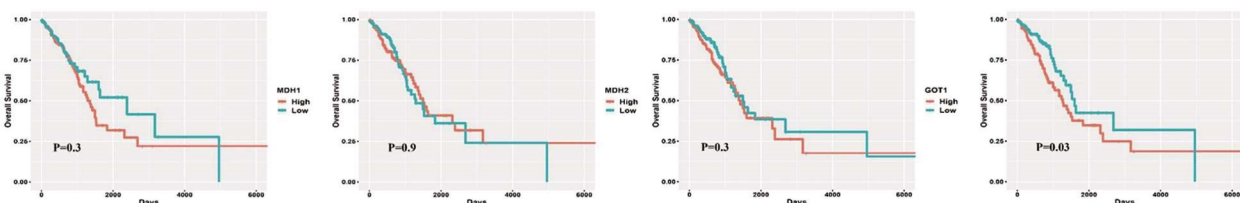


图 2 四种关键酶表达量和肺腺癌总生存期的关系

Fig.2 Relationship between expression of four key enzymes and overall survival of lung adenocarcinoma

2.3 GOT2 的表达和肺腺癌临床病理特征的相关性

采用卡方检验进一步分析 GOT2 的表达和肺腺癌患者年龄、性别、TNM 参数以及临床分期的关系,结果见表 1。GOT2 的表达和肺腺癌患者年龄、性别、TNM 参数、淋巴结转移、远处转移以及临床分期均无显著相关性($P>0.05$)。

2.4 GOT2 的表达和肺腺癌恶性标志物表达的关系

MKI67 和 PCNA 都是肺腺癌恶性增殖的重要标志物。我们分析了 GOT2 和这二者的相关性,结果显示 GOT2 的表达和 MKI67 无明显相关性,而和 PCNA 的表达呈显著正相关($r=0.2, P<0.05$),见图 3。

表 1 GOT2 表达和肺腺癌临床病理特征的关系

Table 1 Correlation between GOT2 expression and clinicopathological characteristics of LUAD

Variables	Case(n=253)	GOT2 expression		P value
		High(n=126)	Low(n=127)	
Age (years)				1
>66	125	62	63	
≤ 66	128	64	64	
Gender				0.29
male	121	65	56	
female	132	61	71	
Tumor size				0.98
T12	226	112	114	
T34	27	14	13	
Lymph node metastasis				0.06
No	162	73	89	
Yes	91	53	38	
Distant metastasis				0.58
No	240	121	119	
Yes	13	5	8	
Stage				0.27
I - II	199	95	104	
III-IV	54	31	23	

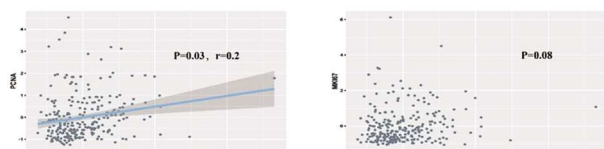


图 3 GOT2 和肺腺癌恶性标志物的相关关系

Fig.3 Correlation between GOT2 and malignant markers of lung adenocarcinoma

3 讨论

有氧糖酵解可以为肿瘤细胞的生物大分子合成提供充足原料,如糖酵解衍生的磷酸戊糖途径为脂质等物质合成提供 NADPH,并且磷酸戊糖途径还为核苷酸的合成提供了碳骨架^[22];糖酵解的中间产物如 3-磷酸甘油醛可以转化为甘油,进而运用于脂质的合成,而 3-磷酸甘油醛则可以转化为丝氨酸,进一步通过一碳单位的构建,运用于核苷酸的合成^[23-25]。有氧糖酵解是包括肺腺癌在内的恶性肿瘤的重要特点,和肿瘤迁移浸润密切相关,糖酵解造成肿瘤微环境的酸化,促进了肿瘤细胞的浸润和迁移,可能的分子机制涉及到金属蛋白酶对细胞外基质的降解^[12]。此外,有氧糖酵解产生的酸性环境可以上调血管内皮生长因子(Vascular endothelial growth factor, VEGF),促进新生血管生成、肿瘤细胞的播散和定殖^[12]。近年来,研究表明有氧糖酵解产生的大量乳酸可以抑制 NK 细胞和 T 细胞的功能,从而促进肿瘤的免疫逃逸^[26]。肺腺癌是常见的恶性肿瘤,同样也具有有氧糖酵解的特点,而且临床上应用这个特点的 PET-CT

为肺癌的诊断提供很多帮助。

一系列代谢途径的重要蛋白是有氧糖酵解的关键。这些蛋白主要包括代谢途径的关键酶和转运体,肿瘤也通过调控这些关键分子的含量和活性来促进有氧糖酵解的高效进行^[9,10]。例如,肿瘤细胞可以通过激活蛋白激酶 B (Protein kinase B, PKB/Akt)通路上调葡萄糖转运蛋白 1(Glucose transporter Type 1, GLUT1) 的 mRNA 含量以及促进 GLUT1 的细胞膜定位,进而促进肿瘤细胞对葡萄糖的大量摄入^[9]。而且活化的 Akt 通路还可以激活己糖激酶 (Hexokinase, HK) 和磷酸果糖激酶 (Phosphofructokinase, PFK),HK2 和 PFK 都是糖酵解进程的关键酶,进而加速了糖酵解进程^[10]。再者,肿瘤细胞内活跃的癌蛋白 C-myc、缺氧诱导因子(Hypoxia-inducible factor-1, HIF-1)等转录因子可以上调乳酸脱氢酶 A (Lactate dehydrogenase A, LDHA),而 LDHA 则介导了丙酮酸向乳酸的转化^[27]。在许多肿瘤的研究中,干扰这些关键分子也能起到较好的肿瘤的抑制效果,其中一些如 LDHA 也作为分子抑制剂的靶点,开展了一系列抗肿瘤的临床试验^[28]。

有氧糖酵解的持续运行需要 NAD⁺ 的不断补充,而苹果酸-天冬氨酸穿梭途径则是真核细胞内主要的 NAD⁺ 补充代谢活动。其中,MDH 和 GOT 是该穿梭途径的关键酶。线粒体内的苹果酸在 MDH 作用下生成草酰乙酸,而将 NAD⁺ 转化为 NADH,接着草酰乙酸和谷氨酸在 GOT 的作用下,转化为天冬氨酸和 α -酮戊二酸。天冬氨酸和 α -酮戊二酸在转运蛋白的作用下,由线粒体转运到细胞质中,在细胞质的 GOT 和 MDH 的

作用下再转化为苹果酸, NADH 也转化为 NAD⁺, 进而提供有氧糖酵解进程的重要辅酶。MDH 和 GOT 在机体内各存在两种亚型: MDH1、GOT1 存在于细胞质中, MDH2、GOT2 存在于线粒体中。多项研究表明这些关键酶和肿瘤的恶性进展密切相关, 如子宫癌中高表达的 MDH2 可以介导阿霉素抵抗, 机制可能涉及促进肿瘤细胞对化疗药物的泵出, 而在前列腺癌中敲低 MDH2, 则促进多西他赛对肿瘤的杀伤, 分子机制涉及 JNK 通路^[17,20]。胰腺癌中, 高表达的 GOT1 则促进了肿瘤细胞在酸性条件下的存活, 而乙酰化修饰介导的 GOT2 的活性增强, 促进了胰腺癌细胞的增殖^[16,30]。

然而, 苹果酸 - 天冬氨酸穿梭及途径中的关键酶在肺腺癌中的作用尚缺乏充分的研究, 我们对 MDH1/2、GOT1/2 在肺腺癌中的表达情况以及和肺腺癌预后等临床特征的关系进行了研究, 结果显示苹果酸 - 天冬氨酸途径中的四种关键酶大部分都在肺腺癌中高表达, 提示苹果酸 - 天冬氨酸途径可能在肺腺癌中是活跃的, 这些酶可能扮演癌基因的作用。进一步分析其与肺腺癌临床特征的关联, 我们发现只有 GOT2 和生存显著相关, 高表达 GOT2 的病人具有较差的预后, 这提示 GOT2 可能和肺腺癌的恶性进展关系更大。此外, GOT2 和 PCNA 具有正相关关系, 而 PCNA 是肿瘤恶性增殖的指标, 提示 GOT2 可能在肺腺癌恶性进展中扮演促进角色。但是在其他临床参数包括 TNM 参数、肿瘤分期乃至 MKI67 关系的研究中, 我们并没有发现 GOT2 显著的统计学结果, 可能和肿瘤的广泛异质性以及样本量尚不够充分有关。

本研究也存在一定的缺陷, 首先如上述所指, 样本量需要进一步扩大, 从而使得样本代表性更强, 一定程度上应对肺腺癌的广泛异质性; 再者, 我们缺乏体外细胞实验验证, 和分子机制的深入探讨; 最后, 我们还需要体内的动物学实验验证 GOT2 对肺腺癌的影响。下一步我们将针对这些问题继续深入研究。

综上所述, 本研究探索了苹果酸 - 天冬氨酸穿梭途径中四种关键酶和肺腺癌临床特征的关联, 结果表明 GOT2 可能通过影响有氧糖酵解促进肺腺癌的发生发展, 其具体机制尚有待于进一步的研究证实。

参考文献(References)

- [1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012[J]. CA Cancer J Clin, 2015, 65(2): 87-108
- [2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019 [J]. CA Cancer J Clin, 2019[Epub ahead of print]
- [3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018 [J]. CA Cancer J Clin, 2018, 68(1): 7-30
- [4] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer[J]. Nature, 2018, 553(7689): 446-454
- [5] Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments [J]. Lancet, 2017, 389(10066): 299-311
- [6] Metro G. EGFR targeted therapy for lung cancer: are we almost there? [J]. Transl Lung Cancer Res, 2018, 7(Suppl 2): S142-S145
- [7] Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer [J]. N Engl J Med, 2017, 377 (9): 849-861

- [8] Thomas A, Liu SV, Subramaniam DS, et al. Refining the treatment of NSCLC according to histological and molecular subtypes[J]. Nat Rev Clin Oncol, 2015, 12(9): 511-526
- [9] Vander Heiden MG, DeBerardinis RJ. Understanding the Intersections between Metabolism and Cancer Biology [J]. Cell, 2017, 168 (4): 657-669
- [10] Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism[J]. Cell Metab, 2016, 23(1): 27-47
- [11] Martinez-Outschoorn UE, Peiris-Pages M, Pestell RG, et al. Cancer metabolism: a therapeutic perspective [J]. Nat Rev Clin Oncol, 2017, 14(1): 11-31
- [12] Lehuede C, Dupuy F, Rabinovitch R, et al. Metabolic Plasticity as a Determinant of Tumor Growth and Metastasis [J]. Cancer Res, 2016, 76(18): 5201-5208
- [13] Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? [J]. Nat Rev Cancer, 2016, 16 (10): 635-649
- [14] Warburg O. On the origin of cancer cells [J]. Science, 1956, 123 (3191): 309-314
- [15] Dang CV. Links between metabolism and cancer [J]. Genes Dev, 2012, 26(9): 877-890
- [16] Yang H, Zhou L, Shi Q, et al. SIRT3-dependent GOT2 acetylation status affects the malate-aspartate NADH shuttle activity and pancreatic tumor growth[J]. Embo j, 2015, 34(8): 1110-1125
- [17] Lo YW, Lin ST, Chang SJ, et al. Mitochondrial proteomics with siRNA knockdown to reveal ACAT1 and MDH2 in the development of doxorubicin-resistant uterine cancer[J]. J Cell Mol Med, 2015, 19(4): 744-759
- [18] Cascon A, Comino-Mendez I, Curras-Freixes M, et al. Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene[J]. J Natl Cancer Inst, 2015, 107(5)
- [19] Selamat SA, Chung BS, Girard L, et al. Genome-scale analysis of DNA methylation in lung adenocarcinoma and integration with mRNA expression[J]. Genome Res, 2012, 22(7): 1197-1211
- [20] Landi MT, Dracheva T, Rotunno M, et al. Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival[J]. PLoS One, 2008, 3(2): e1651
- [21] Weinstein JN, Collisson EA, Mills GB, et al. The Cancer Genome Atlas Pan-Cancer analysis project [J]. Nat Genet, 2013, 45 (10): 1113-1120
- [22] Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism[J]. Cell, 2012, 149(3): 656-670
- [23] Santos CR, Schulze A. Lipid metabolism in cancer [J]. Febs j, 2012, 279(15): 2610-2623
- [24] Ye J, Mancuso A, Tong X, et al. Pyruvate kinase M2 promotes de novo serine synthesis to sustain mTORC1 activity and cell proliferation [J]. Proc Natl Acad Sci U S A, 2012, 109(18): 6904-6909
- [25] Xiong Y, Wang L, Feng Y, et al. Flexibility in metabolism bestows tenacious viability on cancer[J]. Life Sci, 2018, 208: 20-25
- [26] Brand A, Singer K, Koehl GE, et al. LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells[J]. Cell Metab, 2016, 24(5): 657-671

- [14] Yamaguchi M, Uemura H, Arisawa K, et al. Association between brain-muscle-ARNT-like protein-2 (BMAL2) gene polymorphism and type 2 diabetes mellitus in obese Japanese individuals: A cross-sectional analysis of the Japan Multi-institutional Collaborative Cohort Study [J]. Diabetes research and clinical practice, 2015, 110 (3): 301-308
- [15] Crnko S, Cour M, Van Laake L W, et al. Vasculature on the clock: Circadian rhythm and vascular dysfunction[J]. Vascular pharmacology, 2018, 108: 1-7
- [16] Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm [J]. The journal of physiological sciences: JPS, 2018, 68(3): 207-219
- [17] Caba M, Gonzalez-Mariscal G, Meza E. Circadian Rhythms and Clock Genes in Reproduction: Insights From Behavior and the Female Rabbit's Brain[J]. Frontiers in endocrinology, 2018, 9: 106
- [18] Ishii T, Warabi E, Mann G E. Circadian control of p75 neurotrophin receptor leads to alternate activation of Nrf2 and c-Rel to reset energy metabolism in astrocytes via brain-derived neurotrophic factor [J]. Free radical biology & medicine, 2018, 119: 34-44
- [19] Kalsbeek A, La Fleur S, Fliers E. Circadian control of glucose metabolism[J]. Molecular metabolism, 2014, 3(4): 372-383
- [20] Sundar I K, Yao H, Sellix M T, et al. Circadian molecular clock in lung pathophysiology[J]. American journal of physiology Lung cellular and molecular physiology, 2015, 309(10): L1056-1075
- [21] Xiong H, Yang Y, Yang K, et al. Loss of the clock gene PER2 is associated with cancer development and altered expression of important tumor-related genes in oral cancer [J]. International journal of oncology, 2018, 52(1): 279-287
- [22] Mteyrek A, Filipski E, Guettier C, et al. Clock gene Per2 as a controller of liver carcinogenesis [J]. Oncotarget, 2016, 7 (52): 85832-85847
- [23] Mazzocchi G, Panza A, Valvano M R, et al. Clock gene expression levels and relationship with clinical and pathological features in colorectal cancer patients[J]. Chronobiology international, 2011, 28(10): 841-851
- [24] Wang Y, Hua L, Lu C, et al. Expression of circadian clock gene human Period2 (hPer2) in human colorectal carcinoma[J]. World journal of surgical oncology, 2011, 9: 166
- [25] Sotak M, Polidarova L, Ergang P, et al. An association between clock genes and clock-controlled cell cycle genes in murine colorectal tumors[J]. International journal of cancer, 2013, 132(5): 1032-1041
- [26] Sun C M, Huang S F, Zeng J M, et al. Per2 inhibits k562 leukemia cell growth in vitro and in vivo through cell cycle arrest and apoptosis induction [J]. Pathology oncology research: POR, 2010, 16 (3): 403-411
- [27] Wood P A, Yang X, Taber A, et al. Period 2 mutation accelerates ApcMin/+ tumorigenesis [J]. Molecular cancer research: MCR, 2008, 6(11): 1786-1793
- [28] Yang X, Wood P A, Ansell C M, et al. Beta-catenin induces beta-TrCP-mediated PER2 degradation altering circadian clock gene expression in intestinal mucosa of ApcMin/+ mice [J]. Journal of biochemistry, 2009, 145(3): 289-297
- [29] Wood P A, Yang X, Hrushesky W J. Clock genes and cancer[J]. Integrative cancer therapies, 2009, 8(4): 303-308
- [30] Okazaki F, Matsunaga N, Okazaki H, et al. Circadian Clock in a Mouse Colon Tumor Regulates Intracellular Iron Levels to Promote Tumor Progression[J]. The Journal of biological chemistry, 2016, 291 (13): 7017-7028
- [31] Oshima T, Takenoshita S, Akaike M, et al. Expression of circadian genes correlates with liver metastasis and outcomes in colorectal cancer[J]. Oncology reports, 2011, 25(5): 1439-1446
- [32] Storcelova M, Vician M, Reis R, et al. Expression of cell cycle regulatory factors hus1, gadd45a, rb1, cdkn2a and mre11a correlates with expression of clock gene per2 in human colorectal carcinoma tissue [J]. Molecular biology reports, 2013, 40(11): 6351-6361

(上接第 2686 页)

- [27] Feng Y, Xiong Y, Qiao T, et al. Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy [J]. Cancer Med, 2018, 7(12): 6124-6136
- [28] Vernieri C, Casola S, Foiani M, et al. Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions [J]. Cancer Discov, 2016, 6 (12): 1315-1333
- [29] Liu Q, Harvey CT, Geng H, et al. Malate dehydrogenase 2 confers docetaxel resistance via regulations of JNK signaling and oxidative metabolism[J]. Prostate, 2013, 73(10): 1028-1037
- [30] Abrego J, Gunda V, Vernucci E, et al. GOT1-mediated anaplerotic glutamine metabolism regulates chronic acidosis stress in pancreatic cancer cells[J]. Cancer Lett, 2017, 400: 37-46