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髓细胞性白血病患者 PTEN 蛋白表达及其与免疫表型的关系*

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摘要 目的:探讨髓细胞性白血病(AML)患儿 PTEN 蛋白表达及其与免疫表型的关系。**方法:**选择 AML 患儿 143 例,根据免疫表型的不同分为两组:免疫分型为 LY+AML 型 59 例,LY-AML 84 例。所有患儿都给予免疫表型分析,检测 PTEN 蛋白表达情况并进行相关性分析。**结果:**LY+AML 患儿 CD34⁺ 阳性、CD117⁺ 阳性比例显著高于 LY-AML 患儿($P < 0.05$),染色体核型异常比例显著低于 LY-AML 患儿($P < 0.05$)。LY+AML 患儿的 PTEN 蛋白表达量为 $(65.33 \pm 2.34)\%$,阳性表达率为 94.9%;而 LY-AML 分别为 $(20.11 \pm 4.11)\%$ 和 13.1%,与 LY+AML 患儿对比差异都有统计学意义($P < 0.05$)。在 AML 患儿中,Spearman 相关分析显示 PTEN 蛋白表达水平与免疫分型呈现显著相关性 ($r = 0.653, P = 0.000$)。多因素 logistic 回归方法显示 PTEN 蛋白表达、CD34⁺ 阳性、CD117⁺ 阳性、染色体核型异常为影响 AML 患儿免疫表型的主要独立危险因素 ($OR = 1.098, 1.045, 1.092, 0.294, P < 0.05$)。**结论:**AML 患儿骨髓单个核细胞的 PTEN 蛋白表达上调使得 LY+AML 型发生风险显著增加,可作为 AML 患儿病情判断与预后预测的参考指标之一。

关键词:髓细胞性白血病;PTEN 蛋白;免疫表型;相关性

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Expression of PTEN Protein and Its Relationship with Immunophenotype in Children with Myeloid Leukemia*

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ABSTRACT Objective: To investigate the expression of PTEN protein and its relationship with immunophenotype in children with acute myeloid leukemia (AML). **Methods:** 143 children with AML were selected. According to the different of immunophenotype, they were divided into two groups: 59 cases of LY+AML type and 84 cases of LY-AML. All the children were given immunophenotypic analysis, and the expression of PTEN protein were detected and given the correlation analysis. **Results:** The proportion of CD34⁺ positive and CD117⁺ positive in children with LY+AML were significantly higher than that in children with LY-AML ($P < 0.05$), and the abnormal proportion of karyotype were significantly lower than that in children with LY-AML ($P < 0.05$). The expression of PTEN protein in children with LY+AML were $(65.33 \pm 2.34)\%$, and the positive expression rates were 94.9%. The LY-AML were $(20.11 \pm 4.11)\%$ and 13.1%, respectively, compared he difference were statistically significant in children with LY+AML($P < 0.05$). In children with AML, Spearman correlation analysis showed a significant correlation between PTEN protein expression and immunophenotyping ($r = 0.653, P = 0.000$). Multivariate logistic regression showed that PTEN protein expression, CD34⁺ positive, CD117⁺ positive, and karyotypic abnormalities were the main independent risk factors affected the immunophenotype of children with AML($OR = 1.098, 1.045, 1.092, 0.294, P < 0.05$). **Conclusion:** The upregulation of PTEN protein expression in the bone marrow mononuclear cells can significantly increase the risk of LY+AML. It can be used as the reference index of the prognosis of children with AML.

Key words: Myeloid leukemia; PTEN protein; Immunophenotype; Correlation

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前言

白血病是由于基因组发生变化而导致的造血干 / 祖细

胞疾病,主要特征为大量异常造血细胞恶性增殖、凋亡减少、分化受阻,正常血细胞明显减少等^[1,2]。髓细胞性白血病 (Acute myeloid leukemia, AML) 是小儿白血病中最常见的类

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型,我国每年新增的 AML 患儿约 10 万人,而死于白血患儿也达约 6 万人^[3]。AML 属于造血干细胞异常而导致的克隆性疾病,其特点是高度异质性、分化差异性大,只有部分 AML 能够通过传统细胞形态学分型法得以准确分型,为此很难判断病情与预后^[4,5]。AML 的免疫表型分析是 AML 分型最为重要的检查之一,当前应用越来越广泛,其能更加有效反映疾病的本质,更有利于预后判断和治疗策略的制定^[6,7]。目前,AML 的发病原因和机理尚未完全明确,研究显示 AML 患儿多伴有免疫状态紊乱,也伴随有细胞因子网络失衡,从而导致肿瘤细胞的恶性增殖、生长^[8,9]。

磷酸酶及张力蛋白同源物(PTEN)基因定位于 10q23,可通过 PI3K/Akt 依赖性和非依赖性途径诱导细胞周期静止以及程序性细胞死亡,对细胞黏连、转移及分化也有调节作用^[10,11]。PTEN 是 PI3K/AKT 信号通路激活过程的负调控因子,其能够去磷酸化 PIP3 为 PIP2,抑制 PIK3 的致癌活性,并使肿瘤细胞的侵袭具有转移的可能性,从而达到抑制肿瘤的目的^[12,13]。本研

究主要探讨了 AML 患儿 PTEN 蛋白的表达及其与免疫表型的关系,旨在探索 PTEN 对 AML 治疗、预后的影响,现报道如下。

1 资料与方法

1.1 研究对象

研究时间为 2013 年 2 月到 2018 年 1 月,采用回顾性研究方法,选择我院白血科收治的 AML 患儿 143 例,纳入标准:经骨髓细胞学及免疫学检测确诊;临床资料完整;家长知情同意本研究;医院伦理委员会批准了此次研究;年龄 3-12 岁。排除标准:其他血液系统疾病患儿;合并有严重心肺、脑、肝肾等重要脏器功能障碍患儿;临床资料缺乏者。143 例患儿中,包括男 84 例,女 59 例,平均年龄(6.24±1.29)岁,平均白细胞(WBC)数量为(36.10±7.19)×10⁹/L,根据免疫分型的不同分为两组:LY+AML 型 59 例,LY-AML 型 84 例。两组患儿的性别、年龄、WBC 对比差异均无统计学意义($P>0.05$),见表 1。进行比较分析。

表 1 不同表型患儿一般资料对比
Table 1 Comparison of the general data between children with different phenotypes

immunophenotyping	n	Sex (male/female)	Age(years)	WBC(× 10 ⁹ /L)
LY+AML	59	32/27	6.44± 1.42	36.20± 10.41
LY-AML	84	52/32	6.02± 1.43	36.01± 8.01
t/ χ^2		0.841	0.555	0.451
P		0.359	0.340	0.414

1.2 免疫表型分析

采用 FACSCanto II 流式细胞仪,检测抗体包括 CD14、CD15、CD33、CD2、CD4、CD13、CD10、CD19、CD7、CD3、CD79a、CD20、CD64 等。取患儿肝素抗凝骨髓液 1-2 mL,加入荧光标记抗体 20 μ L 与肝素抗凝的骨髓液 50 μ L,混匀后避光孵育 15 min,继续加入 2 mL 红细胞溶解液,混匀后室温放置 10 min,离心进行 PBS 洗涤,上机进行检测。免疫判断标准:LY+AML:存在淋系抗原表达阳性,不满足急性混合细胞白血病诊断标准者;LY-AML:不伴淋系抗原表达。

1.3 PTEN 蛋白表达检测

取患儿外周静脉血 2 mL,采用离心法分离单个核细胞,采用流式细胞术检测 PTEN 蛋白的表达,检测试剂由上海生工生物技术有限公司提供(原装品为美国 SIGMA 公司产品),分装后进行检测,严格按照说明书进行操作。PTEN 表达≤20%代表为 PTEN 表达阴性,PTEN 表达 >20%代表为 PTEN

表达阳性。

1.4 统计学分析

采用 SPSS for windows version20.00 统计软件包进行分析处理,计量数据用均数±标准差描述,计数数据用频数和构成比描述,符合正态分布的数据对比采用配对 t 检验、样本 t 检验、卡方检验,相关性分析采用 Spearman 相关分析与多因素 logistic 回归方法,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 不同免疫分型患儿 CD34⁺、CD117⁺ 阳性率和染色体核型异常比例比较

LY+AML 患儿 CD34⁺ 阳性、CD117⁺ 阳性比例显著高于 LY-AML 患儿 ($P<0.05$),染色体核型异常比例显著低于 LY-AML 患儿($P<0.05$)。见表 2。

表 2 不同免疫分型患儿 CD34⁺、CD117⁺ 阳性率和染色体核型异常比例比较
Table 2 Comparison of CD34⁺, CD117⁺ positive rate and karyotype abnormality in children with different immunophenotypes

immunophenotyping	n	CD34 ⁺ positive	CD117 ⁺ positive	Chromosome karyotype abnormality
LY+AML	59	48(81.4%)	36(61.0%)	10(16.9%)
LY-AML	84	38(45.2%)	9(10.7%)	42(50.0%)
t/ χ^2		18.860	54.44	16.360
P		0.000	0.000	0.000

2.2 不同免疫分型患儿 PTEN 表达情况对比

LY+AML 患儿的 PTEN 蛋白表达量为 $(65.33 \pm 2.34)\%$, 阳性表达率为 94.9%; 而 LY-AML 分别为 $(20.11 \pm 4.11)\%$ 和

13.1%, 与 LY+AML 患儿对比差异都有统计学意义 ($P < 0.05$), 见表 3。

表 3 不同表型患儿 PTEN 表达情况对比

Table 3 Comparison of the PTEN expression between children with different phenotypes

immunophenotyping	n	Expression of PTEN protein	Positive rate of PTEN protein
LY+AML	59	65.33 ± 2.34	56(94.9%)
LY-AML	84	20.11 ± 4.11	11(13.1%)
t/χ^2	-	17.204	93.175
P	-	0.00	0.000

2.3 PTEN 蛋白的表达与 AML 患儿免疫分型、临床指标的相关性

在 AML 患儿中, Spearman 相关分析显示 PTEN 蛋白表达水平与免疫分型呈现显著相关性 ($r = 0.653, P = 0.000$)。多因素 logistic 回归方法显示 PTEN 蛋白表达上调、CD34⁺ 阳性、

CD117⁺ 阳性、染色体核型异常为 AML 患儿免疫表型的影响因素 ($OR = 1.098, 1.045, 1.092, 0.294, P < 0.05$), PTEN 蛋白表达上调、CD34⁺ 阳性、CD117⁺ 阳性患儿 LY+AML 表型发生的风险显著增加。见表 4。

表 4 影响 AML 患儿免疫表型的主要独立危险因素(n=143)

Table 4 The major independent risk factors affecting immunophenotype in AML(n=143)

Indexs	B	SE	Wald	P	OR	95%CI
Expression of PTEN protein	0.089	0.012	50.378	0.000	1.098	1.043-1.155
CD34 ⁺ positive	0.056	0.017	10.902	0.000	1.045	1.023-1.139
CD117 ⁺ positive	0.022	0.006	14.444	0.000	1.092	1.009-1.852
Chromosome karyotype abnormality	1.294	0.541	5.442	0.021	0.294	0.110-0.829

3 讨论

白血病是常见的血液系统恶性肿瘤之一, 其中急性髓细胞白血病(acute myelogenous leukemia, AML)发病率最常见的白血病类型, 约占所有白血病的 60%。目前针对 AML 的治疗主要是应用化疗药物与放疗治疗, 促进白血病患者缓解率增加、病死率降低, 但是很多患者由于对化疗药的耐受, 导致治疗失败。AML 系造血干细胞突变引起的造血系统恶性肿瘤, 也是高度异质性恶性克隆性疾病。当前 AML 的早期确诊主要依据组织病理学诊断, 虽然检测精确度高, 但是为有创性检查, 该检查手段并不能反映 AML 的肿瘤转移、临床分期与侵袭情况^[12]; 细胞形态学检测有一定的局限性, 主观性比较强。AML 的免疫学分型是指利用单克隆抗体检测白血病细胞的细胞膜抗原、细胞浆进行表型, 通过这一途径可了解白血病细胞的分化程度^[13]。免疫分型对诊断每例 AML 患儿有很好的应用价值^[14], 如微小残留白血病、混合型白血病、形态学类似急性淋巴细胞白血病、细胞形态学、细胞化学不典型的白血病。当前白血病致病相关特异突变位点对于肿瘤患者临床特征及预后的提示作用, 及靶向相关通路小分子靶向抑制剂的研发, 将使得白血病临床评估及治疗系统更加丰富, 为进一步提高患者疗效与生存时间提供新的途径。

目前难治性 AML 的发病机制还不明确, 被认为是多种因

素共同作用的结果。现代研究表明, 多条信号通路交互作用是肿瘤发生发展的一个重要过程, 其中涉及了多条信号通路的调控^[15,16]。本研究显示不同表型患儿的 CD34⁺、CD117⁺、染色体核型等对比差异有统计学意义 ($P < 0.05$)。当前相关研究显示部分 AML 患儿可伴 CD2、CD4、CD7、CD19 等淋系抗原的表达, CD2 与 T 淋巴细胞的活化与增殖有关, CD19 是 B 淋巴细胞系列标记性抗原正常人淋巴细胞的各个阶段, CD7 是 AML 最常表达的 T 淋巴系抗原标志^[15]。但是白血病细胞的分化及发育并没有非常严格的规律性, 会表达某一系列或阶段不应有的抗原, 也会出现不同系列抗原交叉表达, 对于免疫分型的要求更高^[16]。

随着分子生物学、细胞生物学、检验医学、遗传学、表观遗传学的快速发展, 使得早期诊断肿瘤成为可能, 也使得 AML 的缓解率和长期生存时间逐渐提高, 但是提高早期诊断的效果, 也能继续改善患儿预后。PTEN 抑癌基因定位于 10q23, 在正常组织广泛表达, 尤其是在心、肝、肾、肺、脑中表达水平较高^[17]。PTEN 通过 PI3K/Akt 依赖性和非依赖性途径诱导使得细胞周期静止以及程序性细胞死亡, 对细胞黏连及分化进行调节。研究结果显示, PTEN 蛋白可使 3, 4, 5- 磷酸磷脂酰肌醇化为 4, 5- 磷酸磷脂酰肌醇, 诱导 Caspase-9 等蛋白表达, 介导肿瘤细胞凋亡^[18]。本研究显示 LY+AML 患儿的 PTEN 蛋白表达量为 $(65.33 \pm 2.34)\%$, 阳性表达率为 94.9%, 而 LY-AML 分别为 $(20.11 \pm 4.11)\%$ 和 13.1%, 对比差异都有统计学意义 ($P < 0.05$)。

相关研究显示 PTEN 蛋白具有脂质磷酸酶和蛋白磷酸酶活性,可发挥肿瘤抑制功能^[19]。包括白血病在内的多种肿瘤中 PTEN 基因存在不同程度的突变、缺失,PTEN 蛋白表达降低及缺失会影响其抑制肿瘤生长的功能^[20]。

PTEN 是具有双特异性磷酸酶活性的抑癌基因,有 9 个外显子和 8 个内含子,全长 200 kb,PTEN 蛋白定位于细胞质浆,呈网格状分布,其正常表达可抑制肿瘤细胞侵袭、转移和生长^[21,22]。通过下调肿瘤相关信号传导通路,PTEN 基因在肝癌、子宫内膜癌、卵巢癌、乳腺癌等组织中可实现突变及失活,从而达到肿瘤抑制的目的^[23,24]。PTEN 主要通过参与 PTEN/PI3K/Akt 的多条信号传导通路,诱导细胞凋亡、阻滞细胞周期、激活脂质磷酸酶与蛋白磷酸酶活性,来实现抑癌功能^[25,26]。本研究直线相关性分析显示 AML 患儿的 PTEN 蛋白表达水平与免疫分型呈现显著相关性($r=0.653$, $P=0.000$);多因素 logistic 回归方法显示 PTEN 蛋白表达、CD34⁺ 阳性、CD117⁺ 阳性、染色体核型异常为影响 AML 患儿免疫表型的主要独立危险因素 (OR =1.098, 1.045, 1.092, 0.294, $P<0.05$)。PTEN 蛋白在白血病中存在不同程度的缺失、低表达、甲基化,PTEN 在区分白血病干细胞和正常造血干细胞中也发挥了关键作用^[27]。髓系抗原的表达有利于区分白血病细胞与正常造血细胞,利于微小残留病的检测^[28]。染色体核型是影响不同免疫表型 AML 患儿疗效及预后的主要因素之一,同时当染色体核型正常的情况下,混合免疫表型可能是影响 AML 预后的主要因素^[29]。有研究表明,PTEN 缺失会导致 pre-B ALL 细胞发生快速死亡,并且能够彻底清除模型小鼠体内的白血病细胞。此外,高度激活 AKT 能够触发检查点,以达到清除自身反应性 B 细胞的目的,在 pre-B AML 细胞中 PTEN 功能丧失,等同于自身反应性 pre-B AML 细胞受体通路被急性激活,可参与自身反应性 B 细胞的清除^[30,31]。有研究利用 PTEN 小分子抑制剂处理人类 pre-B ALL 细胞,结果发现这会导致 AKT 的高度激活,并且还会激活 p53 肿瘤抑制因子介导的细胞周期暂停和细胞死亡^[32,33]。

总之,AML 患儿骨髓单个核细胞的 PTEN 蛋白表达与免疫表现有很好的相关性,PTEN 蛋白表达上调可使得 LY+AML 型发生风险显著增加,可作为 AML 患儿病情判断与预后预测的参考指标之一。

参考文献(References)

- [1] Zhang J, Xiang Z, Malaviarachchi PA, et al. PTEN is indispensable for cells to respond to MAPK inhibitors in myeloid leukemia [J]. Cell Signal, 2018, 28(50): 72-79
- [2] Savona MR, Pollyea DA, Stock W, et al. Phase Ib Study of Glasdegib, a Hedgehog Pathway Inhibitor, in Combination with Standard Chemotherapy in Patients with AML or High-Risk MDS [J]. Clin Cancer Res, 2018, 24(10): 2294-2303
- [3] Ishikawa C, Senba M, Mori N. Mitotic kinase PBK/TOPK as a therapeutic target for adult T-cell leukemia/lymphoma[J]. Int J Oncol, 2018, 53(2): 801-814
- [4] Chen Y, Wang T, Du J, et al. The Critical Role of PTEN/PI3K/AKT Signaling Pathway in Shikonin-Induced Apoptosis and Proliferation Inhibition of Chronic Myeloid Leukemia [J]. Cell Physiol Biochem, 2018, 47(3): 981-993
- [5] Whitson RJ, Lee A, Urman NM, et al. Noncanonical hedgehog pathway activation through SRF-MKL1 promotes drug resistance in basal cell carcinomas[J]. Nat Med, 2018, 24(3): 271-281
- [6] Li Z, Yang L, Liu X, et al. Long noncoding RNA MEG3 inhibits proliferation of chronic myeloid leukemia cells by sponging microRNA21[J]. Biomed Pharmacother, 2018, 8(104): 181-192
- [7] Punzo F, Manzo I, Tortora C, et al. Effects of CB2 and TRPV1 receptors' stimulation in pediatric acute T-lymphoblastic leukemia[J]. Oncotarget, 2018, 9(30): 21244-21258
- [8] Yin J, Li X, Zhang Z, et al. SPAG6 silencing induces apoptosis in the myelodysplastic syndrome cell line SKM-1 via the PTEN/PI3K/AKT signaling pathway *in vitro* and *in vivo* [J]. Int J Oncol, 2018, 53(1): 297-306
- [9] Wu J, Song Y. Expression and clinical significance of serum MMP-7 and PTEN levels in patients with acute myeloid leukemia [J]. Oncol Lett, 2018, 15(3): 3447-3452
- [10] Salman H, Shuai X, Nguyen-Lefebvre AT, et al. SALL1 expression in acute myeloid leukemia[J]. Oncotarget, 2017, 9(7): 7442-7452
- [11] Täger M, Horn S, Latuske E, et al. SHIP1, but not an AML-derived SHIP1 mutant, suppresses myeloid leukemia growth in a xenotransplantation mouse model[J]. Gene Ther, 2017, 24(11): 749-753
- [12] Zhao WH, Huang BT, Zhang JY, et al. Distinct EphB4-mediated mechanisms of apoptotic and resistance to dasatinib in human chronic myeloid leukemia and K562 cell lines [J]. Leuk Res, 2017, 12(63): 28-33
- [13] Mohammadi S, Zahedpanah M, Ghaffari SH, et al. Osteopontin plays a unique role in resistance of CD34⁺/CD123⁺ human leukemia cell lines KG1a to parthenolide[J]. Life Sci, 2017, 15(189): 89-95
- [14] Vu LP, Pickering BF, Cheng Y, et al. The N (6)-methyladenosine (m (6)A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells [J]. Nat Med, 2017, 23(11): 1369-1376
- [15] Zahed Panah M, Nikbakht M, Sajjadi SM, et al. Anti-Apoptotic Effects of Osteopontin via the Up-Regulation of AKT/mTOR/β-Catenin Loop in Acute Myeloid Leukemia Cells [J]. Int J Hematol Oncol Stem Cell Res, 2017, 11(2): 148-157
- [16] Hay JF, Lappin K, Liberante F, et al. Integrated analysis of the molecular action of Vorinostat identifies epi-sensitised targets for combination therapy[J]. Oncotarget, 2017, 8(40): 67891-67903
- [17] Yao S, Zhong L, Chen M, et al. Epigallocatechin-3-gallate promotes all-trans retinoic acid-induced maturation of acute promyelocytic leukemia cells via PTEN[J]. Int J Oncol, 2017, 51(3): 899-906
- [18] Zhao L, Shan Y, Liu B, et al. Functional screen analysis reveals miR-3142 as central regulator in chemoresistance and proliferation through activation of the PTEN-AKT pathway in CML[J]. Cell Death Dis, 2017, 8(5): e2830
- [19] Russo M, Milito A, Spagnuolo C, et al. CK2 and PI3K are direct molecular targets of quercetin in chronic lymphocytic leukaemia[J]. Oncotarget, 2017, 8(26): 42571-42587
- [20] Song Z, Du Y, Tao Y. Blockade of sonic hedgehog signaling decreases viability and induces apoptosis in retinoblastoma cells: The key role of the PI3K/Akt pathway [J]. Oncol Lett, 2017, 14(4): 1-10

4099-4105

- [21] Abdolmaleki M, Mojtabavi N, Zavvar M, et al. Scrutinizing the Expression and Blockade of Inhibitory Molecules Expressed on T Cells from Acute Myeloid Leukemia Patients [J]. Iran J Allergy Asthma Immunol, 2018, 17(3): 265-273
- [22] Owen HC, Appiah S, Hasan N, et al. Phytochemical Modulation of Apoptosis and Autophagy: Strategies to Overcome Chemoresistance in Leukemic Stem Cells in the Bone Marrow Microenvironment[J]. Int Rev Neurobiol, 2017, 8(135): 249-278
- [23] Oberley MJ, Gaynon PS, Bhojwani D, et al. Myeloid lineage switch following chimeric antigen receptor T-cell therapy in a patient with TCF3-ZNF384 fusion-positive B-lymphoblastic leukemia [J]. Pediatr Blood Cancer, 2018, 5(24): e27265
- [24] Sydor S, Jafoui S, Wingerter L, et al. Bcl-2 degradation is an additional pro-apoptotic effect of polo-like kinase inhibition in cholangiocarcinoma cells [J]. World J Gastroenterol, 2017, 23(22): 4007-4015
- [25] Chaudhry P, Singh M, Triche TJ, et al. GLI3 repressor determines Hedgehog pathway activation and is required for response to SMO antagonist glasdegib in AML[J]. Blood, 2017, 129(26): 3465-3475
- [26] Latuske EM, Stamm H, Klokow M, et al. Combined inhibition of GLI and FLT3 signaling leads to effective anti-leukemic effects in human acute myeloid leukemia [J]. Oncotarget, 2017, 8 (17): 29187-

29201

- [27] Jia J, Martin TA, Ye L, et al. Fibroblast activation protein- α promotes the growth and migration of lung cancer cells via the PI3K and sonic hedgehog pathways[J]. Int J Mol Med, 2018, 41(1): 275-283
- [28] Yu T, Jia W, An Q, et al. Bioinformatic Analysis of GLI1 and Related Signaling Pathways in Chemosensitivity of Gastric Cancer [J]. Med Sci Monit, 2018, 29(24): 1847-1855
- [29] Chen C, Breslin MB, Lan MS. Sonic hedgehog signaling pathway promotes INSM1 transcription factor in neuroendocrine lung cancer [J]. Cell Signal, 2018, 6(46): 83-91
- [30] Chaturvedi NK, Kling MJ, Coulter DW, et al. Improved therapy for medulloblastoma: targeting hedgehog and PI3K-mTOR signaling pathways in combination with chemotherapy [J]. Oncotarget, 2018, 9 (24): 16619-16633
- [31] Fukushima N, Minami Y, Kakiuchi S, et al. Small-molecule Hedgehog inhibitor attenuates the leukemia-initiation potential of acute myeloid leukemia cells[J]. Cancer Sci, 2016, 107(10): 1422-1429
- [32] Dagklis A, Demeyer S, De Bie J, et al. Hedgehog pathway activation in T-cell acute lymphoblastic leukemia predicts response to SMO and GLI1 inhibitors[J]. Blood, 2016, 128(23): 2642-2654
- [33] Shahi MH, Farheen S, Mariyath MP, et al. Potential role of Shh-Gli1-BMI1 signaling pathway nexus in glioma chemoresistance [J]. Tumour Biol, 2016, 37(11): 15107-15114

(上接第 1919 页)

- [24] Yang B, Wang F, Cao H, et al. Caffeoylxanthiazonoside exerts cardioprotective effects during chronic heart failure via inhibition of inflammatory responses in cardiac cells [J]. Experimental & Therapeutic Medicine, 2017, 14(5): 4224-4230
- [25] Sukoyan G V, Ionov D I, Galenko-Iaroshevsky P A, et al. Severity of Symptoms of Systemic Inflammatory Response Syndrome and Congestive Heart Failure Caused by Chronic Aortic Stenosis and Its Pharmacological Correction [J]. World Journal of Cardiovascular Diseases, 2017, 07(12): 465-476
- [26] Sharma A, Stevens S R, Lucas J, et al. Utility of Growth Differentiation Factor-15, A Marker of Oxidative Stress and Inflammation, in Chronic Heart Failure: Insights From the HF-ACTION Study[J]. Jacc Heart Fail, 2017, 5(10): 724-734
- [27] Grande D, Leone M, Rizzo C, et al. A Multiparametric Approach

Based on NT-proBNP, ST2, and Galectin3 for Stratifying One Year Prognosis of Chronic Heart Failure Outpatients [J]. Journal of Cardiovascular Development & Disease, 2017, 4(3): 0009

- [28] Bobbio E, Isgaard J, Swedberg K, et al. NT-proBNP Levels Are Reduced Following Treatment With Growth Hormone in Chronic Heart Failure Due to Ischemic Heart Disease. A Randomized Double Blind Placebo Controlled Trial [J]. Journal of Heart & Lung Transplantation, 2018, 37(4): S187-S188
- [29] Davarzani N, Sandersvan W S, Karel J, et al. N-Terminal Pro-B-Type Natriuretic Peptide-Guided Therapy in Chronic Heart Failure Reduces Repeated Hospitalizations-Results From TIME-CHF [J]. Journal of Cardiac Failure, 2017, 23(5): 382
- [30] Stienen S, Salah K, Moons A H, et al. NT-proBNP-Guided Therapy in Acute Decompensated Heart Failure: The PRIMA II Randomized Controlled Trial[J]. Circulation, 2017, 23(5): 811-821