doi: 10.13241/j.cnki.pmb.2018.04.030

# 法舒地尔联合舒利迭对 COPD 合并 PAH 患者肺功能及血清 BNP、CRP、IL-8、TNF-α 水平的影响 *

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**摘要 目的：**探讨法舒地尔联合舒利迭对慢性阻塞性肺疾病(COPD)合并肺动脉高压(PAH)患者的肺功能及血清脑钠肽(BNP)、C 反应蛋白(CRP)、白介素 -8(IL-8)、肿瘤坏死因子 -α(TNF-α)水平的影响。**方法：**选择我院 2015 年 2 月 ~2017 年 1 月收治的 108 例 COPD 合并 PAH 患者作为研究对象，根据患者入院顺序编号，采取随机数字表分成观察组(n=54)与对照组(n=54)。两组均给予常规治疗，观察组在常规治疗基础上联合给予法舒地尔与舒利迭治疗，对两组患者进行疗效评估，比较两组患者治疗前后的肺功能、血气分析指标以及血清 BNP、CRP、IL-8、TNF-α 水平的变化。**结果：**治疗后，两组患者的 FEV1%pre、FEV1/FVC、$PaO_2$ 均较治疗前显著升高(P<0.05)，且观察组 FEV1%pre、FEV1/FVC、$PaO_2$ 明显高于对照组(P<0.05)；两组患者的 $PaCO_2$、SPAP、Tei 指数、血清 BNP、CRP、IL-8、TNF-α 水平均较治疗前显著下降(P<0.05)，且观察组 $PaCO_2$、SPAP、Tei 指数、血清 BNP、CRP、IL-8、TNF-α 水平均明显低于对照组(P<0.05)。**结论：**法舒地尔联合舒利迭治疗 COPD 合并 PAH 能有效改善患者的肺功能，减轻炎症反应，降低肺动脉压，疗效确切。

**关键词：**法舒地尔；舒利迭；慢性阻塞性肺疾病；肺动脉高压；炎症反应

**中图分类号：**R563 **文献标识码：**A **文章编号：**1673-6273(2018)04-737-04

# Effect of Fasudil Combined with Seretide on Lung Function and Serum Levels of BNP, CRP, IL-8 and TNF-α of Patients with COPD and PAH*

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**ABSTRACT Objective:** To investigate the effect of Fasudil combined with Seretide on the pulmonary function and serum levels of serum brain natriuretic peptide (BNP), C reactive protein (CRP), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) of patients with chronic obstructive pulmonary disease (COPD) complicated with pulmonary arterial hypertension (PAH). **Methods:** 108 cases of COPD combined with PAH patients treated in our hospital from February 2015 to January 2017 were selected and numbered according to the admission order and then they were divided into the observation group (n=54) and the control group with the method of random number table (n=54). Both groups were given conventional treatment, and the observation group was combined with Fasudil and Seretide on the basis of conventional treatment. Then the curative effect of the two groups of patients was evaluated. The lung function, blood gas analysis index, and serum BNP, CRP, IL-8 and TNF-α levels were compared between two groups before and after the treatment. **Results:** After the treatment, the FEV1%pre, FEV1/FVC and $PaO_2$ of patients in both groups were significantly higher than those before the treatment(P<0.05), which were obviously higher in the observation group than those of the control group(P<0.05). The $PaCO_2$, SPAP, Tei index serum BNP, CRP, IL-8, TNF-α levels of both groups were significantly higher than those before the treatment (P<0.05), which were significantly lower in the observation group than those of the control group (P<0.05). **Conclusion:** Fasudil combined with Seretide can effectively improve the pulmonary function, relieve the inflammation and reduce the pulmonary artery pressure in the treatment of COPD combined with PAH.

**Key words:** Fasudil; Seretide; Chronic obstructive pulmonary disease; Pulmonary arterial hypertension; Inflammatory reaction

**Chinese Library Classification(CLC): R563 Document code: A**

**Article ID: 1673-6273(2018)04-737-04**

## 前言

慢性阻塞性肺疾病(COPD)是常见的慢性呼吸系统疾病之一，临床主要表现为胸闷、胸痛、呼吸困难、易疲劳、晕厥、周围性水肿等[1]。COPD 患者多可因肺血管异常改变及炎症应激反应而致肺动脉高压(PAH)，引起肺动脉压力与肺血管阻力升高，随着病情进展最终可致右心负荷增加，引发右心衰竭，乃至死亡[2,3]。目前，临床对于 COPD 合并 PAH 尚缺乏特异性治疗方

* 基金项目：陕西省自然科学基金项目(2002C255)

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（收稿日期：2017-06-26 接受日期：2017-07-18）

法，主要以抗感染、吸氧、化痰、平喘等对症支持治疗为主，但疗效欠佳。研究显示 PAH 患者存在 Rho 激酶通路被激活，作为新型 Rho 激酶抑制剂的，法舒地尔能有效降低肺动脉压力，并可逆转肺血管以及右心室重构[4]。舒利迭是一种长效 β-2 受体激动剂与糖皮质激素的复合制剂，目前已被证实能有效缓解 COPD 症状，改善患者的肺功能[5]。本研究将法舒地尔与舒利迭联合用于 COPD 合并 PAH 的治疗，取得了满意疗效，现报道如下。

## 1 资料与方法

### 1.1 一般资料

选择我院 2015 年 2 月 ~2017 年 1 月收治的 108 例 COPD 合并 PAH 患者作为研究对象，根据患者入院顺序编号，采取随机数字表分成观察组(n=54)与对照组(n=54)。其中观，察组男 38 例，女 16 例，年龄 47~83 岁，平均(65.7± 9.4 岁)，病程 3~16 年，平均(9.6± 3.7)年，有吸烟史 43 例。对照组男 40 例，女 14 例，年龄 45~84 岁，平均(66.3± 8.7)岁，病程 3~17 年，平均(9.2± 3.2)年，有吸烟史 41 例。两组一般临床资料对比差异均无统计学意义(P>0.05)，具有可比性。

纳入标准：(1)符合 COPD 诊断标准[6]，并具备 PAH 的典型症状及体征，获得 X 线片及超声心动图支持诊断；(2) 年龄 40~85 岁，NYHA 心功能分级 I~III 级；(3)近 4 周内未使用过抗生素或皮质类固醇激素；(4)对此次研究知情，自愿签署同意书。排除标准：(1)合并肺动脉瓣与右室流出道狭窄；(2)合并肺癌、肺结核、支气管哮喘、肺栓塞、肺间质性疾病、气胸、先天性心脏病、心脏瓣膜病、呼吸衰竭、恶性肿瘤；(3)合并免疫系统、血液系统及内分泌系统疾病；(4)严重肝肾功能不全；(5)近 2 个月内有急性心脑血管事件史；(6)近 6 个月内有手术或外伤史；(7)下肢功能障碍；(8)体循环压较低(血压 <90/50 mmHg)或高血压(血压 >170/110 mmHg)；(9)合并意识障碍或认知障碍；(10)对研究药物过敏。

### 1.2 治疗方法

两组患者均给予常规治疗，包括给予低流量吸氧、盐酸氨溴索化痰止咳、多索茶碱解痉、糖皮质激素、头孢类抗生素等。观察组在常规治疗基础上联合给予法舒地尔与舒利迭治疗，将 30 mg 盐酸法舒地尔 (天津红日药业，批号 150126,151108, 160724) 溶于 0.9%氯化钠注射液 100 mL 中静脉滴注，每日 2 次。局部使用舒利迭(葛兰素史克，批号 141223,151124, 160802)，每次 1 喷，每日 2 次。

### 1.3 观察指标

分别于治疗前后采用心脏彩色多普勒超声仪测定肺动脉收缩压(SPAP)，计算右心室 Tei 指数；采用肺功能仪测定 1 秒用力呼气容积(FEV1)/ 用力肺活量(FVC)及 FEV1 实测值 / 预计值(FEV1%pre)；采用动脉血气分析仪测定氧分压($PaO_2$)及二氧化碳分压($PaCO_2$)；空腹抽取 5ml 静脉血，离心分离血清，采用采用双抗体夹心免疫荧光法测定血清脑钠肽(BNP)水平，采用酶联免疫吸附试验(ELISA)测定血清 C 反应蛋白(CRP)水平，采用放射免疫法测定血清白介素 -8 (IL-8)、肿瘤坏死因子 -α (TNF-α)水平。

### 1.4 统计学分析

采取统计软件 SPSS19.0 处理数据，计数资料以%表示，采取 $x^2$ 检验，计量资料以($\bar{x}\pm s$)表示，采取 t 检验，以 P<0.05 为差异有统计学意义。

## 2 结果

### 2.1 两组治疗前后肺功能指标的比较

治疗后，组患者的 FEV1%pre、FEV1/FVC 均较治疗前显著升高(P<0.05)，且观察组 FEV1%pre、FEV1/FVC 明显高于对照组(P<0.05)。见表 1。

表 1 两组治疗前后肺功能指标变化的比较($\bar{x}\pm s$)

Table 1 Comparison of the changes of pulmonary function indexes between two groups before and after treatment($\bar{x}\pm s$)

| Groups | n | FEV1% pre | | FEV1/FVC | |
|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 54 | 55.63± 5.63 | 80.52± 9.23[1)] | 53.46± 7.86 | 86.67± 8.45[1)] |
| Control group | 54 | 56.17± 6.12 | 67.35± 8.14[1)] | 54.08± 8.35 | 70.56± 10.09[1)] |
| P | | 0.634 | 0.000 | 0.692 | 0.000 |

Note: compared with the same group before treatment, [1)]P<0.05.

### 2.2 两组治疗前后血气分析指标变化的比较

治疗后，两组患者的 $PaO_2$ 水平均较治疗前显著上升，$PaCO_2$ 水平显著下降(P<0.05)；观察组治疗后 $PaO_2$ 水平显著高于对照组，$PaCO_2$ 水平显著低于对照组(P<0.05)。见表 2。

表 2 两组治疗前后血气分析指标变化情况比较($\bar{x}\pm s$, mmHg)

Table 2 Comparison of the blood gas analysis index between two groups before and after treatment ($\bar{x}\pm s$, mmHg)

| Groups | n | $PaO_2$ | | $PaCO_2$ | |
|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 54 | 44.56± 5.12 | 66.78± 7.45[1)] | 69.78± 6.56 | 53.12± 5.34[1)] |
| Control group | 54 | 45.35± 4.98 | 57.12± 8.05[1)] | 68.63± 6.12 | 60.06± 4.98[1)] |
| P | | 0.418 | 0.000 | 0.348 | 0.000 |

Note: compared with the same group before treatment, [1)]P<0.05.

### 2.3 两组治疗前后 SPAP、Tei 指数变化情况的比较

治疗后，两组患者的 SPAP、Tei 指数均较治疗前显著降低(P<0.05)，且观察组治疗后 SPAP、Tei 指数均明显低于对照组(P<0.05)。见表 3。

**表 3 两组治疗前后 SPAP、Tei 指数变化情况的比较($\bar{x}\pm s$)**

Table 3 Comparison of the changes of SPAP and Tei index between two groups before and after treatment ($\bar{x}\pm s$)

| Groups | n | SPAP(mmHg) | | Tei | |
|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 54 | 50.47± 9.36 | 31.14± 7.34[1)] | 0.69± 0.04 | 0.44± 0.02[1)] |
| Control group | 54 | 48.93± 10.22 | 40.06± 8.17[1)] | 0.68± 0.04 | 0.59± 0.03[1)] |
| P | | 0.416 | 0.000 | 0.197 | 0.000 |

Note: compared with the same group before treatment, [1)]P<0.05.

### 2.4 两组治疗前后各项血清指标变化情况的比较

治疗后，两组患者的血清 BNP、CRP、IL-8、TNF-α 水平均较治疗前显著下降(P<0.05)，且观察组治疗后血清 BNP、CRP、IL-8、TNF-α 水平均明显低于对照组(P<0.05)，见表 4。

**表 4 两组治疗前后各项血清指标变化情况比较($\bar{x}\pm s$)**

Table 4 Comparison of the changes of serum index between two groups before and after treatment ($\bar{x}\pm s$)

| Groups | Time | BNP(pg/ml) | CRP(mg/L) | IL-8(ng/L) | TNF-α(mg/L) |
|---|---|---|---|---|---|
| Observation group(n=54) | Before treatment | 483.56± 45.62 | 17.67± 6.25 | 32.66± 7.24 | 36.45± 8.35 |
| | After treatment | 77.35± 14.24[1,2)] | 8.24± 7.78[1,2)] | 18.45± 5.78[1,2)] | 21.45± 10.24[1,2)] |
| Control group(n=54) | Before treatment | 477.57± 58.35 | 18.22± 5.87 | 33.12± 6.95 | 37.02± 7.76 |
| | After treatment | 198.45± 49.52[1)] | 13.51± 8.24[1)] | 25.56± 7.08[1)] | 30.56± 9.46[1)] |

Note: compared with the same group before treatment, [1)]P<0.05; compared with the control group after treatment, [2)]P<0.05.

## 3 讨论

COPD 以气道、肺血管、肺实质的慢性炎症改变为主要病理表现，随着病情进展，长期慢性炎症及缺氧可引发血管收缩，引起肺血管内皮受损以及肺血管重构，最终诱导 PAH 形成[7-9]。COPD 并发 PAH 后可严重影响患者的运动耐力及生存质量，因此采取积极有效的治疗措施，缓解肺动脉压升高，减轻炎症反应对于改善患者的预后具有重要价值[10]。目前，COPD 并发 PAH 确切的发生机制尚不明确，临床也缺乏特异性的治疗手段，主要采取的仍是以吸氧、抗感染、止咳化痰平喘等常规治疗为主，但疗效多欠佳[11]。

组织病理学研究表明即使是轻中度 COPD 肺肌型动脉外膜也有炎性细胞浸润，且浸润程度和肺血管内皮功能、肺血管内膜厚度密切相关。此外，部分炎性蛋白在肺血管的重构、调节 PAH 中可起到关键作用，表明慢性炎症是诱发肺血管重塑及 PAH 的关键因素[12,13]。CRP、IL-8、TNF-α 均是常见的炎性细胞因子，其中 CRP 是反映全身炎症反应的敏感指标，在血栓栓塞性疾病、原发性 PAH 等疾病中，患者血清 CRP 水平可明显升高，在由 COPD 引发的 PAH 患者中同样存在高表达[14]。TNF-α 是机体内重要的前炎性细胞因子，可放大全身炎症反应，研究表明 TNF-α 水平的异常升高可引起血管内皮细胞 NOS 的异常，使肺动脉平滑肌细胞合成 PG 减少，导致血管内皮功能受损及肺血管收缩[15]。IL-8 可参与 COPD 患者肺内炎症反应，引起气道重塑。由此可见，在治疗 COPD 合并 PAH 时，缓解机体内炎症反应是关键[16]。

舒利迭是由沙美特罗与丙酸氟替卡松组成的一种长效吸入剂，其中沙美特罗属长效β2 肾上腺素受体激动剂，对支气管收缩功能可起到保护作用，支气管扩张作用可长达 12h，并能长效抑制肥大细胞介质的释放，有效缓解呼吸道症状；丙酸氟替卡松能在肺内生成糖皮质激素，从而发挥抗炎作用，并能促进肺功能的改善，延缓病情进展[17,18]。郑权等[19]的研究显示，舒利迭能有效改善老年 COPD 合并呼吸衰竭患者的动脉血气及肺功能；张仕国等[20]的研究则显示，对于 COPD 合并尘肺病患者，舒利迭同样能起到改善患者肺功能的作用。Rho 激酶是经细胞内信号转导作用对血管收缩、细胞增殖、凋亡等进行调节的一种酶类。研究显示 Rho/Rho 激酶信号通路的异常激活和肺血管收缩、结构重构及 PAH 形成密切相关，低氧引起的内皮型一氧化氮合酶经 Rho 介导后表达降低，导致一氧化氮减少，引起血管收缩[21]。研究表明严重 PAH 患者与野百合碱及慢性缺氧所致大鼠 PAH 模型肺组织及肺动脉中存在 Rho 激酶活性明显升高[22]。法舒地尔是 Rho 激酶抑制剂，可渗透至血管平滑肌细胞内，与 ATP 竞争 Rho 激酶催化区 ATP 结合位点，特异性阻断 Rho 激酶活性，进而扩张血管以及减轻 PAH 程度[23]。彩色多普勒超声心动图可通过测定肺动脉压力进而评估 PAH 严重程度，而对于超声心动图无明显征象的 PAH 患者，通过计算右心室 Tei 指数则能提供有效的诊断信息，同时其对 COPD 右室功能也能起到有效的评估作用。

本研究结果显示：两组治疗后 SPAP、Tei 指数均较治疗前显著降低，观察组下降更明显，其原因可能主要与法舒地尔具有的特异性阻断 Rho 激酶活性的作用密切相关[24]。经治疗后两组患者的血清 CRP、IL-8、TNF-α 水平均较治疗前显著下降，而观察组这几项炎性因子的改善效果显著优于对照组，表明法舒

地尔联合舒利迭能有效改善 COPD 合并 PAH 患者机体内炎症反应，缓解肺内慢性炎症。此外，本研究通过对比两组患者治疗前后的血气分析及肺功能，发现观察组改善幅度更大。BNP 既是反映心力衰竭的重要指标，也是反映 PAH 严重程度的敏感指标[25]，其水平异常升高是目前诊断 COPD 并发 PAH 的有力证据。COPD 并发 PAH 患者血清 BNP 升高的机制可能是缺氧可刺激 BNP 的合成与释放；肺循环是 BNP 的重要代谢场所，因 COPD 肺泡体积增大可压迫毛细血管，引起血管受损，BNP 的清除能力可因此下降；COPD 可使右下肺动脉横径以及右室前壁厚度增加，导致肺动脉压升高，加重右心室负荷，从而使心室过多地合成及分泌 BNP[26]。本研究中，两组治疗后血清 BNP 均有明显下降，但治疗后观察组血清 BNP 水平要明显低于对照组。其原因可能主要是法舒地尔联合舒利迭能有效改善动脉血气、减轻肺内炎症反应，并改善肺功能。

综上所述，在常规治疗基础上给予法舒地尔联合舒利迭治疗 COPD 合并 PAH 的临床疗效显著，可有效改善患者的动脉血气及肺功能，缓解肺内炎症反应，控制肺动脉高压。

## 参 考 文 献(References)


[1] Liu Qian, Wang Xi-chun, Gan Dan, et al. Therapies of simvastatin on AECOPD combined with PAH through affecting VEGF and the pulmonary function[J]. Chongqing Med, 2015, 44(6): 761-762, 765

[2] Wang Li-yun. Effect of Feikangning composition in improving the pulmonary function in patients with COPD complicated with pulmonary arterial hypertension [J]. Journal of Hainan Medical University, 2016, 22(24): 3108-3110

[3] Fritz JS, Blair C, Oudiz RJ, et al. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension[J]. Chest, 2013, 143(2): 315-323

[4] Hu Yan-xia, Liu Yi. Randomized controlled study of the effects of fasudil on elderly patients with chronic obstructive pulmonary disease complicated with pulmonary arterial hypertension [J]. Practical Pharmacy And Clinical Remedies, 2015, 18(1): 108-111

[5] Donohue JF, Worsley S, Zhu CQ, et al. Improvements in lung function with umeclidinium/ vilanterol versusfluticasone propionate/ salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations[J]. Respir Med, 2015, 109(7): 870

[6] Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD[J]. Eur Respir J, 2008, 32(5): 1371-1385

[7] Labib S, Wagih K, Wagih Y. Evaluation of antiendothelial cell antibodies in COPD patients, with and without corpulmonale [J]. Egyptian Journal of Chest Diseases and Tuberculosis, 2014, 63 (3): 125-129

[8] Alkhayat K, Eid M. Sildenafil citrate therapy for secondary pulmonary arterial hypertension due to chronic obstructive lung disease [J]. Egyptian Journal of Chest Diseases & Tuberculosis, 2016, 65 (4): 805-809

[9] Karina P, Yolanda T, Isabel B, et al. Pulmonary hemodynamic profile in chronic obstructive pulmonary disease [J]. International Journal of Chronic Obstructive Pulmonary Disease, 2015, 10(Issue 1): 1313-1320

[10] Wang Chang-feng, Wu Xue-hua, Zhang Hua-xi. Influence of fasudil on inflammatory factors in patients combined with COPD exacerbation and pulmonary hypertension[J]. Lab Med Clin, 2013, 10 (20): 2679-2682

[11] Nan Jing-long, Xue Li-ying, Wang Ling, et al. Clinical Observation on Milrinone in the Treatment of Chronic Obstructive Pulmonary Disease Complicated with Pulmonary Hypertension [J]. Chin J Integr Med Cardio, 2016, 14(20): 2345-2347

[12] Ekkernkamp E, Storre JH, Windisch W, et al. Impact of intelligent volume-assured pressure support on sleep quality in stable hypercapnic chronic obstructive pulmonary disease patients: a randomized, crossover study[J]. Respiration, 2013, 88(4): 270-276

[13] Matura LA, Palevsky H, Lederer D, et al. First Place: Inflammation and Symptoms in Pulmonary Arterial Hypertension [J]. Journal of Cardiovascular Nursing, 2016, 31(1): 10

[14] Xue Hua. Relationship of CRP and D-D levels to pulmonary arterial hypertension in COPD patients at stable phase [J]. Journal of Clinical Pulmonary Medicine, 2015, 20(6): 1117-1119

[15] Hong Yong-qing, Zhu Rong, Meng Zi-li. The role of inflammatory mediators in patients with chronic obstructive pulmonary disease and pulmonary hypertension[J]. China Journal of Modern Medicine, 2013, 23(33): 27-31

[16] Jin Wei, Xu Jing-hua, Liu Jian-guang, et al. Effect of Seretide and Noninvasive Ventilation on the Pulmonary Function and Arterial Blood Analysis of Patients with Chronic Obstructive Pulmonary Disease Combined with Respiratory Failure [J]. Progress in Modern Biomedicine, 2016, 16(26): 5085-5087, 5144

[17] Lu Kun-qin, Chen Long, Zhang Hua-jun, et al. Therapeutic effect of Fasudil combined Salmeterol Xinafoate and fluticasone propionate powder for inhalation on patients with COPD complicated PAH [J]. Chin J Cardiovasc Rehabil Med, 2017, 26(1): 90-94

[18] Zheng Quan, Tang Ju-mei, Huang Qin, et al. Observation on effectiveness of seretide combined with noninvasive positive pressure ventilation for elderly patients with chronic obstructive pulmonary disease and respiratory failure[J]. Chin J Diffic and Compl Cas, 2015, 14(1): 36-38, 41

[19] Zhang Shi-guo, Zhou Jiang, Luo Shi-lin, et al. Study of the Seretide anapnotherapy in treatment of chronic obstructive pulmonary disease patients complicated with pneumoconiosis [J]. Journal of Clinical Pulmonary Medicine, 2012, 17(4): 661-662

[20] Chen Su-qin, Gao Hai-yan, Chen Chen, et al. Influence of Fasudil on plasma brain natriuretic pepetide of patients with chronic obstructive pulmonary disease and pulmonary hypertension [J]. Chin J Lung Dis (Electronic Edition), 2014, 7(6): 642-645

[21] Shang Ping, Zhou Hong-ling, Feng Cai-li, et al. Changes of Rho Kinase in Pulmonary Hypertension Mice Induced by Chronic Hypoxic-hypercapnia [J]. Chinese Journal of Cell Biology, 2013, 35 (3): 296-301

[22] Li Yuan-yuan, Yu Shu-hui, Hu Ke. Meta Analysis of the Treatment of Fasudil Hydrochloride Injection to the Pulmanory Hypertension Related Chronic Obstructive Pulmonary Disease[J]. J Med Res, 2015, 44(9): 31-35

[23] Nishimura K, Nishimura T, Onishi K, et al. Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease [J]. Int J Chron Obstruct Pulmon Dis, 2014, 9(default): 155-162


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大学学报 (医学版), 2017, 38(1): 31-35
Pei Hui-lin. Expression of Twist and MMP-2 in human gastric carcinoma and their clinical pathological significance [J]. Medical Journal of Wuhan University, 2017, 38(1): 31-35

[8] Liang XQ, Cao EH, Zhang Y, et al. A p53 target gene, PIG11, contributes to chemosensitivity of cells to arsenic trioxide [J]. FEBS Lett, 2004, 569(1-3): 94-98

[9] Liang XQ, Cao EH, Zhang Y, et al. p53-induced gene 11 (PIG11) involved in arsenic trioxide induced apoptosis in human gastric cancer MGC-803 cells[J]. Oncol Rep, 2003, 10(5): 1265-1269

[10] Ramachandran C, Rodriguez S, Ramachandran R, et al. Expression profiles of apoptotic genes induced by curcumin in human breast cancer and mammary epithelial cell lines[J]. Anticancer Res, 2005, 25 (5): 3293-3302

[11] 李松. PIG11 基因在人脑胶质瘤细胞中的表达及对胶质瘤 U251 细胞增殖和凋亡的影响[D]. 成都: 四川大学, 2007
Li Song. Experimental study on the expression of PIG11 in human gliomas and the effect of PIG11 gene on proliferation and apoptosis in U251 cells[D]. Chengdu: Sichuan University, 2007

[12] Liu XM, Xiong XF, Song Y, et al. Possible roles of a tumor suppressor gene PIG11 in hepatocarcinogenesis and $As_2O_3$-induced apoptosis in liver cancer cells [J]. J Gastroenterol, 2009, 44 (5): 460-469

[13] Wu Y, Liu XM, Wang XJ, et al. PIG11 is involved in hepatocellular carcinogenesis and its over-expression promotes Hepg2 cell apoptosis [J]. Pathol Oncol Res, 2009, 15(3): 411-416

[14] 王燕, 胡蓉, 梁晓秋, 等. PIG11 基因沉默与 HepG2 细胞凋亡关系的研究[J].中华肿瘤防治杂志, 2010, 17(8): 594-597
Wang Yan, Hu Rong, Liang Xiao-qiu, et al. Relationship of PIG11 gene silencing and the induced apoptosis of HepG2 cells [J]. Chinese Journal of Cancer Prevention and Treatment, 2010, 17(8): 594-597

[15] Hassan M, Watari H, AbuAlmaaty A, et al. Apoptosis and Molecular Targeting Therapy in Cancer [J]. Biomed Res Int, 2014, 2014: 150845, 23 pages

[16] Mohammad RM, Muqbil I, Lowe L, et al. Broad targeting of resistance to apoptosis in cancer [J]. Semin Cancer Biol, 2015, 35(0): S78-S103

[17] Shalini S, Dorstyn L, Dawar S, et al. Old, new and emerging functions of caspases[J]. Cell Death Differ, 2015, 22(4): 526-539

[18] Poreba M, Szalek A, Kasperkiewicz P, et al. Small molecule active site directed tools for studying human caspases [J]. Chem Rev, 2015, 115(22): 12546-12629

[19] Snigdha S, Smith ED, Prieto GA, et al. Caspase-3 activation as a bifurcation point between plasticity and cell death [J]. Neurosci Bull, 2012, 28(1): 14-24

[20] 李敏, 林俊. 细胞凋亡途径及其机制 [J]. 国际妇产科学杂志, 2014, 41(2): 103-107
Li Min, Lin Jun. The apoptotic pathways and their mechanisms [J]. Journal of International Obstetrics and Gynecology, 2014, 41 (2): 103-107

[21] Wang F, Wang L, Zhao Y, et al. A novel small-molecule activator of procaspase-3 induces apoptosis in cancer cells and reduces tumor growth in human breast, liver and gallbladder cancer xenografts [J]. Mol Oncol, 2014, 8(8): 1640-1652

[22] Ma J, Zou C, Guo L, et al. A novel Death Defying Domain in Met entraps the active site of Caspase-3 and blocks apoptosis in hepatocytes[J]. Hepatology, 2014, 59(5): 2010-2021

[23] Zhao LY, Liu YX, Tong DD, et al. MeCP2 Promotes Gastric Cancer Progression Through Regulating FOXF1/Wnt5a/β-Catenin and MYOD1/Caspase-3 Signaling Pathways[J]. EBioMedicine, 2017, 16: 87-100

[24] 陈永春, 庄英帜, 梁晓秋, 等. Caspase-8 和 Bcl-2 在 PIG11 诱导 HepG2 细胞凋亡中的作用[J]. 现代肿瘤医学, 2011, 19(9): 1716-1720
Chen Yong-chun, Zhuang Ying-zhi, Liang Xiao-qiu, et al. The effect of Caspase-8 and Bcl-2 in the apoptosis induced by PIG11 protein in human hepatocellular carcinoma HepG2 cells [J]. Journal of Modern Oncology, 2011, 19(9): 1716-1720

[25] 杨静, 王明娟, 程玉, 等. 胃癌组织中 Caspase 3、Caspase 9 的表达及其临床意义[J].临床与实验病理学杂志, 2016, 32(10): 1159-1161
Yang Jing, Wang Ming-juan, Cheng Yu, et al. Expression and clinical significance of Caspase 3 and Caspase 9 in human gastric carcinoma [J]. Chinese Journal of Clinical and Experimental Pathology, 2016, 32 (10): 1159-1161

(上接第 740 页)

[24] Sanjari N, Pakravan M, Nourinia R, et al. Intravitreal Injection of a Rho Kinase Inhibitor (Fasudil) for Recent Onset Nonarteritic Anterior Ischemic Optic Neuropathy [J]. Journal of Clinical Pharmacology, 2016, 56(6): 749-753

[25] Partridge EA, Hanna BD, Rintoul NE, et al. Brain-type natriuretic peptide levels correlate with pulmonary hypertension and requirement for extracorporeal membrane oxygenation in congenital diaphragmatic hernia [J]. Journal of Pediatric Surgery, 2015, 50 (2): 263-266

[26] Kate CAT, Tibboel D, Kraemer US, et al. B-type natriuretic peptide as a parameter for pulmonary hypertension in children. A systematic review[J]. European Journal of Pediatrics, 2015, 174(10): 1267-1275