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注射罗格列酮对多发性骨髓瘤小鼠细胞免疫功能 与 Caspase-3 表达的影响*

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摘要 目的:探讨注射罗格列酮对多发性骨髓瘤小鼠细胞免疫功能与 Caspase-3 表达的影响。**方法:**多发性骨髓瘤小鼠随机平分为三组-模型组、红细胞组与罗格列酮组,红细胞组与罗格列酮组分别给予尾静脉注射重组鼠源促红细胞生成素 5.0 mg/kg 与罗格列酮 5 mg/kg 100 μ L,模型组给予尾静脉注射等体积生理盐水,每天给药 1 次,检测细胞免疫功能与 Caspase-3 表达变化情况。**结果:**三组治疗第 7 d 与治疗第 14 d 的肿瘤体积高于治疗第 1 d($P<0.05$),红细胞组与罗格列酮组低于模型组($P<0.05$),罗格列酮组低于红细胞组($P<0.05$)。红细胞组与罗格列酮组治疗第 7 d 与治疗第 14 d 的血清白介素(Interleukin, IL)-6 与肿瘤坏死因子(Tumor necrosis factor, TNF)- α 水含量低于模型组($P<0.05$),罗格列酮组低于红细胞组($P<0.05$)。红细胞组与罗格列酮组治疗第 14 d 与治疗第 28 d 的脾脏 B 淋巴细胞、T 淋巴细胞比例对比高于模型组($P<0.05$),罗格列酮组高于红细胞组($P<0.05$)。红细胞组与罗格列酮组治疗第 14 d 与治疗第 28 d 的脑黑质 Caspase-3 蛋白表达水平低于模型组($P<0.05$),罗格列酮组低于红细胞组($P<0.05$)。**结论:**注射罗格列酮在多发性骨髓瘤小鼠的应用能改善细胞免疫功能,抑制脑黑质 Caspase-3 的表达,同时也能促进小鼠体重恢复,抑制炎症因子的表达。

关键词:罗格列酮;多发性骨髓瘤;免疫功能;Caspase-3;炎症因子;体重

中图分类号:R-33;R733.3;R551.3 **文献标识码:**A **文章编号:**1673-6273(2022)09-1642-05

Effect of Rosiglitazone Injection on Cellular Immune Function and Caspase-3 Expression in Mice with Multiple Myeloma*

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ABSTRACT Objective: To investigate the effect of rosiglitazone injection on cellular immune function and Caspase-3 expression in mice with multiple myeloma. **Methods:** Multiple myeloma mice were randomly divided into three groups-model group, red blood cell group and rosiglitazone group. The red blood cell group and rosiglitazone group were given tail vein injection of recombinant mouse erythropoietin 5.0 mg/kg and rosiglitazone 5 mg/kg 100 μ L, the model group were given equal volume of normal saline via tail vein injection, once a day, the cellular immune function and Caspase-3 expression changes were detected. **Results:** The tumor volume on the 7th and 14th day of treatment in the three groups were higher than that on the 1st day of treatment ($P<0.05$), the red blood cell group and rosiglitazone group were lower than the model group($P<0.05$), and the rosiglitazone group were lower than the red blood cell group ($P<0.05$). The serum levels of interleukin (IL)-6 and tumor necrosis factor (TNF)- α in the red blood cell group and rosiglitazone group on the 7th and 14th day of treatment were lower than those of the model group ($P<0.05$), the rosiglitazone group were lower than the red blood cell group ($P<0.05$). The ratio of splenic B lymphocytes and T lymphocytes on the 14th day and 28th day of treatment between the red blood cell group and the rosiglitazone group were higher than that of the model group ($P<0.05$), and the rosiglitazone group were higher than the red blood cell group ($P<0.05$). The expression of Caspase-3 protein in the substantia nigra of the erythrocyte group and rosiglitazone group were lower on the 14th and 28th day of treatment than the model group ($P<0.05$), and the rosiglitazone group were lower than that of the red blood cell group ($P<0.05$). **Conclusion:** The application of rosiglitazone injection in multiple myeloma mice can improve cellular immune function and inhibit the expression of Caspase-3 in the substantia nigra of the brain. At the same time, it can also promote the weight recovery of mice and inhibit the expression of inflammatory factors.

Key words: Rosiglitazone; Multiple myeloma; Immune function; Caspase-3; Inflammatory factor; Body weight

Chinese Library Classification(CLC): R-33; R733.3; R551.3 **Document code:** A

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前言

多发性骨髓瘤(multiple myeloma, MM)为临床上相对少见的恶性肿瘤,不过当前其发病人数逐年增多^[1]。多发性骨髓瘤是一种来源于B细胞起源的浆细胞恶性肿瘤,很多患者在临床上可表现为骨质破坏、贫血、高钙血症、免疫力下降与肾功能损害等特征^[2-3]。多数多发性骨髓瘤患者的中位生存期在3年左右,传统化疗措施也只能让1/4左右的患者获得超过5年的生存时间,为此在临床上需要探寻更加有效的治疗药物^[4,5]。有研究显示来那度胺、硼替佐米等靶向药物的应用能提高多发性骨髓瘤患者的生存率,但是患者最终还是会上复发,为此可认为是无法治愈的恶性肿瘤^[6,7]。过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptors, PPARs)是核受体超家族成员,可参与调控机体的炎症反应、糖脂代谢、脂肪细胞分化等过程^[8,9]。罗格列酮为人工合成的过氧化物酶体增殖物激活受体激动剂,可阻止神经元变性,对神经元有保护作用,也可通过抑制胰岛细胞凋亡而发挥降血糖作用^[10,11]。有研究显示罗格列酮具有降低Th2型细胞因子、影响树突状细胞迁移、抑制气道嗜酸粒细胞浸润等功能,从而发挥免疫调节作用^[12,13]。本文具体探讨了注射罗格列酮对多发性骨髓瘤小鼠细胞免疫功能与含半胱氨酸的天冬氨酸蛋白水解酶(cysteiny aspartate specific proteinase, Caspase)-3表达的影响,以明确罗格列酮的应用效果与机制。现报道如下。

1 材料与方 法

1.1 主要研究材料

SPF级别雌性BALB/c-nu纯合子小鼠购自北京维通利华公司(n=48, 4-6周龄,体重25~30g),饲养于SPF级无菌层流动物饲养系统。小鼠均自由饮水与饮食,在室温25±2℃单笼喂养,饲料及饮用水均经过无菌处理,垫料及饲养笼高温消毒,研究得到了医院动物伦理委员会的批准(批准号为38838481)。

淋巴细胞分离液购自美国Gibco公司,酶联免疫检测试剂盒购自美国Peninsula Laboratories公司,抗Caspase-3抗体购自美国Abcam公司,流式细胞仪购自美国BD公司,罗格列酮购自葛兰素史克公司(批号82311142),预染蛋白Marker购自福州迈新公司,人源多发性骨髓瘤细胞系RPMI8226保存于本实验室。

1.2 多发性骨髓瘤小鼠模型的建立

调整人源多发性骨髓瘤细胞系RPMI8226密度为 2×10^8 个/mL,每只小鼠接种100 μL于左后肢背部皮下,然后进行肿瘤观察,肿瘤体积 $\geq 200 \text{ mm}^3$ 表明建模成功。本次研究中共有42只建模成功,3只小鼠在建模中死亡,3只小鼠没有成功成瘤。

1.3 小鼠分组与治疗

将建模成功的小鼠随机平分为三组-模型组、红细胞组与罗格列酮组,红细胞组与罗格列酮组分别给予经尾静脉注射重组鼠源促红细胞生成素5.0 mg/kg与罗格列酮5 mg/kg 100 μL,模型组给予尾静脉注射等体积生理盐水,每天给药1次。

1.4 观察指标

(1)所有小鼠在治疗第1 d、治疗第7 d与治疗第14 d进行小鼠成瘤观察,测定肿瘤体积。(2)所有小鼠在治疗第7 d与治疗第14 d抽取腹腔血0.2 mL,分离血清后,采用酶联免疫法检测血清白介素(Interleukin, IL)-6与肿瘤坏死因子(Tumor necrosis factor, TNF)-α水平。(3)在治疗第14 d与治疗第28 d每组各处死7只小鼠,于无菌下取出脾脏,研磨后进行胰酶小鼠并进行过滤,加入红细胞裂解液,分离后鼠B淋巴细胞、T淋巴细胞后进行常规培养,采用MTT法检测B淋巴细胞、T淋巴细胞的增殖水平。(4)取处死的小鼠,分离小鼠中脑黑质部分,低温匀浆,加入蛋白裂解液4℃震荡30 min后,12 000 r/min, 4℃离心15 min,取上清液。95℃变性10 min,进行蛋白电泳,每孔蛋白上样量约为30 μg,电泳后进行转膜,加入封闭液室温下封闭1 h,取相应条带分别加入兔抗鼠Caspase-3多克隆抗体(1:500)和大鼠抗β-actin单克隆抗体(1:2000),4℃过夜,室温孵育1 h后,清洗后加入二抗室温孵育1 h,然后进行显色曝光,扫描蛋白印迹条带,作定量分析。

1.5 统计方法

本研究统计软件为SPSS 23.00,计量资料以均数±标准差表示(对比为t检验与方差分析),以P<0.05为差异有统计学意义,检验水准为α=0.05。

2 结果

2.1 肿瘤体积变化对比

三组治疗第7 d与治疗第14 d的肿瘤体积高于治疗第1 d(P<0.05),红细胞组与罗格列酮组低于模型组(P<0.05),罗格列酮组低于红细胞组(P<0.05)。见表1。

表1 三组治疗不同时间点的肿瘤体积变化对比(mm³)
Table 1 Comparison of tumor volume changes in three groups(mm³)

Groups	n	1 d after treatment	7 d after treatment	14 d after treatment	F	P
Rogsiglitazone group	14	234.82± 21.85* [#]	313.44± 41.49* [#]	376.98± 56.10* [#]	11.773	0.000
Erythrocyte group	14	235.09± 30.18*	376.27± 50.29*	467.98± 45.17*	21.014	0.000
Model group	14	235.01± 28.47	463.98± 35.10	666.28± 56.16	36.092	0.000
F		0.424	15.025	23.015		
P		0.695	0.000	0.000		

Note: Compared with the model group, *P<0.05; compared with the red blood cell group, [#]P<0.05.

2.2 血清炎症因子表达变化对比

红细胞组与罗格列酮组治疗第7 d与治疗第14 d的血清

IL-6与TNF-α含量低于模型组(P<0.05),罗格列酮组低于红细胞组(P<0.05)。见表2。

表 2 三组治疗不同时间点的血清炎症因子表达变化对比(pg/mL)

Table2 Comparison of serum inflammatory factor expression in three groups at different time points(pg/mL)

Groups	n	IL-6		TNF-α	
		7 d after treatment	14 d after treatment	7 d after treatment	14 d after treatment
Rogsiglitazone group	14	41.98± 2.87* [#]	36.87± 3.15* [#]	23.76± 3.28* [#]	18.77± 2.57* [#]
Erythrocyte group	14	78.22± 6.93*	56.87± 9.18*	56.88± 4.19*	39.26± 7.81*
Model group	14	246.15± 21.58	246.47± 18.48	113.87± 12.49	113.35± 14.20
F		29.013	31.842	13.855	15.002
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the red blood cell group, [#]P<0.05.

2.3 B 淋巴细胞、T 淋巴细胞比例对比

红细胞组与罗格列酮组治疗第 14 d 与治疗第 28 d 的脾脏

B 淋巴细胞、T 淋巴细胞比例对高于模型组(P<0.05), 罗格列酮

组高于红细胞组(P<0.05)。见表 3。

表 3 三组治疗不同时间点的脾脏 B 淋巴细胞、T 淋巴细胞比例对比(%)

Table 3 Comparison of spleen B lymphocytes and T lymphocytes at different treatment points(%)

Groups	n	B lymphocytes		T lymphocytes	
		7 d after treatment	14 d after treatment	7 d after treatment	14 d after treatment
Rogsiglitazone group	7	17.21± 3.28* [#]	21.58± 2.18* [#]	21.76± 4.38* [#]	27.83± 4.19* [#]
Erythrocyte group	7	13.87± 2.66*	18.76± 3.17*	17.88± 3.28*	24.09± 6.88*
Model group	7	8.88± 0.38	8.89± 0.44	10.02± 1.58	10.11± 1.57
F		9.813	13.853	11.095	15.772
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the red blood cell group, [#]P<0.05.

2.4 Caspase-3 蛋白表达水平对比

红细胞组与罗格列酮组治疗第 14 d 与治疗第 28 d 的脑黑

质 Caspase-3 蛋白表达水平低于模型组(P<0.05), 罗格列酮组低

于红细胞组(P<0.05)。见表 4。

表 4 三组治疗不同时间点的脑黑质 Caspase-3 蛋白表达水平对比

Table 4 Comparison of cerebral melanCaspase-3 protein expression levels in three groups at different time points

Groups	n	14 d after treatment	28 d after treatment
Rogsiglitazone group	7	3.87± 0.44* [#]	2.53± 0.33* [#]
Erythrocyte group	7	7.92± 1.22*	5.82± 0.73*
Model group	7	17.25± 2.91	17.33± 1.57
F		31.842	38.757
P		0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the red blood cell group, [#]P<0.05.

3 讨论

多发性骨髓瘤是浆细胞克隆样增生的恶性肿瘤,也为血液系统的常见恶性肿瘤^[14]。该病多发生于中老年人,男性发病率高于女性,多伴随有多种临床症状,在临床上不能根除治愈,使得患者的预后比较差^[15]。当前对于多发性骨髓瘤的治疗方法主要包括化疗、造血干细胞移植等,但是治疗的有效率在 50.0 % 左右,完全缓解率低于 20.0 %^[16,17]。因此,亟待寻找能够有效治疗多发性骨髓瘤的重要方法与药物,对于改善患者的预后具有

重要价值。随着多发性骨髓瘤发病机制研究的进展与靶向药物研究的进展,当前针对多发性骨髓瘤的靶向治疗药物也逐渐增多^[18]。但是由于人体试验所涉及的医学伦理问题,因此构建多发性骨髓瘤小鼠模型并进行药物试验分析具有重要价值。

过氧化物酶体增殖物激活受体是一类核激素受体,在上皮细胞、内皮细胞气道平滑肌细胞均可表达,其被激活后可发挥相应的生理性效应^[19,20]。罗格列酮可以可增加 2 型糖尿病小鼠脂肪细胞线粒体 DNA 含量,升高淋巴细胞线粒体膜电位,上调琥珀酸脱氢酶、ATP 合酶的蛋白表达水平^[21];其也可增加脂肪

细胞线粒体含量,降低气道高反应性,调节线粒体生物合成,从而有利于发挥抑癌作用^[22]。本研究显示三组治疗第 7 d 与治疗第 14 d 的肿瘤体积高于治疗第 1 d,红细胞组与罗格列酮组低于模型组($P<0.05$),罗格列酮组低于红细胞组($P<0.05$);红细胞组与罗格列酮组治疗第 7 d 与治疗第 14 d 的血清 IL-6 与 TNF- α 含量低于模型组 ($P<0.05$), 罗格列酮组低于红细胞组 ($P<0.05$), 表明注射罗格列酮在多发性骨髓瘤小鼠的应用能促进体重恢复,抑制炎症因子的表达。多发性骨髓瘤患者的 IL-6 与 TNF- α 存在高表达状况,在疾病发作过程中发挥重要作用。相关研究显示:骨髓瘤细胞自身可以分泌 IL-6 与 TNF- α ,而分泌的 IL-6 与 TNF- α 又可以促进骨髓瘤细胞增殖,从而形成恶性循环,且炎症反应时巨噬细胞分泌的 IL-6 与 TNF- α 能够通过损伤血管内皮细胞,促进血管平滑肌细胞增殖,促进巨噬细胞的黏附作用,诱发凝血过程^[23,24]。另外,Zhou YQ^[25]等研究显示:注射罗格列酮可以抑制 IL-6 与 TNF- α 的分泌,还可抑制 NF- κ B 的活性,从而可以抑制骨髓瘤细胞的生长,与本研究结果一致。

当前化疗是治疗多发性骨髓瘤最基本的方法之一,能稍微延长患者的生存时间,但是其存在耐药率高、治疗费用高、并发症多等问题,使得患者的复发率也比较高。同时化疗对多发性骨髓瘤患者的免疫功能有一定的负面影响,可导致脾脏 B 淋巴细胞、T 淋巴细胞比例下降,也不利于患者预后康复^[26]。免疫系统是机体重要的防御系统,其中细胞免疫为免疫系统的主要组成部分,能够迅速与入侵病原体反应,利用树突状细胞、NK 细胞、主要包括巨噬细胞、 $\gamma\delta$ T 细胞和相关免疫分子等清除入侵的病原体等^[27]。本研究显示:治疗第 14 d 与治疗第 28 d,红细胞组与罗格列酮组的脾脏 B 淋巴细胞、T 淋巴细胞比例对高于模型组,罗格列酮组高于红细胞组($P<0.05$),表明注射罗格列酮在多发性骨髓瘤小鼠的应用能改善小鼠的免疫功能。相关研究^[28,29]也显示罗格列酮能增强多发性骨髓瘤机体巨噬细胞吞噬能力,提高机体的免疫调节能力,与本研究结论一致。另外,结合 Kundu A^[30]和 Szoka L^[31]分析其作用机制在于:罗格列酮是调节线粒体生物合成的关键因子,可抑制气道黏液分泌,还可对外周血中的淋巴细胞产生调控作用,从而可改善多发性骨髓瘤小鼠的免疫功能。

目前对多发性骨髓瘤的治疗仅限于对症和神经保护性治疗,但是很难持续发挥效应,且长期应用会产生一系列并发症。不过凋亡和多发性骨髓瘤的发病存在着密切的关系,那么抑制凋亡的发生必然成为治疗多发性骨髓瘤的重要手段。本研究显示红细胞组与罗格列酮组治疗第 14 d 与治疗第 28 d 的脑黑质 Caspase-3 蛋白表达水平低于模型组($P<0.05$),罗格列酮组低于红细胞组($P<0.05$),表明注射罗格列酮在多发性骨髓瘤小鼠的应用能抑制凋亡。相关研究显示罗格列酮可通过减少小胶质细胞释放炎症因子,可以通过抑制凋亡蛋白的表达,减轻多巴胺能神经元变性丢失,改善机体的运动功能^[32]。同时罗格列酮可通过抑制神经元凋亡,减轻黑质多巴胺能神经元丢失,刺激导致线粒体细胞色素 C 释放,Caspase-3 的活化又诱发凋亡过程^[33]。本研究也存在一定的不足,没有进行细胞学分析,设置的组别比较少,没有进行剂量学分析,将在后续研究中探讨。

总之,注射罗格列酮在多发性骨髓瘤小鼠的应用能改善细

胞免疫功能,抑制脑黑质 Caspase-3 的表达,也能促进小鼠体重恢复,抑制炎症因子的表达。

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