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阿魏酸钠对肺结核模型小鼠免疫功能及肺泡巨噬细胞吞噬功能的调控作用研究 *

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摘要 目的:探讨与分析阿魏酸钠对肺结核模型小鼠免疫功能及肺泡巨噬细胞吞噬功能的调控作用。**方法:**肺结核模型小鼠(n=36)随机分为模型组、利福平组、阿魏酸钠组,每组各 12 只。利福平组、阿魏酸钠组分别给予 100 mg/kg 剂量的利福平与阿魏酸钠,模型组小鼠灌胃等量生理盐水,1 次 /d,给药 6 周,观察与记录所有小鼠的一般特征;分别于给药第 2 周、第 4 周、第 6 周,HE 染色观察小鼠的病理特征;MDA 检测试剂盒和总 SOD 活性检测试剂盒测定肺组织 MDA 水平与 SOD 活性;流式细胞仪检测小鼠 T 淋巴细胞亚群 -$CD3^+$T 淋巴细胞、$CD4^+$T 淋巴细胞水平; 酶联免疫法检测血清 IL-6、IL-8 含量;AnnexinV-FITC 检测肺泡巨噬细胞凋亡率。**结果:**利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺组织丙二醛(Malondialdehyde,MDA)水平低于模型组(P<0.05),超氧化物歧化酶(superoxide dismutase,SOD)活性高于模型组(P<0.05),利福平组与阿魏酸钠组对比也有明显差异(P<0.05)。利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血液 $CD3^+$T 淋巴细胞、$CD4^+$T 淋巴细胞比例明显高于模型组(P<0.05),阿魏酸钠组也高于利福平组(P<0.05)。利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血清 IL-6、IL-8 含量明显低于模型组(P<0.05),阿魏酸钠组也低于利福平组(P<0.05)。利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺泡灌洗液(broncho alveolar lavage fluid,BALF)巨噬细胞凋亡率明显低于模型组(P<0.05),阿魏酸钠组也明显低于利福平组(P<0.05)。**结论:**阿魏酸钠在肺结核模型小鼠的应用可抑制炎症因子的表达,并改善氧化状况,还能增强小鼠的免疫功能,降低肺泡灌洗液巨噬细胞凋亡率。

关键词:阿魏酸钠;肺结核;炎症因子;氧化应激;免疫功能;肺泡灌洗液;巨噬细胞
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Study on the Regulatory Effect of Sodium Ferulate on the Immune Function and Phagocytic Function of Alveolar Macrophages in Pulmonary Tuberculosis Model Mice*

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ABSTRACT Objective: To explore and analysis the regulatory effect of sodium ferulate on the immune function and phagocytic function of alveolar macrophages in pulmonary tuberculosis model mice. **Methods:** Pulmonary tuberculosis model mice (n=36) were randomly divided into model group, rifampicin group and sodium ferulate group, with 12 mice in each group. Rifampicin group and sodium ferulate group were given 100 mg/kg dose of rifampicin and sodium ferulate respectively, and the mice in the model group were given the same amount of normal saline, once a day, for 6 weeks, and the general characteristics of all mice were observed and recorded; the pathological characteristics of the mice were observed by HE staining at the 2nd, 4th, and 6th weeks of administration; MDA detection kit and total SOD activity detection kit were used to determine the level of MDA and SOD activity in lung tissue; Flow cytometry was used to detect the levels of mouse T lymphocyte subsets-$CD3^+$T lymphocytes and $CD4^+$T lymphocytes; Serum IL-6 and IL-8 levels were detected by enzyme-linked immunosorbent assay; The apoptosis rate of alveolar macrophages was detected by AnnexinV-FITC. **Results:** The levels of MDA in the lung tissue of the rifampicin group and the sodium ferulate group were lower than those of the model group (P<0.05),

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and the SOD activity were higher than that of the model group (P<0.05) in the 2nd, 4th, and 6th weeks after administration, and there were also significant difference between the rifampicin group and the sodium ferulate group (P<0.05). The ratios of blood $CD3^+$T lymphocytes and $CD4^+$T lymphocytes in the rifampicin group and sodium ferulate group were significantly higher than those in the model group in the 2nd, 4th, and 6th weeks of administration (P<0.05). The sodium group were also higher than the rifampicin group (P<0.05). The serum levels of IL-6 and IL-8 in the rifampicin group and the sodium ferulate group were significantly lower than those in the model group in the 2nd, 4th, and 6th weeks after administration (P<0.05), and the sodium fululate group were also lower than the model group. in the rifampicin group (P<0.05). The apoptosis rate of macrophages in BALF in the rifampicin group and sodium ferulate group at the 2nd, 4th, and 6th weeks of administration were significantly lower than that in the model group (P<0.05). the sodium ferulate group were also significantly lower than the rifampicin group (P<0.05). **Conclusion:** The application of sodium ferulate in pulmonary tuberculosis model mice can inhibit the expression of inflammatory factors, improve the oxidation status, enhance the immune function of mice, and reduce the apoptosis rate of macrophages in BALF.

Key words: Sodium ferulate; Pulmonary tuberculosis; Inflammatory factors; Oxidative stress; Immune function; BALF; Macrophages

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前言

肺结核是一种由结核分枝杆菌所引发的传染性疾病,其发病率逐年上升。由于各种因素的影响,当前结核病的发患者数逐年增加,还出现很多新型及多重耐药菌株,且死亡率一直居高不下,严重威胁着全球人类的身体健康[1,2]。当前治疗肺结核的药物比较多,但是治疗效果欠佳,且反复使用西药容易导致患者出现耐药性,还可出现不良反应[3,4]。同时肺结核患者多伴随有免疫功能低下,主要表现为细胞增殖能力下降、细胞表面抑制性受体增加、细胞因子分泌能力降低、细胞毒作用丧失等[5,6]。特别是肺结核抗原特异性的 $CD4^+$ 和 $CD8^+$T 细胞分泌干扰素与抑炎因子的能力下降,T 细胞免疫球蛋白黏蛋白 -3、程序性死亡受体表达增高,说明结核分枝杆菌的持续感染可引起机体免疫功能异常与肺泡巨噬细胞吞噬功能下降[7,8]。肺结核患者在中医上可归为 " 阴虚发热 " 等范畴,曰骨蒸、曰劳嗽、曰吐血,则成尸疰,在治疗上需要扶正培本[9]。扶正培本能够提高脾和肾的免疫功能,也能有效调动机体的抵抗能力,从而对肺结核病患者免疫功能发挥增强作用。阿魏酸钠是从川芎、阿魏等植物中提取分离得到的化合物,具有抗菌、抗炎、抗病毒等多种药理活性,对肺组织有一定的修复作用[10,11]。本文探讨与研究了阿魏酸钠对肺结核模型小鼠免疫功能及肺泡巨噬细胞吞噬功能的调控作用,以明确阿魏酸钠的应用价值与机制。

1 材料与方法

1.1 实验材料

1.1.1 实验动物 SPF 级 CD2F1 雌性小鼠北京维通利华实验动物技术有限公司,体重 25± 2 g,饲养于本院动物实验中心屏障动物实验设施,本文研究实验过程均按照国际动物伦理相关文件要求实施。饲养条件:相对湿度 35.0 %,室温 22.0 ℃左右,饲养于干净笼子里,喂饮纯净水,适应性喂养 1 周。

1.1.2 实验试剂 PE 标记的小鼠抗人相关抗体购自美国 sigma 公司,磷酸盐缓冲液购自上海恒斐生物科技有限公司,阿魏酸钠购自国药集团。MDA 检测试剂盒(硫代巴比妥酸法)和总 SOD 活性检测试剂盒(NBT 法)均购自上海碧云天生物科技有限公司。酶联免疫检测试剂盒购自北京博奥森生物技术有限公司,人型结核分枝杆菌 H37Rv 标准菌株保存于本实验室,利福平胶囊购自沈阳红旗制药有限公司。

1.2 肺结核小鼠分组与治疗

选用人型结核分枝杆菌 H37Rv 标准菌株感染小鼠,取 0.4 mL 含 6.6×10^5 CFU 的结核分支杆菌 H37Rv 菌悬液注入小鼠尾静脉,建立肺结核小鼠模型。在建模成功后,将肺结核小鼠(n=36)随机分为模型组、利福平组、阿魏酸钠组,每组各 12 只。

利福平组、阿魏酸钠组分别给予 100 mg/kg 剂量的利福平与阿魏酸钠,模型组小鼠灌胃等量生理盐水,1 次 /d,给药 6 周。

1.3 观察指标

(1)在给药第 2 周、第 4 周、第 6 周每组分别处死大鼠 4 只,在无菌、低温条件下取小鼠肺组织,在 4.0%多聚甲醛中浸泡、固定,然后进行 HE 染色处理,观察小鼠的病理特征。(2)分离大鼠的肺组织,匀浆后离心取上清液,分别按照 MDA 检测试剂盒(硫代巴比妥酸法)和总 SOD 活性检测试剂盒(NBT 法)说明书测定肺组织匀浆中 MDA 水平与 SOD 活性。(3)同时取处死小鼠的尾静脉血 2-3 mL,使用肝素钠行抗凝处理,使用流式细胞仪检测小鼠 T 淋巴细胞亚群 -$CD3^+$T 淋巴细胞、$CD4^+$T 淋巴细胞水平。另外一部分血液样本分离血清后,采用酶联免疫法检测血清 IL-6、IL-8 含量。(4)分离处死大鼠的 BALF,4 ℃下 2000 r/min 离心 15 min,弃去上清液,分离肺泡巨噬细胞。使用 AnnexinV-FITC 结合液及 AnnexinV-FITC 处理细胞,上流式细胞仪,检测肺泡巨噬细胞凋亡率。

1.4 统计方法

本次研究统计软件为 SPSS24.00,计量数据与计数数据以均数± 标准差、率等表示,两两对比方法为 t 检验与卡方分析等,三组间对比采用单因素方差分析,检验水准为 α=0.05。

2 结果

2.1 肺组织 MDA 水平与 SOD 活性对比

利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺组织 MDA 水平低于模型组(P<0.05),SOD 活性高于模型组(P<0.05),利福平组与阿魏酸钠组对比也有明显差异(P<0.05)。见表2。

表 1 三组给药不同时间点的肺组织 MDA 水平与 SOD 活性对比

Table 1 Comparison of MDA levels in lung tissue and SOD activity at different time points in the three groups

Groups	n	MDA(nmol/mgprot)			SOD(U/mgprot)		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
Model group	4	2.11± 0.18	2.13± 0.23	2.14± 0.11	47.33± 2.18	47.44± 1.48	47.59± 1.68
Rifampin group	4	1.76± 0.28[a]	1.34± 0.17[a]	1.00± 0.25[a]	54.29± 3.39[a]	58.91± 4.14[a]	62.47± 3.15[a]
Sodium ferulic acid group	4	1.32± 0.21[ab]	0.98± 0.14[ab]	0.73± 0.13[ab]	62.49± 4.10[ab]	66.38± 4.42[ab]	71.37± 4.40[ab]
F		12.383	15.033	16.044	22.104	25.855	28.174
P		＜0.001	＜0.001	＜0.001	＜0.001	＜0.001	＜0.001

Note: Compared with the model group, [a]*P*<0.05; compared with the rifampicin group, [b]*P*<0.05 the same below.

2.2 $CD3^+T$ 淋巴细胞、$CD4^+T$ 淋巴细胞比例对比

利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血液 $CD3^+T$ 淋巴细胞、$CD4^+T$ 淋巴细胞比例明显高于模型组(*P*<0.05)，阿魏酸钠组也高于利福平组(*P*<0.05)。见表 2。

表 2 三组给药不同时间点的血液 $CD3^+T$ 淋巴细胞、$CD4^+T$ 淋巴细胞比例对比

Table 2 Comparison of proportions of blood $CD3^+T$ lymphocytes and $CD4^+T$ lymphocytes at different time points of administration in the three groups

Groups	n	$CD3^+T$ lymphocytes			$CD4^+T$ lymphocytes		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
Model group	4	43.33± 2.83	43.23± 4.14	43.14± 3.38	19.33± 1.48	19.32± 1.11	19.43± 2.18
Rifampin group	4	48.22± 3.14[a]	52.48± 3.18[a]	57.28± 3.18[a]	24.88± 2.47[a]	28.17± 3.13[a]	32.10± 4.38[a]
Sodium ferulic acid group	4	56.28± 4.28[ab]	61.84± 5.14[ab]	68.35± 4.55[ab]	31.48± 3.19[ab]	35.69± 2.86[ab]	39.58± 3.15[ab]
F		14.644	19.382	22.103	14.482	16.533	20.104
P		＜0.001	＜0.001	＜0.001	＜0.001	＜0.001	＜0.001

2.3 血清 IL-6、IL-8 含量对比

利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血清 IL-6、IL-8 含量明显低于模型组(*P*<0.05)，魏酸钠组也低于利福平组(*P*<0.05)。见表 3。

表 3 三组给药不同时间点的血清 IL-6、IL-8 含量对比(pg/mL)

Table 3 Comparison of serum IL-6 and IL-8 content at different time points (pg/mL)

Groups	n	IL-6			IL-8		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
Model group	4	66.39± 2.38	66.33± 3.19	66.29± 3.19	26.23± 3.18	26.29± 1.49	26.44± 2.77
Rifampin group	4	48.48± 4.19[a]	35.11± 3.39[a]	28.19± 2.47[a]	19.22± 2.29[a]	15.79± 1.67[a]	12.47± 3.13[a]
Sodium ferulic acid group	4	26.93± 3.82[ab]	21.48± 1.11[ab]	15.59± 1.18[ab]	12.87± 1.84[ab]	8.87± 0.82[ab]	6.31± 0.23[ab]
F		40.111	42.023	39.842	14.044	18.932	20.444
P		＜0.001	＜0.001	＜0.001	＜0.001	＜0.001	＜0.001

2.4 肺泡灌洗液巨噬细胞凋亡率对比

利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺泡灌洗液巨噬细胞凋亡率明显低于模型组(*P*<0.05)，阿魏酸钠组也明显低于利福平组(*P*<0.05)。见表 4。

表 4 三组给药不同时间点的肺泡灌洗液巨噬细胞凋亡率对比(%)

Table 4 Comparison of apoptosis rates of alveolar lavage cells at different time points(%)

Groups	n	Week 2	Week 4	Week 6
Model group	4	23.57± 1.28	23.49± 0.84	23.84± 1.11
Rifampin group	4	14.59± 1.48[a]	10.03± 1.11[a]	9.17± 0.36[a]
Sodium ferulic acid group	4	11.83± 1.22[ab]	8.87± 0.38[ab]	5.49± 0.46[ab]
F		12.013	15.014	18.881
P		＜0.001	＜0.001	＜0.001

3 讨论

结核病是由结核分枝杆菌感染所导致的疾病，其传染途径多样，具有高患病率、高耐药率、高死亡率、高感染率等特征，当前随着多重耐药因素的影响以及社会环境的变化，导致肺结核的发病率逐年升高[12]。特别是由于不规律用药、不合理的联合用药、及免疫损害宿主的增多等，致使我国结核病患者中耐药者比例越来越高，也出现了大量复治患者[13]。

中医医学认为肺结核为一种＂肺痨＂、为＂虚症＂疾病，是由各种原因耗伤人体元气，减低免疫功能而导致的感染性疾病，在治疗上需要驱灭＂痨虫＂与调补元气[14]。本研究显示利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺组织 MDA 水平低于模型组(P<0.05)，SOD 活性高于模型组(P<0.05)，利福平组与阿魏酸钠组对比也有明显差异(P<0.05)；利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血清 IL-6、IL-8 含量明显低于模型组(P<0.05)，魏酸钠组也低于利福平组(P<0.05)，表明阿魏酸钠在肺结核模型小鼠的应用能抑制炎症因子的表达，还可改善氧化状况，结合 Li S[15]和 Barbero A M[16]可知：阿魏酸钠是由从伞形科植物阿魏、川芎等植物中提取得到的阿魏酸进一步成盐得到的化合物，具有抗炎、抗病毒、抗感染、增强前列腺素活性、抑制血小板血栓素 A2 生成、抗血小板聚集、抑制血小板 5- 羟色胺释放等作用；另外，并且阿魏酸钠对多种病菌的核酸与蛋白质合成具有明显抑制作用，因此可进一步抑制脂多糖诱导的急性肺损伤体内炎性介质释放，从而发挥很好的肺功能保护作用[17,18]。

随着医疗费用的不断增长，研究肺结核的发病机制具有重要价值。肺结核属于一种免疫相关性疾病，患者可调节免疫细胞的生长、分化，可启动负反馈调节限制过度的炎症反应给机体所带来的损伤，从而促进杀灭分枝杆菌[19,20]。结核免疫的重要组成部分为细胞，可有效杀灭结核分枝杆菌，还可启动负反馈调节限制过度的炎症反应给机体所带来的损伤[21]。特别是当患者感染结核杆菌后，细胞免疫功能会显著降低，$CD4^+T$ 细胞的反应性与结核病的严重程度存在相关性[22]。中医认为肺结核患者发生了脾、肺、肾三脏亏虚，在治疗上需要扶正培本[23]。本研究显示利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的血液 $CD3^+T$ 淋巴细胞、$CD4^+T$ 淋巴细胞比例明显高于模型组(P<0.05)，阿魏酸钠组也高于利福平组(P<0.05)，表明阿魏酸钠在肺结核模型小鼠的应用能提高免疫功能，分析其作用机制可能为：阿魏酸钠能抑制肺部胶原蛋白合成，能抑制肺纤维化，还可有效改善机体的肺通气功能，从而可进一步降低氧化应激诱导的炎性复合体及成纤维细胞的活性，因此对肺结核小鼠的免疫功能具有改善作用[24,25]。

机体的免疫状态是个动态过程，机体的免疫系统也是一个复杂精细的平衡系统。特别是结核分枝杆菌进入机体后，巨噬细胞通过表面受体识别结核分枝杆菌，进入巨噬细胞后与溶酶体融合，在其内部多种酶的作用下杀死结核杆菌，激活体内特异性免疫过程，能被巨噬细胞呈递给 T 淋巴细胞，从而发挥杀死结核分枝杆菌的作用[26,27]。阿魏酸钠能提高细胞免疫、促进淋巴细胞转化，对结核杆菌有不同程度的抑制和杀灭作用，还可通过其介导的免疫提高了巨噬细胞的杀菌效应[28,29]。本研究显示利福平组、阿魏酸钠组给药第 2 周、第 4 周、第 6 周的肺泡灌洗液巨噬细胞凋亡率明显低于模型组(P<0.05)，阿魏酸钠组也明显低于利福平组(P<0.05)，表明阿魏酸钠在肺结核模型小鼠的应用能降低肺泡灌洗液巨噬细胞凋亡率，结合 Stutz M D 等研究[30]分析其作用机制可能在于 -- 阿魏酸钠具有显著的增强免疫的作用，抑制氧化应激损伤，可抑制巨噬细胞内部结核杆菌的释放，从而改善患者的肺功能。此外，本研究不足之处在于 -- 由于经费投入比较少，没有设置空白对照组，也没有进行剂量分析探讨，将在后续研究中分析。

总之，阿魏酸钠在肺结核模型小鼠的应用能抑制炎症因子的表达，还可改善氧化状况，还能提高小鼠的免疫功能，降低肺泡灌洗液巨噬细胞凋亡率。

参 考 文 献（References）

[1] Xu W, Snell L M, Guo M, et al. Early innate and adaptive immune perturbations determine long-term severity of chronic virus and Mycobacterium tuberculosis coinfection [J]. Immunity, 2021, 54 (3): 526-541

[2] Yadav B, Rai A, Mundada P S, et al. Safety and efficacy of Ayurvedic interventions and Yoga on long term effects of COVID-19: A structured summary of a study protocol for a randomized controlled trial [J]. Trials, 2021, 22(1): 378-385

[3] Zhao Y, Zhang J, Xue B, et al. Serum levels of inhibitory costimulatory molecules and correlations with levels of innate immune cytokines in patients with pulmonary tuberculosis [J]. J Int Med Res, 2021, 49(8): 36832-36839

[4] Dijkman K, Aguilo N, Boot C, et al. Pulmonary MTBVAC vaccination induces immune signatures previously correlated with prevention of tuberculosis infection[J]. Cell Rep Med, 2021, 2(1): 100187-100189

[5] Dornelas Moreira J, Freire Campos Nunes F, Cristina Gontijo Evangelista F, et al. Circulating microparticles from subjects with active pulmonary tuberculosis infection modulate immune response [J]. Eur J Immunol, 2021, 51(5): 1282-1284

[6] 顾小燕,胡春梅,尹春阳,等.莫西沙星联合用药方案对耐多药肺结核患者血清游离氨基酸和免疫功能的影响 [J]. 现代生物医学进展, 2020, 20(6): 1087-1090+1115

[7] Bernard-Raichon L, Colom A, Monard S C, et al. A Pulmonary Lactobacillus murinus Strain Induces Th17 and RORγt (+) Regulatory T Cells and Reduces Lung Inflammation in Tuberculosis[J]. J Immunol, 2021, 207(7): 1857-1870

[8] Bewket G, Kiflie A, Abate E, et al. Helminth species specific expansion and increased TNF-alpha production of non-classical monocytes during active tuberculosis [J]. PLoS Negl Trop Dis, 2021, 15 (3): e0009194

[9] 蔡剑飞,刘忠达,徐磊,等. 穴位贴敷联合中西药治疗老年复治肺结核阴虚火旺证的临床观察[J]. 上海针灸杂志, 2022, 41(3): 231-237

[10] Bhatt K, Bhagavathula M, Verma S, et al. Rapamycin modulates pulmonary pathology in a murine model of Mycobacterium tuberculosis infection[J]. Dis Model Mech, 2021, 14(10): 1113-1118

[11] Devalraju K P, Neela V S K, Krovvidi S S, et al. Defective expansion and function of memory like natural killer cells in HIV+ individuals with latent tuberculosis infection [J]. PLoS One, 2021, 16 (9): e0257185

[12] Gong Z, Han S, Liang T, et al. Mycobacterium tuberculosis effector PPE36 attenuates host cytokine storm damage via inhibiting macrophage M1 polarization [J]. J Cell Physiol, 2021, 236 (11): 7405-7420

[13] Hu B, Ren G, Zhao L. Effect of Health Education Combined with Dietary Guidance on Nutritional Indicator, Immune Level, and Quality of Life of Patients with Pulmonary Tuberculosis [J]. Comput Math Methods Med, 2021, 7(15): 9463577

[14] 周劲勇. 百合固金汤合肺痨汤治疗阴虚火旺证耐药性肺结核疗效观察[J].四川中医, 2020, 38(08): 73-76

[15] Li S, Wang D, Wei P, et al. Elevated Natural Killer Cell-Mediated Cytotoxicity Is Associated with Cavity Formation in Pulmonary Tuberculosis Patients[J]. J Immunol Res, 2021, 8(14): 7925903

[16] Barbero A M, Trotta A, Genoula M, et al. SLAMF1 signaling induces Mycobacterium tuberculosis uptake leading to endolysosomal maturation in human macrophages [J]. J Leukoc Biol, 2021, 109 (1): 257-273

[17] Xiong K, Sun W, Wang H, et al. The frequency and dynamics of CD4 (+) mucosal-associated invariant T (MAIT) cells in active pulmonary tuberculosis[J]. Cell Immunol, 2021, 365(9): 104381

[18] Li X, Wang M, Ming S, et al. TARM-1 Is Critical for Macrophage Activation and Th1 Response in Mycobacterium tuberculosis Infection[J]. J Immunol, 2021, 207(1): 234-243

[19] Liu S, Wu M, A E, et al. Factors associated with differential T cell responses to antigens ESAT-6 and CFP-10 in pulmonary tuberculosis patients[J]. Medicine (Baltimore), 2021, 100(8): e24615

[20] María Irene C C, Juan Germán R C, Gamaliel L L, et al. Profiling the immune response to Mycobacterium tuberculosis Beijing family infection: a perspective from the transcriptome [J]. Virulence, 2021, 12 (1): 1689-1704

[21] 顾小燕,胡春梅,尹春阳,等.莫西沙星联合用药方案对耐多药肺结核患者血清游离氨基酸和免疫功能的影响[J].现代生物医学进展, 2020, 20(06): 1087-1090+1115

[22] Valdez-Palomares F, Muñoz Torrico M, Palacios-González B, et al. Altered Microbial Composition of Drug-Sensitive and Drug-Resistant TB Patients Compared with Healthy Volunteers [J]. Microorganisms, 2021, 9(8): 1113-1119

[23] Varzari A, Deyneko I V, Tudor E, et al. Synergistic effect of genetic polymorphisms in TLR6 and TLR10 genes on the risk of pulmonary tuberculosis in a Moldavian population [J]. Innate Immun, 2021, 27 (5): 365-376

[24] Mata E, Tarancon R, Guerrero C, et al. Pulmonary BCG induces lung-resident macrophage activation and confers long-term protection against tuberculosis[J]. Sci Immunol, 2021, 6(63): eabc2934

[25] Menzies N A, Quaife M, Allwood B W, et al. Lifetime burden of disease due to incident tuberculosis: a global reappraisal includ ing post-tuberculosis sequelae [J]. Lancet Glob Health, 2021, 9 (12): e1679-e1687

[26] 刘冬梅,韩晓群,杨婧,等.PPARγ/CD36 信号通路在结核分枝杆菌感染巨噬细胞脂质代谢中的作用[J].中华微生物学和免疫学杂志, 2021, 41(10): 749-756

[27] Nathan A, Beynor J I, Baglaenko Y, et al. Multimodally profiling memory T cells from a tuberculosis cohort identifies cell state associations with demographics, environment and disease[J]. Nat Immunol, 2021, 22(6): 781-793

[28] Palma Albornoz S P, Fraga-Silva T F C, Gembre A F, et al. Obesity-Induced Dysbiosis Exacerbates IFN-γ Production and Pulmonary Inflammation in the Mycobacterium tuberculosis Infection [J]. Cells, 2021, 10(7): 1114-1119

[29] Thiel B A, Worodria W, Nalukwago S, et al. Immune cells in bronchoalveolar lavage fluid of Ugandan adults who resist versus those who develop latent Mycobacterium tuberculosis infection [J]. PLoS One, 2021, 16(4): e0249477

[30] Stutz M D, Allison C C, Ojaimi S, et al. Macrophage and neutrophil death programs differentially confer resistance to tuberculosis[J]. Immunity, 2021, 54(8): 1758-1771

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[22] 徐芳琴, 张新睿, 郭凤伟, 等. 中成药质量控制研究进展[J]. 现代生物医学进展, 2014, 14(31): 6159-6163

[23] 付明海, 阿丽沙, 包保全, 等. 蒙药材芹叶铁线莲对海虾幼虫的致死活性[J]. 内蒙古民族大学学报, 2011, 17(2): 79-80

[24] Zhang Q, Lu Y-Y, Yang L, et al. New triterpenoid saponins from the whole plants of Clematis heracleifolia [J]. Fitoterapia, 2022, 159: 105179

[25] Lin TF, Wang L, Zhang Y, et al. Uses, chemical compositions, pharmacological activities and toxicology of Clematidis Radix et Rhizome- a review[J]. J Ethnopharmacol, 2021, 270: 113831

[26] Tian X-R, Feng J-T, Ma Z-Q, et al. Three new glycosides from the whole plant of Clematis lasiandra Maxim and their cytotoxicity [J]. Phytochem Lett, 2014, 10: 168-172