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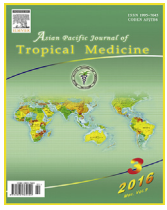

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Immune formulation-assisted conventional therapy on anti-infective effectiveness of multidrug-resistant *Mycobacterium tuberculosis* infection mice

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ABSTRACT

Objective: To study the effect of immune formulation-assisted conventional therapy on anti-infective ability of multidrug-resistant *Mycobacterium tuberculosis* infection mice.
Methods: BALB/c mice were used as experimental animals, multidrug-resistant *M. tuberculosis* infection models were built, randomly divided into model group, moxifloxacin group, thymopentin group and combined treatment group and given corresponding drug intervention, and then colony numbers in the spleen and lung, T lymphocyte subset contents and programmed death-1 (PD-1) expression levels in peripheral blood were detected.
Results: Colony numbers in lung and spleen of moxifloxacin group and thymopentin group were significantly lower than those of model group and colony numbers in lung and spleen of combined treatment group were significantly lower than those of moxifloxacin group and thymopentin group; contents of $CD3^+CD4^+$T cells, Th1 and Th17 in peripheral blood of moxifloxacin group and thymopentin group were higher than those of model group, and contents of $CD3^+CD8^+$T cells, Th2 and Treg were lower than those of model group; contents of $CD3^+CD4^+$T cells, Th1 and Th17 in peripheral blood of combined treatment group were higher than those of moxifloxacin group and thymopentin group, and contents of $CD3^+CD8^+$T cells, Th2 and Treg were lower than those of moxifloxacin group and thymopentin group; PD-1 expression levels on T lymphocyte, B lymphocyte and monocyte surface in peripheral blood of moxifloxacin group and thymopentin group were lower than those of model group, and PD-1 expression levels on T lymphocyte, B lymphocyte and monocyte surface in peripheral blood of combined treatment group were lower than those of moxifloxacin group and thymopentin group.
Conclusions: Immune formulation thymopentin can enhance the anti-infective ability of multidrug-resistant *M. tuberculosis* infection mice, decrease bacterial load in lung and spleen, and enhance immune function.

1. Introduction

Tuberculosis is a respiratory infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), and affected by bacterial mutation, wide use of chemotherapy drugs and other factors, the incidence of multidrug-resistant tuberculosis caused by multidrug-resistant *M. tuberculosis* infection is rising [1,2]. The killing effect of conventional chemotherapy drugs on multidrug-resistant *M. tuberculosis* is not ideal, and second-line anti-tubercular drugs have longer course of treatment, more adverse reactions and lower cure rate [3–5]. In recent years, more and more studies have realized that weakened immune function is associated with multidrug-resistant tuberculosis infection, and targeted immune formulation adjuvant therapy has become an important part of anti-tuberculosis comprehensive treatment [6]. Thymopentin is a drug enhancing immune activity and clinical common immune formulation [7]. In the following

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research, the effect of immune formulation-assisted conventional therapy on anti-infective ability of multidrug-resistant *M. tuberculosis* infection mice was analyzed.

2. Materials and methods

2.1. Experimental materials

Experimental animals were 48 SPF level BALB/c mice weighted (18–22) g, were randomly divided into model group, moxifloxacin group, thymopentin group and combined treatment group, each group with 12 cases. Thymopentin was from Beijing Double-Crane Pharmaceuticals Co., Ltd., moxifloxacin was from Bayer Healthcare Co., Ltd., and fluorescent antibodies were from Santa Cruz Company.

2.2. Model establishment and drug intervention methods

7H9 liquid medium containing 1×10^6/mL multidrug-resistant *M. tuberculosis* was prepared, and multidrug-resistant *M. tuberculosis* infection models of aerosol infection mice were built and given drug intervention from the 21 d after infection. Moxifloxacin group received intragastric administration of 100 mg/kg moxifloxacin, thymopentin group received subcutaneous infection of 1 mg/kg thymopentin, combined treatment group received intragastric administration of 100 mg/kg moxifloxacin and subcutaneous infection of 1 mg/kg thymopentin, and model group received subcutaneous infection and intragastric administration of same doses of saline.

2.3. Detection of colony numbers in visceral organs

Four weeks, eight weeks and sixteen weeks after treatment, mice were killed and anatomized under sterile conditions to get the lung and spleen, appropriate amount of tissue was cut off, homogenized, diluted, then inoculated in 7H11 medium and continuously cultured for 4 weeks, and then colony forming unit was counted.

2.4. Detection of T lymphocyte subset contents in peripheral blood

Sixteen weeks after treatment, mice were taken and killed by decapitation to collect peripheral blood, fluorescent antibodies of CD3, CD4 and CD8 as well as IFN-γ, IL-4, Th17 and CD25 were incubated respectively away from light, hemolysin was added for 15 min of hemolysis, then DPBS 1 000 μL was added to re-suspend cells, contents of different T cell subsets were detected in flow cytometer, and at the time of detection, excitation light was argon ion laser 488 nm.

2.5. Detection of PD-1 expression in lymphocytes in peripheral blood

Sixteen weeks after treatment, mice were taken and killed by decapitation to collect peripheral blood, fluorescent antibodies of CD3, CD19 and CD14 as well as programmed death-1 (PD-1) were incubated away from light respectively, hemolysin was added for 15 min of hemolysis, then DPBS 1 000 μL was added to re-suspend cells, contents of different T cell subsets were detected in flow cytometer, and at the time of detection, excitation light was argon ion laser 488 nm.

2.6. Statistical process methods

SPSS19.0 software was used to input and process data, comparison among groups was by variance analysis, pair wise comparison was by LSD-*t* method, and $P < 0.05$ was the standard of statistical significance in differences.

3. Results

3.1. Colony numbers in lung and spleen

Four weeks, eight weeks and sixteen weeks after treatment, analysis of colony numbers in lung and spleen was as follows: (1) variance analysis showed that colony numbers in lung and spleen of four groups were different. (2) Pair wise comparison showed that colony numbers in lung and spleen of moxifloxacin group and thymopentin group were significantly lower than those of model group and colony numbers in lung and spleen of combined treatment group were significantly lower than those of moxifloxacin group and thymopentin group (Table 1).

3.2. Contents of T lymphocyte subsets in peripheral blood

Contents of $CD3^+CD4^+$T cells in peripheral blood of moxifloxacin group and thymopentin group were higher than that of

Table 2
Comparison of T lymphocyte subset contents in peripheral blood.

	n	$CD3^+CD4^+$T cells	$CD3^+CD8^+$T cells
Model group	12	37.35 ± 4.25	39.22 ± 5.19
Moxifloxacin group	12	41.18 ± 5.29[a]	33.61 ± 3.88[a]
Thymopentin group	12	46.84 ± 5.51[a]	30.17 ± 3.22[a]
Combined treatment group	12	57.31 ± 6.23[abc]	21.36 ± 3.21[abc]

[a]: compared with model group, there were differences, $P < 0.05$; [b]: compared with moxifloxacin group, there were differences, $P < 0.05$; [c]: compared with thymopentin group, there were differences, $P < 0.05$.

Table 1
Comparison of colony numbers in lung and spleen (lg colony forming unit).

	n	4 weeks		8 weeks		16 weeks	
		Lung	Spleen	Lung	Spleen	Lung	Spleen
Model group	12	6.22 ± 0.62	4.35 ± 0.49	6.77 ± 0.82	5.19 ± 0.62	7.67 ± 0.83	5.76 ± 0.59
Moxifloxacin group	12	4.94 ± 0.53[a]	3.35 ± 0.35[a]	5.32 ± 0.62[a]	3.87 ± 0.46[a]	5.91 ± 0.61[a]	4.47 ± 0.65[a]
Thymopentin group	12	5.12 ± 0.59[a]	3.29 ± 0.31[a]	5.77 ± 0.49[a]	4.01 ± 0.48[a]	5.24 ± 0.68[a]	4.69 ± 0.50[a]
Combined treatment group	12	3.15 ± 0.39[abc]	2.21 ± 0.27[abc]	3.47 ± 0.42[abc]	2.85 ± 0.25[abc]	3.08 ± 0.19[abc]	2.32 ± 0.28[abc]

[a]: compared with model group, there were differences, $P < 0.05$; [b]: compared with moxifloxacin group, there were differences, $P < 0.05$; [c]: compared with thymopentin group, there were differences, $P < 0.05$.

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