Establishment of a Systemic Inflammatory Response Syndrome Model and Evaluation of the Efficacy of Umbilical Cord Mesenchymal Stem Cell Transplantation

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Abstract
Based on the characteristics of modern weapon injury, a repetitive model of traumatic systemic inflammatory response syndrome (SIRS) and an evaluation system were established. The models were treated with GFP-labeled tree shrew umbilical cord mesenchymal stem cells (UCMSCs). Forty out of 50 tree shrews were used to make a unilateral femoral comminuted fracture. Lipopolysaccharide was injected intravenously to create a traumatic SIRS model. The other 10 shrews were used as normal controls. After the model was established for 10 days, 20 tree shrews were injected intravenously with GFP-labeled UCMSCs, and 18 tree shrews were not injected as the model control group. The distribution of GFP-labeled cells in vivo was measured at 2 and 10 days after injection. Twenty days after treatment, the model group, the normal control group, and the treatment group were taken to observe the pathological changes in each tissue, and blood samples were taken for the changes in liver, renal, and heart function. Distribution of GFP-positive cells was observed in all tissues at 2 and 10 days after injection. After treatment, the HE staining results of the treatment group were close to those of the normal group, and the model group had a certain degree of lesions. The results of liver, renal, and heart function tests in the treatment group were returned to normal, and the results in the model group were abnormally increased. UCMSCs have a certain effect on the treatment of traumatic SIRS and provide a new technical solution for modern weapon trauma treatment.

Introduction
According to the characteristics of modern weapon injury, a repetitive systemic inflammatory response syndrome (SIRS) tree shrew model and model evaluation system were established to meet the actual needs of post-war medical protection. Blood biochemistry, histopathol-
Inflammation and overall diagnostic indicators were screened, establishing a technical specification for the creation and evaluation of traumatic SIRS tree shrew models [Anderson and Singh, 2017; Garcia-Lamberechts et al., 2018; Li et al., 2018; Mahassadi et al., 2018]. Actually, the most used animals for the development of work related to the inflammatory response are mice or rats; however, in this work, we used tree shrews. In a quick search of the current literature, it was observed that there has been an increase in the number of studies using tree shrews because they have genetic similarity with primates. Tree shrews are climbing animals between insectivores and primates. Evolutionarily closer to primates than rodents, tree shrews as an alternative to primates are being considered for study [Cao et al., 2003]. Recently, the Kunming Institute of Zoology detected and analyzed the tree shrew ge-

Fig. 1. Morphology of tree shrew UCMSCs and GFP labeling. a Tree shrew UCMSCs cultured under a light microscope grew fibrously adherent. b GFP-labeled tree shrew UCMSCs with yellow-green fluorescence.

Fig. 2. Body temperature observation of tree shrews after modeling (n = 10). ‡ Indicates p < 0.05.

Fig. 3. White blood cell count of tree shrews after modeling (n = 10). ‡ Indicates p < 0.05.
Fig. 4. The distribution of fluorescent cells (200-fold) in each organ 2 days after infusion of GFP-labeled cells. 

a Intestinal tissue. b Lung tissue. c Liver tissue. d Spleen tissue. e Renal tissue. f Cardiac tissue. g Pancreatic tissue. 

h The GFP-labeled UCMCSs (%) in different tissue 2 days after infusion (n = 5). Two days after the infusion of UCMSCs, the distribution of fluorescent cells in the pancreatic tissue was more obvious (40%).
**Fig. 5.** The distribution of fluorescent cells (200-fold) in each organ 10 days after infusion of GFP-labeled cells. 

- **a** Intestinal tissue.
- **b** Lung tissue.
- **c** Liver tissue.
- **d** Spleen tissue.
- **e** Renal tissue.
- **f** Cardiac tissue.
- **g** Distribution of fluorescent cells in pancreatic tissue.
- **h** The GFP-labeled UCMCSs (%) in different tissue 10 days after infusion ($n = 5$). Ten days after the infusion of the tree shrew, the distribution of fluorescent cells in the liver tissue was more obvious (42%).
nome [Fan et al., 2013] and proteome [Li et al., 2012]. Tree shrews were found to have genetic characteristics close to those of primates, which laid the foundation for research into clinical disease mechanisms and the development of new drugs.

Umbilical cord mesenchymal stem cells (UCMSCs) were used to evaluate the efficacy and safety of UCMSCs in the treatment of traumatic SIRS. The treatment of trauma was established by optimizing the timing, dosage and route of treatment. A clinical treatment plan was established for traumatic SIRS [Fang et al., 2016]. The ultimate goal is to provide a new animal model for SIRS research that is reproducible and resembles the clinical features of human SIRS. Clinical transformation of UCMSC treatment technology will be applied. Recommendations for UCMSC war treatment were developed, and new technology programs for modern weapon trauma treatment were provided.

Repeatable animal models for traumatic infection, SIRS, shock, and multiple organ failure were established. New treatments based on this animal model have significant military and scientific significance. However, the use of clinical high-dose antibiotics and inflammatory factor antagonists has not effectively reduced the complications and mortality of severe trauma. Therefore, infection is not the only cause of traumatic SIRS [Wagner et al., 2016; Ward et al., 2017; Xu, 2019]. By establishing a model of traumatic SIRS, the efficacy and safety of UCMSC therapy in the treatment of traumatic SIRS could be evaluated. By optimizing the timing, dosage, and route of treatment, UCMSCs for traumatic treatment were established. The SIRS clinical treatment technology program

**Fig. 6.** The distribution of fluorescent cells in each organ of the model tree shrew without the return of cells (×200) using a fluorescence microscope. 

- **a** Intestinal tissue.
- **b** Lung tissue.
- **c** Liver tissue.
- **d** Spleen.
- **e** Kidney.
- **f** Heart.
- **g** Pancreatic tissue. The model tree shrew without the return of cells showed no distribution of fluorescent cells in each tissue.
was established. The ultimate goal is to provide a new animal model for SIRS research that is reproducible and resembles the clinical features of human SIRS. Clinical transformation of UCMSC treatment technology was applied.

We decided to use the impact method to make a unilateral femoral comminuted fracture and then inject lipopolysaccharide (LPS) into the traumatic SIRS tree shrew model to establish a model evaluation technology.

Materials and Methods

Preparation of a Tree Shrew Model of Traumatic SIRS

In total, 50 tree shrews weighing 145 ± 11 g were purchased from the Kunming Institute of Zoology, Chinese Academy of Sciences. In 40 of the 50 tree shrews, unilateral comminuted fractures of the femur were generated by the impact method. At the same time, 0.5 mg LPS (L2880-100 mg, LPS from Escherichia coli O55:B5, Sigma) was injected intravenously to create a traumatic SIRS tree shrew model. The concentration of LPS is 1 mg/mL and the volume is 500 μL. The other 10 were used as normal controls without fractures and LPS injection. Two tree shrews died in the model group 9 days after modeling. It takes 10 days for the SIRS model to establish.

Body Temperature Observation and White Blood Cell Count of Tree Shrews after Modeling

Ten models and 10 controls were used to measure body temperature 6 times after the model was made. At the same time, white blood cells were counted 4 times before the model, 1 day after the model, 4 days after the model, and 10 days after the model.

Culture and Labeling of UCMSCs in Tree Shrews

The umbilical cord of the tree shrews was collected by cesarean section, rinsed with salt water, and soaked in double-resistance. The umbilical cord was cut as much as possible with small scissors and placed into a culture bottle for adherent culture. The adherent cells attached for 2–3 days, the DMEM-F12 medium with 20% fetal bovine serum was changed, and the samples were subcultured until the cells were full. After transfection with the best multiplicity of GFP lentivirus, the optimal concentration of puromycin was added for screening. After changing the solution 3 times, the cell line stably transfected with GFP lentivirus was obtained and photographed under a fluorescence microscope.

Tree Shrew Grouping and Treatment of UCMSCs

After the model was established, at 11 days, 20 tree shrews were given returned UCMSCs through the femoral veins, each tree shrew returns 1 × 10⁶ cells in PBS, the volume is 1 mL. And 18 tree shrews were not returned with cells as the model control group. The distribution of GFP-positive cells in tissues was observed in frozen sections of 5 tree shrews with UCMSC return at

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**Fig. 7.** The results of cardiac HE staining (×200). a) The model group was HE stained. More myocardial fiber edema was seen in the tissue and cytoplasmic loose staining (black arrow). b) HE staining of the treatment group. There was no obvious abnormality in the interstitium, and no obvious inflammation was observed. c) HE staining of the control group. The tissue staining was uniform, the myocardial fiber morphology was normal, the arrangement was regular, the boundary was clear, the interstitium was not obvious, and no obvious inflammation was observed.
2 and 10 days, respectively. Twenty days after treatment, 5 tree shrews each were killed in the model group, the normal control group, and the treatment group, and pathological sections were stained with HE to observe the lesions within the model group and the therapeutic effect of the treatment group. The pathological sections of the normal control group were used as normal controls. Under a light microscope magnified 200×, ten fields of view were observed within the same tissue, and a representative field of view was taken. Each map had at least 5 similar fields of view as representative fields of view. Due to the small size of the tree shrews, X-rays cannot be taken to observe the fractured femur. However, 20 days after the cell therapy, 20 tree shrews in the cell therapy group were observed to be active. Compared with the 18 tree shrews in model group, the mental state was significantly better. It can be inferred that 20 days after cell therapy, the recovery of femoral fractures in the treatment group is better than that in the model group.

**ELISA Detection of Inflammatory Factors in Each Group**

Before treatment and 1 day, 3 days, and 10 days after treatment, the peripheral blood of 3 tree shrews was collected from the model group, normal control group, and treatment group. The inflammatory factors TNF-α, IL-6, and IL-10 were detected by ELISA kit (purchased from Neobioscience Technology Co.).

**Detection of Liver, Kidney, and Heart Functions in Each Group**

Twenty days after cell treatment, peripheral blood of 5 tree shrews was collected in the model group, normal control group and treatment group to detect liver, kidney, and heart functions. 500ul of serum is separated from 1 mL of venous blood and sent to the laboratory to detect the abovementioned functions with an automatic biochemical analyzer.

**Statistical Methods**

Data are expressed as the mean ± standard deviation, and comparisons between groups were analyzed by one-way ANOVA. Pairwise comparison was conducted using the SNK method. The statistical software used was SPSS 17.0, and \( p < 0.05 \) was considered statistically significant.
Results

Cultured tree shrew UCMSCs were observed under a light microscope (Fig. 1a), and GFP-labeled tree shrew UCMSCs were observed under a fluorescence microscope (Fig. 1b).

The cultured tree shrew UCMSCs grew fibrously, were evenly distributed, and grew adherently. The cells were observed with a fluorescence microscope, and the cells were shown to have GFP yellow-green fluorescence.

Tree Shrew Body Temperature Observation after Modeling

The body temperature of the tree shrews began to rise one day after the model was made and reached a maximum of 41.3°C 10 days after the model was made (Fig. 2).

Tree Shrew White Blood Cell Count after Modeling

The tree shrew white blood cell count began to increase 1 day after modeling and reached a maximum of \(8.91 \times 10^9/\text{L}\) 4 days after modeling (Fig. 3).

The Distribution of Fluorescent Cells in Each Organ 2 Days after Tree Shrews Were Infused with Cells

Two days after the tree shrew infusion of cells, each organ was frozen and sectioned, and the nuclei were stained with DAPI, which generated blue fluorescence, and the cells imported into the body carried green fluorescence, representing the distribution of transplanted cells. Two days after the infusion of UCMSCs, the distribution of fluorescent cells in the pancreatic tissue was more obvious (40%; \(n=5\)). A small number of fluorescent cells were distributed in other tissues (Fig. 4).
The Distribution of Fluorescent Cells in Each Organ 10 days after Tree Shrews Were Infused with Cells

Ten days after the infusion of the tree shrew, the distribution of fluorescent cells in the liver tissue was more obvious (42%) \((n=5)\). There was a certain amount of fluorescent cell distribution in other tissues (Fig. 5).

The Distribution of Fluorescent Cells in Each Organ in Model Tree Shrews that Were Not Returned with Cells

The model tree shrew with unreturned cells showed no distribution of fluorescent cells in the tissues (Fig. 6).

HE staining results in various organs in the model group, treatment group and control group are summarized in the following.

(1) HE staining of the heart showed that the model group showed more myocardial fiber edema and loose cytoplasmic staining (black arrow), and the treatment group recovered close to the normal level of the control group (Fig. 7).

(2) Liver HE staining showed that there was more hepatocyte edema in the model group, cytoplasmic loose staining (black arrow), a small amount of hepatocyte edema resembling balloon-like degeneration, cell swelling, nuclear centering, and cytoplasmic vacuolization (yellow arrow). A small amount of lymphocyte infiltration (red arrow) was seen around the bile duct in the local portal area. The treatment group recovered close to the normal levels of the control group (Fig. 8).
(3) The spleen HE staining results showed that the spleen nodules in the model group mostly had lymphocyte-spotted necrosis, deep stenosis, or fragmentation (black arrow). A small amount of extramedullary hematopoietic foci (yellow arrow) was seen in the red pulp. The treatment group recovered close to the normal levels of the control group (Fig. 9).

(4) HE staining results showed that a large amount of alveolar wall thickening was observed in the model group, accompanied by a large number of lymphocytes and neutrophil infiltration (black arrows), more alveolar wall epithelial cell necrosis, and nuclear fragmentation (yellow arrow). The treatment group returned close to the normal levels of the control group (Fig. 10).

(5) Renal HE staining showed that the model group had a small increase in glomerular matrix (black arrow). Renal tubular dilatation was observed in the renal cortex. More lymphocytic focal infiltration was observed in the renal medulla (yellow arrow). The treatment group returned close to the normal levels of the control group (Fig. 11).

(6) Intestinal HE staining results showed that the model group showed spot gland necrosis of individual gland cells (black arrows), cytoplasmic vacuolation, and nucleus shrinkage; scattered neutrophils (blue arrows) were seen in the lamina propria. The treatment group returned close to the normal levels of the control group (Fig. 12).
The results of pancreas HE staining showed that some pancreatic islets in the model group showed nucleus contraction (blue arrows) of individual pancreatic islet cells, and the staining was deepened. The treatment group recovered close to the normal levels of the control group (Fig. 13).

Results of renal PAS and Masson staining in the model group, treatment group and control group (Fig. 14):

Kidney PAS staining of the model group showed more common glomerular basement membrane thickening (black arrow). The treatment group had renal PAS staining. There was no significant thickening of the glomerular basement membrane. Kidney Masson staining of the model group showed a small amount of collagen fiber hyperplasia (black arrow) in the tissue. In the treatment group, kidney Masson staining with no collagen fiber proliferation was observed. The treatment group recovered close to the normal levels of the control group.

Test results of inflammatory factors in the model group, normal control group and treatment group are summarized in the following.

1. TNF-α test results of the 3 groups: TNF-α increased in the model group and decreased after treatment (Fig. 15).
2. IL-6 test results of the 3 groups: IL-6 increased in the model group and decreased after treatment (Fig. 16).
3. IL-10 test results of the 3 groups: IL-10 decreased in the model group and increased after treatment (Fig. 17).

Results of renal, liver, and heart function tests in the model group, normal control group, and treatment group are summarized in the following.

1. Renal function tests (Fig. 18): Urea and creatinine in the model group were significantly increased and were significantly reduced after treatment.
2. Liver function tests (Fig. 19): The model group had significant increases in alanine aminotransferase and aspartate aminotransferase, which were significantly reduced after treatment.
3. Heart function tests (Fig. 20): The creatine kinase and phosphocreatine kinase isoenzymes in the model group were significantly increased and were significantly reduced after treatment.
“Injury” is an important cause of the reduction in troops and the weakening of the combat effectiveness of troops. Therefore, research on the prevention and treatment of war wounds has always been a core focus in the field of military medicine and has been highly valued by the military of various countries [Scap and Kalenic, 1991]. Since decisive battles of most military conflicts in the future will occur in densely populated cities, this will lead to an increase in war damage. Compared with other war wounds, urban war wounds are characterized by large numbers of wounded people and complex injury types and injury classes. Detonation injury, crush injury, multiple injuries, burns, etc., are significantly increased [Scepì, 2007; Xu et al., 2019].

In modern local wars, various explosive weapons are still the main strategic and tactical weapons. They have large explosive power, produce shrapnel, and can be fanned or stereoscopically projected. The killing area is large, and the targets are accurate. The killing effect of modern weapons has the characteristics of high speed, high efficiency, high intensity, and soft killing (3 highs and 1 soft). These characteristics will cause serious injury consequences, mainly manifested as more serious wounds, a greater number of wounds, more burns and multiple injuries. Psychological barriers and physiological imbalances lead to a high attrition rate, high shock rate, and high surgical rate (3 more highs). This causes complicated modern war wounds, damages more troops, causes a large trauma area, and makes early complications more dangerous. Because of the long time that can elapse after an early injury, late complications can increase, making the rescue process more difficult [Hadziahmetovic, 1995; Klausner and Rozin, 1995]. Among various war wounds, firearm injuries caused by high-speed low-quality weapons represent the highest proportion of war wounds in modern local warfare. The characteristics of the injuries are extensive, and serious tissue damage, multiple injuries and multiple injuries are increased. Complicated wounds and serious infection can occur [Patzkowski et al., 2012; Yee et al., 2017]. In the study of

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**Discussion**

**Fig. 13.** Results of pancreas HE staining (×200). **a, b** HE staining of the pancreas in the model groups. Note that the nucleus of individual islet cells is contracted (blue arrows), and the staining is deepened. **c** Pancreas HE staining in the treatment group. There are many islets in the tissue, and there is no obvious abnormality in the morphological structure as well as no abnormality in the morphological structure of the pancreatic exocrine acinar. **d** Control group pancreas HE staining. No obvious abnormalities were observed.
**Fig. 14.** The results of kidney PAS and Masson staining (×200).  

**a** Model group kidney PAS staining showed more common glomerular basement membrane thickening (black arrow).  

**b** Kidney PAS staining in the treatment group with no significant thickening of the glomerular basement membrane.  

**c** Control group kidney PAS staining showed that there was no significant thickening of the glomerular basement membrane.  

**d** Model group kidney Masson staining. A small amount of collagen fiber hyperplasia (black arrow) is seen in the tissue.  

**e** Kidney Masson staining of the treatment group where no collagen fiber proliferation was observed.  

**f** Kidney Masson staining of the control group where no collagen fiber proliferation was observed.
the damage associated with vital organs, it was found that after injury from a high-speed steel ball to the maxillofacial region, the animal’s heart, lung and other important organs showed a small amount of flaky bleeding. If an infection occurred after injury, shock, etc., the conditions and pathological basis were conducive to the occurrence and development of serious complications such as acute respiratory distress syndrome, disseminated intravascular coagulation, or multiple organ failure [Lyons, 2010; Del Sorbo and Slutsky, 2011; Lee et al., 2011; Huang et al.,

**Fig. 15.** Results of TNF-α detection by ELISA. The results are shown as the mean ± standard deviation (n = 3). *p < 0.01, compared with the control group.

**Fig. 16.** Results of IL-6 detection by ELISA. The results are shown as the mean ± standard deviation (n = 3). *p < 0.01, compared with the control group.
This series of posttraumatic syndromes is an important cause of the high death rate. Rapid and effective control and treatment of posttraumatic syndromes are hot topics at home and abroad. Therefore, the establishment of repeatable animal models for combative traumatic infection, SIRS, shock, multiple organ failure, and new treatments based on this animal model have significant military and scientific significance.

We used the impact method to make a unilateral femoral comminuted fracture and then injected LPS into the traumatic SIRS tree shrew model. GFP-labeled UCMSCs were used for transplantation. Two and 10 days after transplantation, sections were taken and observed by fluorescence microscopy. GFP-labeled cells were observed in each tissue, and liver tissue was observed 10 days after transplantation. The distribution of GFP-positive cells was high, indicating that the liver has to deal with a large number of foreign cells. In the model group of untransplanted cells, no fluorescence cell distribution was observed in any organ tissue. Twenty days after cell treatment, HE staining results of the organs of the 3 groups showed that there were some lesions in the tissues of the model group, and the treatment group recovered near to the normal level of the control group. In the model group, PAS staining of the kidney showed more thickening of the glomerular basement membrane. The PAS staining of the kidney in the treatment group and the glomerular base-
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ment membrane showed no obvious thickening and recovered to near the normal level of the control. The model group was stained with Masson staining, and a small amount of collagen fibers was found in the tissue. In the treatment group, Masson staining of the kidney showed no collagen fibrosis, and recovery was near to the normal level of the control.

According to the HE staining results, the establishment of the model of traumatic systemic inflammatory response syndrome in tree shrews was successful. After treatment with umbilical cord mesenchymal stem cells, the indicators of the treatment group tended to improve, indicating that umbilical cord mesenchymal stem cells have roles in treatment. Ten days after cell transplantation in the tree shrew systemic inflammatory response syndrome model, most of the cells were distributed in the liver, and other organs also had a certain distribution that played a role in the tissue so that the damage was restored. The results of liver function, renal function and heart function tests in the model group, normal control group and treatment group showed that the organ functions of the model group were significantly increased and decreased significantly after treatment. These results all indicate that the creation of the model was successful and that the treatment with UCMSCs was effective because all lesions in the treatment group tended to return to the level of the normal control group.

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Statement of Ethics

All experimental protocols were approved by the Experimental Animal Ethics Committee of the 920th Hospital of Joint Logistics Support Force of PLA. All methods were performed in accordance with the relevant guidelines and regulations.

Conflict of Interest Statement

The authors declare that they have no competing interests.
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Author Contributions

P.M., K.W., Z.-L.Y., N.-T.T., M.-Y.L.-G., X.-M.C., G.-P.R., and X.Y. made substantial contributions to study conception and design, data acquisition, or data analysis and interpretation.

Z.-A.L. and R.-Q.P. agreed to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

X.-H.P. and G.-P.R. gave final approval of this version of the manuscript for publication.

G.-P.R., X.-H.P., J.-X.W., X.Y., and R.-Q.P. were involved in drafting the manuscript or revising it critically for important intellectual content.

All authors read and approved the final manuscript.

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