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Study on the functions and mechanism of immune functions of human telomerase reverse transcriptase regulating dendritic cells treating sepsis

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Abstract. – OBJECTIVE: We analyzed the functions and mechanisms of immune functions of human telomerase reverse transcriptase regulating dendritic cells (DC) treating sepsis of mice models.

MATERIALS AND METHODS: Eighty clean grade Balb/c animals aged from 6 to 8 [illegible] weighted from 18 g to 22 g were selected [illegible] th[illegible] study. The DC cells were harvested from [illegible]n-imals and cultivated to transfect with the re[illegible]-binant eukaryotic expression plasmid hT[illegible] IRES2-EGFP construct. The LPS (E. coli 0111:[illegible] 5 mg/kg) was injected into th[illegible]al cavi[illegible] of mice to establish sepsis [illegible]odels. [illegible]erwards, animals were divided ra[illegible]nly into [illegible]e sepsis group (A group), the gro[illegible] hTER[illegible]ect-ing DC (B group), the [illegible]roup[illegible] ed (C group) with 2[illegible]ice in e[illegible]roup. 5 mice were in the norma[illegible]ntrol group [illegible]up), with-out any treatm[illegible]quivalent v[illegible] of nor-mal saline wa[illegible]jecte[illegible]o the abdominal cavity of A group. Subsequent[illegible]l of cell suspension (105/ml) [illegible] transfected i[illegible] and C groups re-specti[illegible]. Five animals from [illegible]B, C groups and one [illegible]al from group D were sacrificed after 24[illegible] 72d[illegible] and 10d respectively.

RE[illegible] [illegible] was fo[illegible]d that median surviv-al time [illegible] group [illegible] hTERT transfecting DC [illegible]remai[illegible] hi[illegible] than that of the untrans-fe[illegible] group[illegible]e sepsis group. The average sc[illegible] of the p[illegible]ology of kidney and intestine at [illegible]h time were significantly lower than that of t[illegible] groups (p<0.05). At each time point, the gro[illegible] of hTERT transfecting DC, levels of [illegible] and Cr were remarkably lower than that of [illegible]her two groups; HLA-DR, CD40 of immune ph[illegible]type and the expression level of peripher-al blood T cells MHC-II molecules were signifi-cantly higher than that of the other two groups; the expression level of IL-12 and TNF-a were sig-n[illegible]antly lower than that of the other two groups; a[illegible]ptosis rate of DC were significantly lower t[illegible] that of the [illegible]r two groups; the content and a[illegible]ity of NF-κ[illegible]ere significantly higher than tha[illegible]he other [illegible]o groups (p<0.05).

C[illegible]: The telomerase reverse tran-scriptase [illegible] can raise the expression and ma-[illegible]ity of DC, reduce apoptosis, induce cytokine [illegible] reduce the inflammatory response [illegible]ease the survival time.

Key Words:

Telomerase, Reverse transcriptase gene, Dendritic cells, Sepsis.

Introduction

Sepsis is characterized by dangerous disease condition, high mortality rate and expensive treatment cost, whose incidence is 700-2400/100 thousand every year. It is increasing every year, and it is estimated that by 2020 there will increase newly one million cases of sepsis[1]. Currently, our understanding of the mechanisms of sepsis has changed from simple "excessive inflammatory response" to more "excessive immune suppression" to participate in the composition[2], in which the apoptosis of dendritic cells (DC) may play a role of middle bridge in sepsis immune disorders[3]. DC is the antigen presenting cells with the strongest function in the body, which activates the initial type of T cells as well. DC is the key factor to start and adjust the innate and acquired immune response[4]. Many studies confirmed[5,6] that the process of DC decreasing synchronizes with the oc-

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currence of sepsis and has continuous influence, which is closely related to mortality rate. Then, exogenous injections of DC can increase the immune level and decrease mortality rate[7]. Therefore, it is reasonable to believe that the prevention of apoptosis of DC can reverse the process of immune suppression in sepsis and improve the immune function of the body, which may become a new feasible method for the prevention and treatment of sepsis.

The discovery of telomeres and telomerase provides a promising prospect for cell immortality; the discovery has important significance for raising and keeping telomerase activity of the cells, increasing cell replication *in vitro*, expanding ability and preventing cell apoptosis[8]. Based on it, this study explored the hTERT gene modifying DC targeting the therapy for sepsis and observed its influence on immune function.

Materials and Methods

Materials

Eighty clean grade Balb/c male mice [illegible] from 6 to 8 weeks old and weighing fro[illegible] 22 g, were purchased from Shanghai S & [illegible]kai Laboratory Animal Co. Ltd, China. The an[illegible]s were kept in an environment of room tempera[illegible] of 22±0.5°C, relative humidity [illegible]±5%, w[illegible] 12h light and 12h dark cy[illegible] [illegible]nlimite[illegible] access to food and water.

Main Reagents an[illegible] Ins[illegible]

Sugar fatty LPS [illegible]. coli 0[illegible]) purchased from Sigma-Ald[illegible] St. Louis, M[illegible]A), mouse anti-human [illegible] labeled by [illegible]C, CD40 monoclonal an[illegible]body ([illegible]gend, San Diego, CA, USA), CD[illegible]c antibody o[illegible]-mouse labeled by PE and [illegible]HC-II of anti-mo[illegible]abeled by CY5 purc[illegible]ed from BD Biosciences (Franklin Lakes, NJ, [illegible]), i[illegible]tu cell apoptosis detection kit (S711[illegible]con Int[illegible]ational, Billerica, MA, [illegible]A), T[illegible] in si[illegible]ell apoptosis detection kit [illegible]d by [illegible]emicon International, Billeric[illegible]A, USA), [illegible]MSA kit (Pierce, Rockford, IL, US[illegible] biotin labeled the NF-κB nucleotide pro[illegible] [illegible]TGAGGGGACTTTCCCAGGC-3' [illegible]-GCCT[illegible]GGAAAGTCCCCTCAACT-3') pur[illegible]ed from Shanghai Yingjun Company, China. H[illegible] speed centrifuge (Heraeus, Hanan, Germany), MiniMACS magnetization cell sorter (Miltenyi Biotec GmbH Company, Bergisch Gladbach, Germany), FACS Calibur flow cytometry instrument (BD Biosciences; Franklin Lakes, NJ, USA), fluorescence microscope (Olympus, Tokyo, Japan).

Separation of DC in Vitro, Cons[illegible] and Transfection of Recombin[illegible] Plasmi[illegible]

Isolation and cultivation of D[illegible] [illegible]he peripheral anticoagulant was diluted [illegible]laced in lymphocyte separation m[illegible]ium t[illegible]rifuge at 1800 rpm for 15 mi[illegible]he periphe[illegible]od mononuclear cells (P[illegible]C) were separa[illegible] density gradient c[illegible]fugatio[illegible] The immuno-magnetic beads we[illegible] connect[illegible]monoclonal antibo[illegible]M2DC[illegible]enyi B[illegible]c GmbH Compa[illegible] Bergisch G[illegible]ermany) and we[illegible]o centrifuge[illegible] precursor cell fro[illegible] PBM[illegible]PMI-1640 culture medium (Beijing Tianrun[illegible]a Biotech Company, [illegible]China) was [illegible]o cultivate cells and [illegible]N-α (Invivogen, San [illegible]iego, CA, USA) was [illegible]dopted to promote the maturity of DC.

[illegible]struction o[illegible]ombinant eukaryotic expres[illegible] plasmi[illegible]hTERT-IRES2-EGFP: The p[illegible]145 pl[illegible]id (Beijing Tianrunshanda Biotech [illegible], Beijing, China) was digested with ECoR I enzyme and hTERT fragments were [illegible]ed. T4 DNA ligase was used to connect a[illegible]ansfer hTERT (human telomerase reverse transcriptase) colonies for obtaining recombinant plasmid hTERT-IRES2-EGFP, which was identified by enzyme digestion and confirmed by sequencing.

Plasmid transfected DC *in vitro*: The liposome mediated transfection method was adopted to import constructed recombinant eukaryotic expression plasmid into cultured human epidermal stem cells. The G418 was used for the filter, the amplification, and the batches. The fluorescence microscope (Olympus, Tokyo, Japan) was used to test whether there was green fluorescence in positive clones or not. Further, PCR was adopted to test whether there was the integration of exogenous NeoR gene in positive clones or not.

Sepsis Models and Experimental Grouping

LPS (5 mg/kg) was injected for one time into the abdominal cavity to prepare models of mouse sepsis. After the development of sepsis mouse model, the animals were divided randomly into the sepsis group (A group), the group of hTERT transfecting DC (B group), the group of DC untransfected (C group), with 25 mice in each group. 5 mice were in the normal control group (D group) without any treatment. An equivalent

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volume of normal saline was injected into the abdominal cavity of A group. 1 ml of cell suspension (10^5/ml) was transfused into B and C groups respectively. 5 mice from A, B, C groups were sacrificed after 24h, 48h, 72d, 7d and 10d, and only a mouse was sacrificed from group D as control.

Observation Index and Test Methods

Following indices were observed (1) Median survival time; (2) Histopathological changes of organ kidney and intestinal lesion.

Immunohistochemistry

The tissue sections were stained with H & E, to observe under an optical microscope (Olympus, Tokyo, Japan) ranging from 0 to 4 scores, the higher score was corresponding to the more serious the inflammatory response.

Levels of Selective Biomarkers

The levels of CPR and Cr was tested with an automatic biochemical analyzer (Hitachi Ltd, Tokyo, Japan). Further, HLA-DR, CD40 [illegible] of DC immune phenotype by flow cy[illegible] and peripheral blood T cells MHC-II lev[illegible] by Western blotting. PBS was used to wash th[illegible] suspension, and later cells were centrifuged fo[illegible] min at 1000 rpm. The phospha[illegible]ered sal[illegible] (PBS) was added to the cell[illegible] a [illegible]entratio[illegible] of 1×10^5/ml. The cell sus[illegible]sion of [illegible] µl was added into the flow cyto[illegible] tube. [illegible]sequently, 10 µl of labeled a[illegible]ibo[illegible] and place inside th[illegible]efrigerat[illegible]4 °C (Haier, Qingdao, China) [illegible]incubate fo[illegible]min. The cells were ce[illegible] [illegible]r 10 min a[illegible]00 rpm, and after wash[illegible]ng wit[illegible] cooled PBS the cells were susp[illegible]ed and analy[illegible] ELISA was used to analyz[illegible]e expression leve[illegible] serum cytokine IL-1[illegible]NF-α (InvivoGen Company, San Diego, CA[illegible]).

[illegible]etectio[illegible] Den[illegible]ic Cells (DC) Apoptosis

[illegible]was pe[illegible] according to situ hybridization. [illegible]he DC c[illegible]uspension of kidney and tissue of [illegible]stine was prepared and adjusted to 1×10^5/ml [illegible] Immediately proper FITC labeled [illegible]UNEL dye mixtures (positive sorting of apoptotic [illegible]) PE-labeled CD11C fluorescent antibody and P[illegible]5 labeled MHC-II of anti-mouse fluorescent antibody (sorted mature DC) was added.

The cells were incubated for 30 min on ice in the dark, and later centrifuged for 20 min at 2000 rpm. The excess dye was washed off and finally cells were resuspended in 1% bovine serum albumin (BSA)-PBS. The flow cytometry was used to detect the expres[illegible] TUNEL+CD11C+ apoptosis DC, T[illegible] D11C+ MHC-II+for mDC. Acco[illegible]g to the instruction of in situ cell apoptos[illegible]etection kit, the TUNEL dye was used to label[illegible]otic cells for observing under a fluo[illegible]cent [illegible]scope. CD11C+TUNEL+ marke[illegible]as used to [illegible]ate apoptosis in DC.

EMSA Electrophore[illegible]y Shift Assay Test

It was co[illegible]ted to de[illegible] content and activit[illegible]-κB in the [illegible]us of DC. After mi[illegible]g eq[illegible]nt single stranded probe, the deionized water [illegible]dded to denature for 10 mi[illegible]°C, slowly [illegible] to 20°C, and then d[illegible]ed with deionized wat[illegible] to 1 µmol/L. The 6% p[illegible]yacrylamide gel was used to establish probe b[illegible]ding protein [illegible]tion system (total 20 L). After e[illegible] mixing, the[illegible]mples were incubated for 20 mi[illegible]om te[illegible]erature and 5 µl of sample buffer was [illegible] each of the sample. The sample was loaded on gel for electrophoresis (volta[illegible]V, electrophoresis buffer 0.5 ×TBE), the [illegible]horesis was stopped once bromine phenol blue got closer to the bottom. Subsequently, 3 filter papers and a nylon film were soaked in TBE (Tris Borate Edta) buffer for 3 min. A sandwich of 3 filter papers- nylon film- gel-3 filter papers was prepared from the positive to negative, and was placed neatly in the splint of the wet transfer film instrument. A glass rod was used to remove any air bubbles. The film was transferred for 45 min at the 380 mA constant current in a buffer of 0.5×TBE. The nylon film was taken to cross-link for 3 min under ultraviolet cross linker, and immune chemiluminescence method was to test DNA fragments labeled biotin.

Statistical Analysis

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The results were presented by $\bar{x} \pm s$. A single factor ANOVA analysis was used to compare the normal distribution data between two groups. The data was represented by the number of cases or percentage (%). While comparing between groups, chi-square test 2 was used. The K-M method was adopted to analyze median survival time. The difference with $p<0.05$ was considered as of statistical significance.

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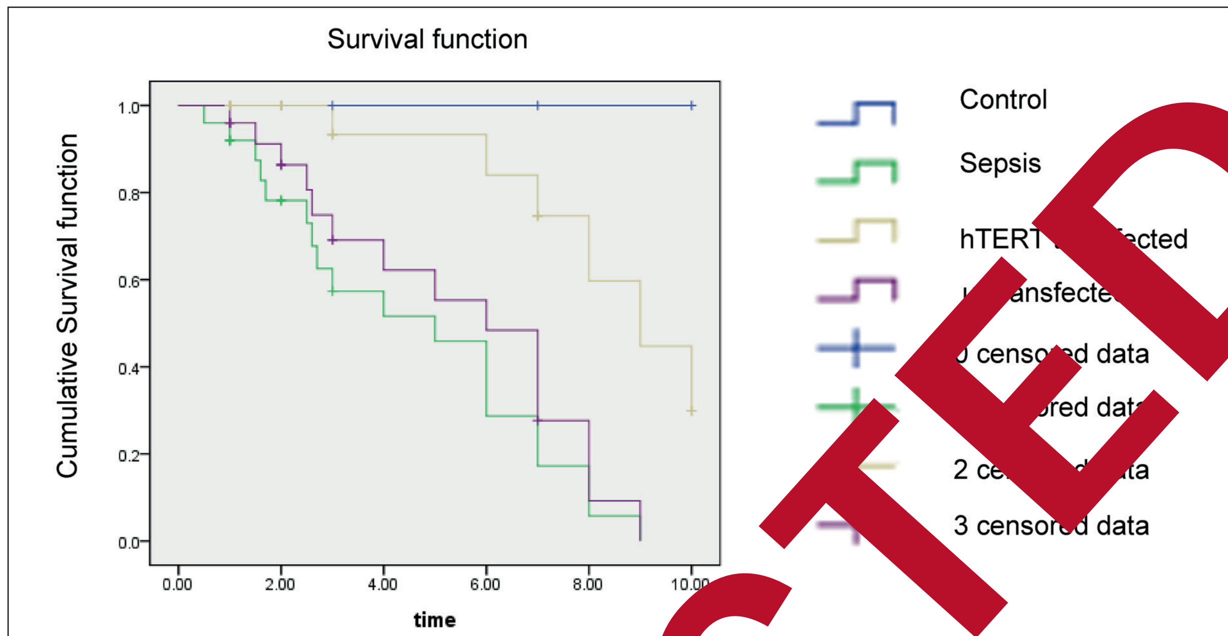

Figure 1. Comparisons of t[illegible] and survival rate[illegible]

Results

Comparisons of Time and Survival [illegible]

The median survival time of the group of [illegible]RT transfecting DC was (9.0±1.2) d, and it wa[illegible]markably higher the untransfected group w[illegible] was (6.0±0.9) d and the sepsis [illegible] which w[illegible] (5.0±1.2) d; the differences [illegible] statistica[illegible] significance (Log-Rank tes[illegible]=21.21[illegible]<0.001) (Figure 1).

Comparisons of [illegible]sue Pa[illegible]gy Scoring and L[illegible] of CRP a[illegible]

At each tim[illegible] [illegible]roup of hT[illegible] (human telomerase re[illegible]erse t[illegible]riptase) transfecting DC, aver[illegible] scores of pa[illegible]gy of kidney and intesti[illegible] were significantl[illegible]er than that of othe[illegible]wo groups ($p<0.05$); compare average sco[illegible]f path[illegible]gy of kidney and intestine among [illegible], and the differences were of no statistical significance ($p>0.05$) (Figure 2).

[illegible]ch time, in the group of hTERT transfec[illegible] DC, the levels of CRP and Cr were significantly lower than that of the other two groups ($p<0.05$) (Table I).

Comparisons of Immune Phenotype of HLA-DR, CD40 and Molecular Level of MHC-II

At each time, in the group of hTERT transfecting DC, HLA-DR and CD40 of immune phenotype and the expression level of peripheral blood T-cells MHC-II molecules were significantly higher than that of the other two groups ($p<0.05$) (Figure 3 (7d flow chart) and Tables II-III).

Table I. C[illegible]son of l[illegible]s of CRP and Cr.

[illegible]p	CRP (mg/L)					Cr (mg/dl)				
	1d	2	3	7	10	1d	2	3	7	10
A	1.[illegible]0.2	2.2±0.4	3.4±0.6	4.1±0.8	4.0±0.5	1.6±0.3	1.8±0.4	2.2±0.5	2.5±0.6	2.3±0.5
[illegible]	1.2±0.3	1.6±0.4	1.9±0.5	1.8±0.4	1.7±0.5	1.1±0.3	1.3±0.3	1.5±0.3	1.4±0.3	1.4±0.3
[illegible]	1.4±0.3	2.0±0.6	2.7±0.8	3.5±0.9	3.4±0.8	1.4±0.5	1.6±0.4	1.8±0.6	2.2±0.7	2.1±0.8
F	4.628	4.935	5.250	5.634	5.769	4.857	5.201	5.634	5.967	6.231
p	0.037	0.035	0.031	0.026	0.023	0.035	0.031	0.026	0.017	0.014

Note: A group, the sepsis group; B group, the group of hTERT transfecting DC; C group, the group of untransfected DC

Table II. Comparisons of levels of HLA - DR and CD40 of immune phenotype (%).

Group	HLA-DR					CD40				
	1d	2	3	7	10	1d	2	3	7	[illegible]
A	36.7±6.8	46.8±9.2	53.5±11.4	69.4±12.3	72.1±12.5	7.8±3.2	9.2±3.6	12.4±4.5	16.6±[illegible]	22.7±6.2
B	53.6±8.2	64.5±10.3	82.7±12.4	96.6±11.5	98.2±13.3	20.4±5.6	32.3±5.9	42.5±6.3	53[illegible]4	56.7±7.7
C	42.4±7.5	56.5±12.5	67.4±13.2	77.8±15.6	82.4±16.4	13.2±4.2	18.7±4.6	24.4±5.7	28.[illegible]	33.3±6.2
F	5.124	5.362	5.648	5.967	6.235	5.236	5.525	5.768	6.23[illegible]	[illegible].627
p	0.032	0.027	0.025	0.017	0.013	0.025	0.022	0.01[illegible]	0.013	[illegible]11

Comparisons of Expression Levels of Cell Factors IL-12, TNF-α

At each time, in the group of hTERT transfecting DC, HLA-DR, the expression levels of IL-12 and TNF-α were significantly lower than that of the other two groups ($p<0.05$) (Table IV).

Comparisons of Apoptosis Rate of DC

At each time, in the group of hTERT transfecting DC, apoptosis rate was significantly lower than that of the other two groups ($p<0.05$) [Figure 4 (7d flow cell chart) and Table V].

Comparisons of Content and Activ[illegible] of NF-κB

At each time, in the group of hTERT [illegible]sfecting DC, content and activity of NF-κB [illegible] significantly higher than that [illegible] other t[illegible] groups ($p<0.05$) (Figure 5).

Disc[illegible]

A telomere [illegible]e repeat se[illegible] [illegible]TAGGG which exis[illegible] end of the [illegible]yotic linear chromoso[illegible]. Du[illegible] the terminal replication of normal somatic cells, [illegible]lomere is shortened with e[illegible] division. E[illegible]me the cells divides, th[illegible]elomeres shortened by [illegible]bout 5-200 bp such a f[illegible]ction of molecular erosion has biological cons[illegible]nts to the ti[illegible] of cell division. Therefore, the le[illegible] of telomer[illegible]eflects the history and potential of [illegible]ation [illegible]cells, which is called "mitosis clock[illegible]ifetime[9]. Telomerase is a kind of [illegible]NA protease that can extend the ends of telome[illegible] [illegible]keep length of telomere[10]. It can use itself [illegible] a template for synthesis of telomere DNA and add it to the ends of chromosomes; complete telomere DNA lost in the chromosome replication to prolong length of the telomere so as to prolong

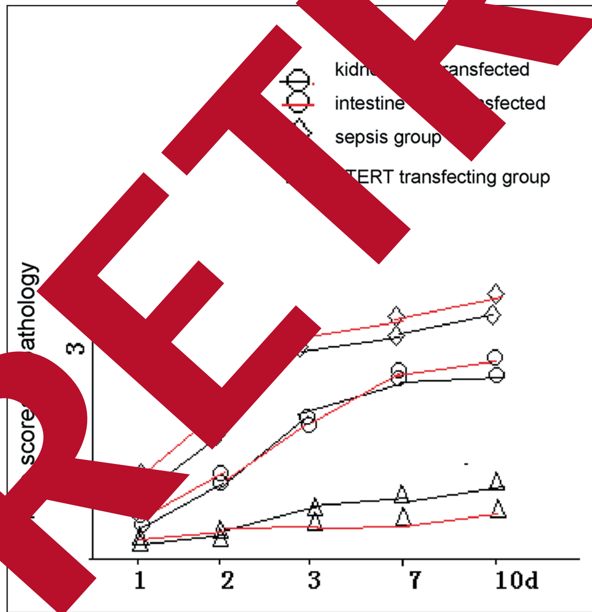

Figure 2. Comparisons of tissue pathology scoring and levels of CRP and Cr.

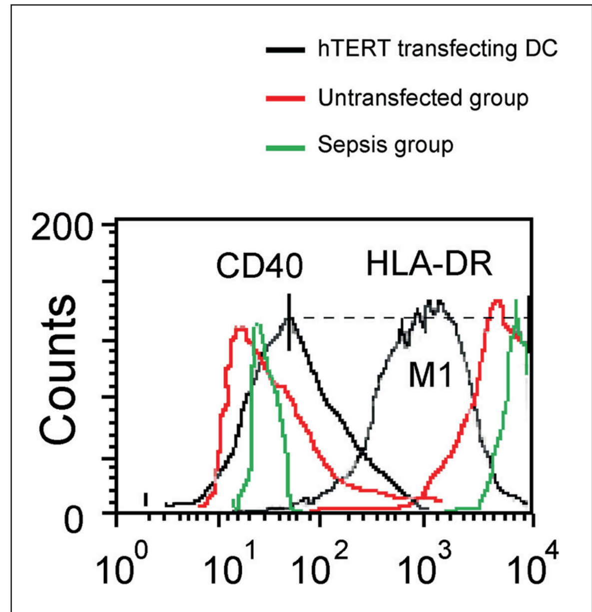

Figure 3. Comparisons of immune phenotype of HLA-DR, CD40

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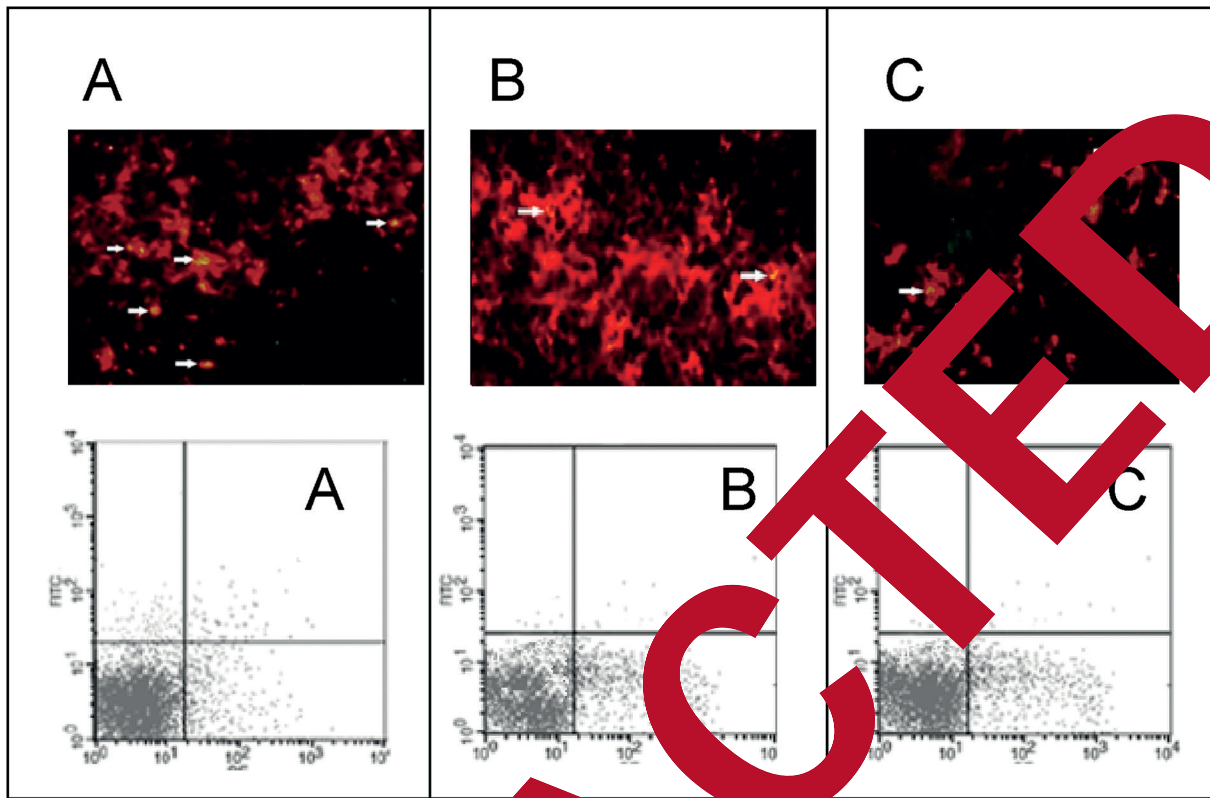

Figure 4. Flow chart showing DC apoptosis (the up, B is transfected group, C is un-transfected group).

the cell lifetime and even make it immortal[11]. lomerase consisted of one RNA it comp mentary to telomere DNA, c ytic unit wit reverse transcription activi (human omerase reverse transcriptase, hT and o relevant proteins (TPI). The e press n of hTERT genes ar e main iting step to determine telome ctivity[12]. Se e analysis showed that t pr r region o hTERT gene contains several t iption factors binding sites inclu g c-Myc, p5 Madl, etc. These factors on the promoter r of hTERT gene singl cooperatively and participate the various deg f tran ptional regulation of hTERT gene[13]. I an body lomerase activity exists i stem c rm c , some of the somatic cells with regenerative capacity and the vast majority of malignant tumor tissues[14]. Its high activity expression is one important condition for the malignant proliferation of tumor cells, but its proper expression has the function of prolonging cell lifetime. Raising and keeping telomerase activity of cells will have important significance on increasing cell replication in vitro, amplifying ability and preventing cell apoptosis[15].

The study showed that the median survival time of the group of hTERT transfecting DC was remarkably higher than the un-transfected group and the sepsis group, and was close to the normal control group, suggesting that hTERT regulating DC was closely related to improving the prognosis of sepsis. At each time, average scores of pa-

Tab III. Comparisons of levels of HLA - DR and CD40 of immune phenotype (%).

	1d	2	3	7	10
	13.4±6.7	23.6±8.9	32.4±12.3	42.1±13.3	53.2±15.2
	42.5±10.2	63.8±11.4	85.7±11.6	96.5±12.2	98.4±15.4
C	26.3±12.4	42.1±13.6	53.6±14.5	76.9±15.2	83.2±15.3
F	5.634	5.967	6.230	6.435	6.769
p	0.025	0.017	0.013	0.006	0.003

Table IV. Comparisons of expression levels of cell factors IL-12, TNF-α (pg/ml).

Group	IL-12					TNF-α				
	1d	2	3	7	10	1d	2	3	7	[illegible]
A	63.2±10.3	85.4±15.4	102.7±20.8	136.5±26.5	152.4±33.2	156.2±23.5	236.4±32.6	289.7±45.5	356.4±5[illegible]	[illegible]76.2±62.5
B	26.4±10.2	38.7±13.2	46.9±16.4	65.8±23.5	73.5±26.9	46.3±13.2	53.2±16.5	64.5±23.4	73.2[illegible]	82.2±30.6
C	45.5±13.6	63.3±18.5	82.4±23.4	96.7±25.7	112.7±34.5	86.5±20.1	123.5±32.6	157.4±38.4	196.[illegible]	[illegible]35.5±53.6
F	5.468	5.762	6.354	6.649	6.968	6.230	6.458	6.695	7.203	[illegible]625
p	0.024	0.018	0.013	0.005	0.001	0.015	0.013	0.006	0.001	[illegible]

Table V. Comparisons of apoptosis rate of DC (%).

Group	1d	2	3	7	[illegible]0
A	35.6±10.5	53.2±13.4	67.8±17.8	[illegible]2.1±23.2	89.2±25.8
B	10.5±4.2	16.2±4.6	21.3±4.9	[illegible]7±5.3	30.2±5.5
C	18.2±4.6	26.4±5.2	32.4±5.8	[illegible]6.4	49.2±6.6
F	5.754	5.825	6.1[illegible]	[illegible]	6.645
p	0.018	0.017	[illegible]15	0.01[illegible]	0.007

thology of kidney and intestine were remarkably lower than that of the other two groups. The [illegible] parison of average scores for kidney pa[illegible]ogy and intestine among groups, showed no sta[illegible]al significance. It was suggested that kidney [illegible]d intestine in sepsis might be the first to be in[illegible] ved, and the involvement is of [illegible] weight. T[illegible] hTERT regulating DC could [illegible]ticeabl[illegible] inflammatory response of t[illegible]e and [illegible]e of duration was rather long ([illegible]ffectiv[illegible]0d after the study). At each ti[illegible] in [illegible] transfecting DC, th[illegible]evels o[illegible] Cr, IL-12 and TNF-α were[illegible]rkably low[illegible] that of the other two [illegible]t suggests [illegible] hTERT regulate DC a[illegible]d it co[illegible]wnregulate the level of inflam[illegible]ory response[illegible]ivo. At each time point, t[illegible]xpression of HLA[illegible], CD40 and the level[illegible]peripheral blood T cells MHC-II molecules [illegible]rema[illegible]bly higher than that of the other two [illegible]ps. It [illegible]s suggested that hTERT could raise t[illegible]ssion of DC, promote maturity, induce the T lymphocyte activation and enhance [illegible] functions. At each time, apoptosis rate of [illegible] remarkably lower than that of the other two groups; the content and activity of NF-κB were remarkably higher than that of the other two groups. It was suggested that hTERT could reduce apoptosis of DC and might be related with the survival of telomerase.

Conclusions

The telomerase reverse transcriptase gene can raise the expression and maturity of DC, reduce the apoptosis, induce cytokine secretion, reduce the inflammatory response and increase the survival time.

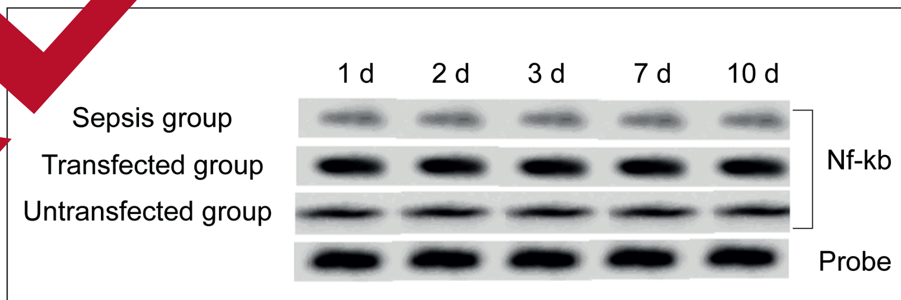

Figure 5. Western blotting for expression of MHC-II among different groups.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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