Human amnion epithelial cells mitigate sepsis-associated acute kidney injury via regulating endothelial dysfunction

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Abstract

Background

Sepsis is characterized by organ dysfunction resulting from patient's dysregulated response to infection. Sepsis-associated acute kidney injury (S-AKI) is the most frequent complication contributing to the morbidity and mortality of sepsis. The prevention and treatment of S-AKI remains a significant challenge worldwide. In recent years, human amnion epithelial cells (hAECs) have drawn much attention in regenerative medicine, yet the therapeutic efficiency of hAECs in S-AKI has not been evaluated.

Objectives

Our study aims to explore the effects of hAECs on S-AKI.

Methods

Septic mice were induced by cecal ligation and puncture (CLP) operation. hAECs were injected into the mice via tail vein right after the CLP surgery. The 7-day survival rate was observed. Serum creatinine level was measured, HE staining of renal sections was performed 16 hours after CLP. Inflammatory mediators, indicators associated with endothelial adhesion and function of septic mice kidney at 16 hours after CLP were detected by real-time PCR. Transmission electron microscopy was used to examine the renal endothelial integrity in CLP mice.

Results

hAECs decreased the mortality of CLP mice, ameliorated septic injury in the kidney and improved kidney function. More precisely, hAECs suppressed renal inflammation and maintained the vascular endothelial integrity in septic mice kidney.

Conclusions

Our results indicate that hAECs and their derived exosomes may ameliorate S-AKI via the prevention of endothelial dysfunction in the early stage of sepsis in mice. Stem cell therapy targeting endothelial disorders may be a promising alternative for treatment of S-AKI.

Keywords

hAECs, sepsis, acute kidney injury, endothelial dysfunction, stem cell therapy

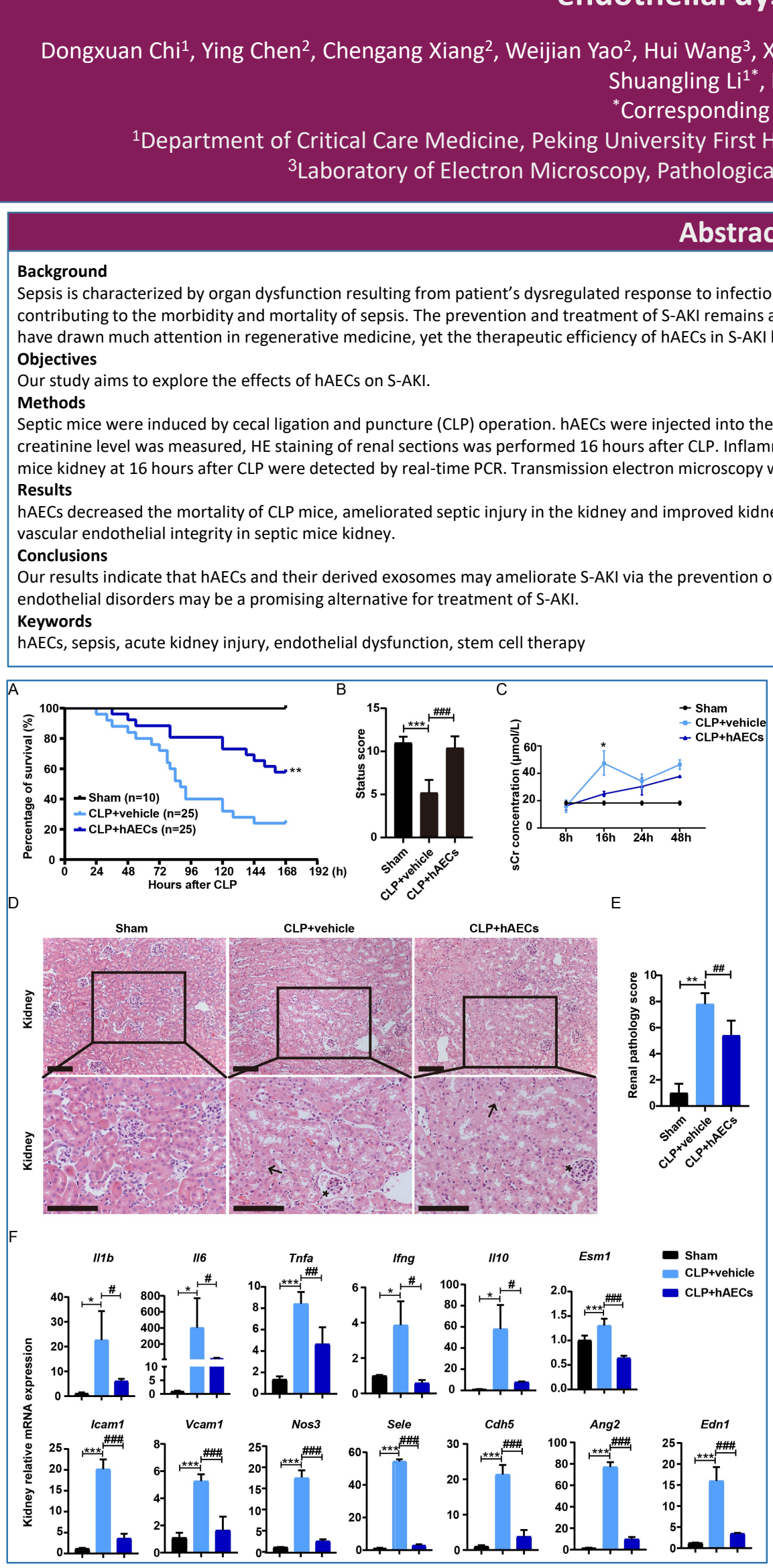

Figure 1. The effects of hAECs on CLP mice. **(A)** Survival rate after induction of sepsis by CLP in mice. **P<0.01 vs CLP+vehicle group. **(B)** Assessment of the clinical signs of mice 16 hours after CLP. ***P<0.001 vs sham group, ### P<0.001 vs CLP+vehicle group. **(C)** Serum creatinine concentration at different times in mice with CLP operation followed by vehicle (n=5) or hAECs (n=5) injection. *P<0.05 vs CLP+vehicle group. **(D)** Renal pathology of septic mice at 16 hours after CLP or CLP with hAECs treatment. Representative micrographs from each group are shown. The arrows indicate tubular epithelial vacuolization and the loss of brush border, the asterisks indicate Bowman's capsule expansion (HE staining; Scale bar, 50 μm). The lesions in the kidney were alleviated by the hAECs treatment. **(E)** Renal pathological scores representing the degree of lesion damage at 16 hours after CLP. **P<0.01 vs sham group; ##P<0.01 vs CLP+vehicle group. **(F)** The mRNA expression of inflammatory mediators, indicators associated with endothelial cell adhesion and function of septic mice kidney at 16 hours after CLP (n=3). *P<0.05, ***P<0.001 vs sham group; #P<0.05, ##P<0.01, ###P<0.001 vs CLP+vehicle group.

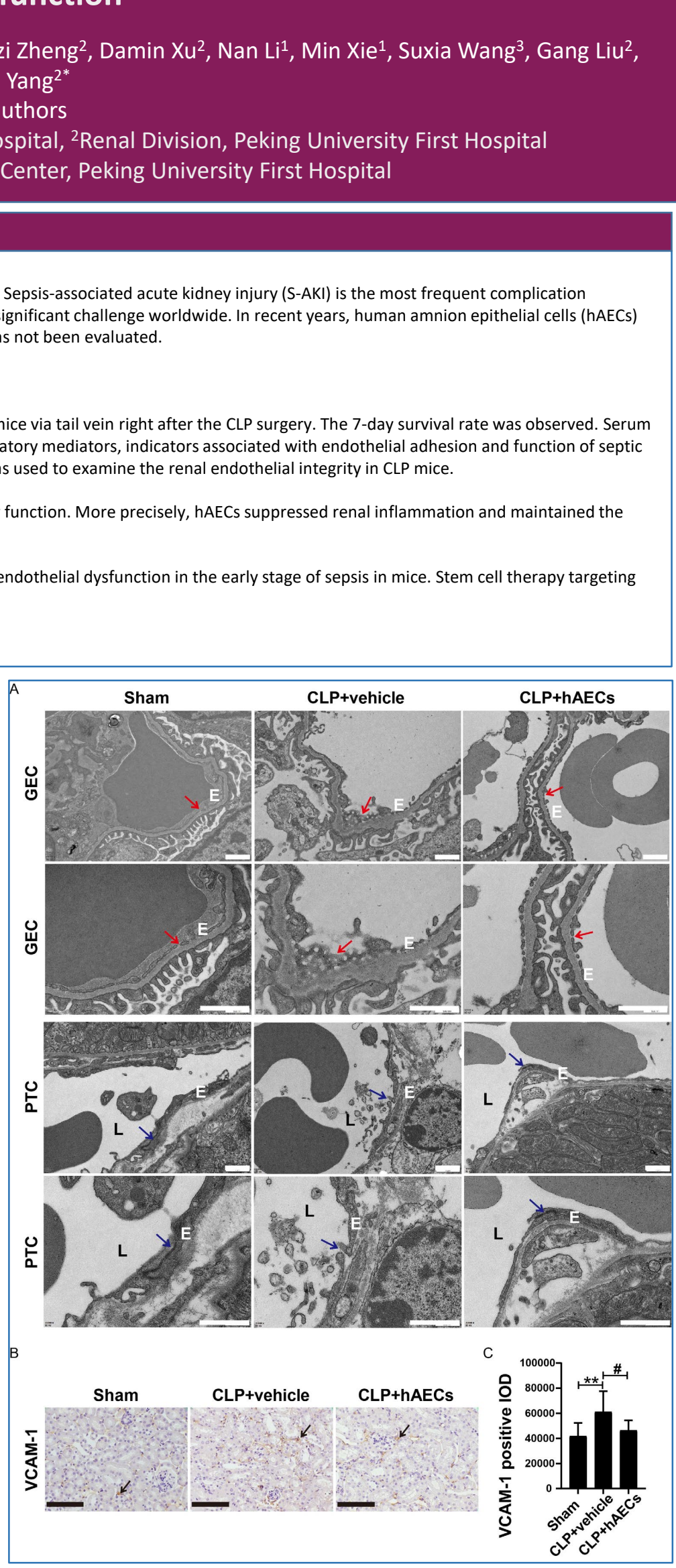

Figure 2. hAECs protected the endothelial cell structure and function from sepsis associated inflammatory injury. **(A)** Electron microscope images shown glomerular endothelial cell (GEC) fenestrae, tight junction disruption and the damage of the peritubular capillary endothelial layer in the septic mice at 16 hours after CLP. The red arrows indicate fenestrae of GECs. The blue arrows indicate tight junctions between two adjacent endothelial cells of the peritubular capillary (PTC). Scale bar, 1 μm. E: endothelial cell. L: peritubular capillary lumen. **(B)** Immunohistochemistry staining of VCAM-1 in kidney paraffin sections from the indicated groups at 16 hours after CLP. Scale bar, 50 μm. Arrows indicate the positive staining. **(C)** Statistical comparison of integrated optical density (IOD) of VCAM-1 positive staining in indicated groups. **P<0.01 vs sham group; #P<0.05 vs CLP+vehicle group.