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## Human bone mesenchymal stem cells transplantation rescuing fulminant hepatic failure in pigs

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Stem cell transplantation provides a promising alternative for the treatment of fulminant hepatic failure (FHF). However, it lacks fundamental understanding of stem cells' activities. Our objective was to clarify stem cell-recipient interactions for overcoming barriers to clinical application. Here, we used an in-house large-animal (pig) model of FHF rescue by human bone marrow mesenchymal stem cells (hBMSCs) and profiled the cells' activities. The control and transplantation groups of pigs (n=15 per group), both received a D-galactosamine (D-Gal) injection (1.5 g/kg). The transplantation group received hBMSCs via intraportal vein infusion ( $3 \times 10^6$  cells/kg) immediately after D-Gal administration. The stem cell-recipient interactions were quantitatively evaluated by biochemical function, cytokine array, metabolite profiling, gene sequencing and immunohistochemistry. The results indicated that all pigs in the control group died within an average of 3.22 days, whereas 13/15 pigs in the transplantation group lived >14 days. The cytokine array and metabolite profiling analyses revealed that hBMSC transplantation suppressed D-Gal- induced life-threatening cytokine storms and stabilized FHF within seven days, while human-derived hepatocytes constituted only ~4.5% of the pig hepatocytes. The functional synergy analysis of the observed profile changes indicated that the implanted hBMSCs altered the pigs' cytokine responses to damage through paracrine effects. Delta-like ligand 4 (DLL4) was validated to assist liver restoration in both pig and rat FHF models. Our results delineated an integrated model of the multifaceted interactions between stem cells and recipients, which may open a new avenue to the discovery of single molecule-based therapeutics that simulate stem cell actions.

### Biography

Jun Li has completed his PhD from Zhejiang University and Post-doctoral studies from Cedars-Sinai Medical Center in USA. He is a Professor of Hepatology and the Vice Director of State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine. He is a Member of American Association for the Study of Liver Diseases (AASLD) and a Member of Standing Committee of Stem cells Translational Medicine in the Chinese Society for Anatomical Sciences (CSAS). He has published more than 40 papers in reputed journals including the *Gut*, *Hepatology* and *Liver International*. He has been serving as an Editorial Board Member of *Scientific Report*.

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