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Substitute mesenchymal stromal cells therapy in graft versus host disease with a chemically defined cocktail

Yap Chui Sun, Xiubo Fan, Dian Yang Guo and **William Ying Khee Hwang**
Singapore General Hospital, Singapore

Mesenchymal stromal cell (MSC) therapy has been shown to be effective in phase I/II clinical trials in the treatment of graft versus host disease (GVHD) after allogeneic hematopoietic cell transplantations. However, MSC trials still face major challenges, such as complex and time-consuming manipulation, requiring a good manufacturing practice facility, difficult and expensive to produce etc. In a screen of MSC-derived factors with serial factorial designs, we first time identified two MSC-derived factors, CXCL5 and CCL24 inhibitor (antibody), which exhibited synergistic immunomodulation effect in mixed lymphocyte reaction. This two-factor (2F) cocktail also showed excellent *in vivo* immunosuppressive effect in ameliorating GVHD symptoms and improving survival. A xenograft GVHD animal model was created by injecting 400×106 cells/kg of cryopreserved human PBMCs into NSG mice respectively. Four consecutive treatments were given on day-10, day-14, day-17 and day-21 post-transplantation. The 2F cocktail exhibited excellent immunosuppressive effect as it could improve mice 36-day survival from 19.0% with severe symptoms to 61.9% with mild symptoms ($p<0.01$). It was significantly better than BM-MSCs (8.3%, $p<0.001$) and Cyclosporine A (26.1%, $p<0.05$). Synergistic effect was again observed between those two factors (CXCL5, 18.2%; anti-CCL24, 9.1%; $p<0.05$). The 2F cocktail treatment reduced cytotoxic T lymphocytes (CTLs), T helper 1 (Th1) cells, Th17 cells, NK cells in the circulation and macrophages in the spleen, but did not affect human hematopoietic stem cells (HSCs) reconstitution in the bone marrow. Concurrently, it reduced pro-inflammatory cytokine IFN-γ, IL-1β, IL-6, IL-12, TNF-α, IL-17A, IL-8, MIP-1β and MCP-1 in the circulation. In conclusion, the efficacy of a novel identified 2F cocktail was validated in an *in vivo* xenograft GVHD model. It demonstrated a robust immunosuppressive effect and kept the development of GVHD under control. The 2F cocktail could be a potential chemically defined substitute for MSCs in GVHD therapy.

Biography

Yap Chui Sun joined the Department of Clinical Translational Research, Singapore General Hospital (SGH) in 2013, and has been working on reprogramming mesenchymal stem cells. Her first postdoctoral position was at Duke-NUS Medical School, where she was studying the contribution of micro RNAs on thyroid hormone function. She obtained her Master's degree in Molecular Immunology at the National University of Singapore and Ph.D. degree in Molecular Oncology at Brown University (U.S.A.).

yap.chui.sun@sgh.com.sg

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