Ex-Vivo Induced Regulatory Human/Murine Mesenchymal Stem Cells as Immune Modulators.

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Abstract

Over the past decade there has been a growing interest in utilizing mesenchymal stem cells (MSCs) as an immune-regulatory agent for prevention and treatment of various immune disorders including graft-versus-host disease (GVHD), transplanted organ rejection and autoimmune diseases. However, the high diversity in the results from clinical trials using MSCs for such disorders emphasizes the need for MSCs to be "professionalized" ex-vivo to a more defined regulatory phenotype before administering to patients. To this aim, we have established an ex-vivo immunomodulatory triple combination treatment (TCT) for MSCs, using IFNγ, TGFβ and kynurenine. We show that pre-treated MSCs acquire an immunomodulatory phenotype, have improved regulatory functions, and up-regulate the expression of iNOS, IDO, COX2, HO-1, LIF and PD-L1. We define the pathway of kynurenine induced AhR activation in MSCs and how it contributes to the up-regulation of COX2 expression and IL-6 down-regulation. The combination of reduced IL-6 secretion with enhanced LIF expression leads to the inhibition of Th17 differentiation in co-culture of TCT MSCs and lymphocytes.

To test the immunomodulatory function of TCT MSCs in vivo, we used the cells as GVHD prophylaxis in a GVHD mouse model. TCT MSCs administration significantly decreased GVHD score and improved mouse survival. Importantly, single administration could attenuate disease symptoms for more than three weeks.

Based on these results, we suggest considering TCT MSCs as an improved cell therapy for systemic diseases with an underlying inflammatory and immunologic etiology.