

IMMUNOMODULATION ALLOWS BETA-PANCREATIC ISLETS REGENERATION AFTER MULTIPOTENT MESENCHYMAL STROMAL CELLS ENDOVENOUS ADMINISTRATION INTO TYPE 1 DIABETIC MICE

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Type 1 diabetes mellitus affects 17 million of people worldwide. Nowadays, any available treatment allows accurate blood glucose levels control. Thus, even under treatment, patients develop severe diabetic complications that significantly compromise their life quality and reduce their life expectancies. Recently, we have demonstrated that endovenous administration of a single dose of 0.5×10^6 bone marrow-derived multipotent mesenchymal stromal cells (MSC) into mice with type 1 diabetes (DMT1) reverted hyperglycemia, increased insulinemia, and reduced glycated-hemoglobin levels. This phenotypic reversion correlated with the recovery of beta-pancreatic islets number, morphology and function.

The aim of the present work was to evaluate the contribution of MSC immunomodulatory potential, to beta-pancreatic islets regeneration observed in DMT1 mice.

First, we assessed -by qRT-PCR- the expression of molecules that enhanced [IL1beta, TGFbeta1, MCP1, ICAM1] or prevent [IL2, IL4, IL5] the destruction, mediated by autoreactive T cell, of beta-pancreatic islets. As expected, in the pancreas of untreated DMT1 mice the levels of expression of pro-damage molecules were higher than in normal animals. Together, the expression of islet-protective genes [IL2 and IL5] was diminished. However, 7 days post-administration, IL1beta, MCP1, ICAM1, IL2 and IL5 were expressed at basal levels in the pancreas of MSC-treated DMT1 mice. Furthermore, 65 days post-administration, IL4 and IL5 were highly expressed in the pancreas of MSC-treated DMT1 mice compared to untreated DMT1 mice.

Second, we analyzed -by flow cytometry-, the presence of regulatory T cells (Treg: CD4+, CD25+, Foxp3+) in bone marrow, spleen and blood of DMT1 mice treated or not with MSC. At days 7 and 65, a significant increase in Treg frequency was observed both in lymphoid organs and systemically in MSC-treated DMT1 mice, compared to untreated DMT1 or normal mice.

Third, we determined -by flow cytometry- the biodistribution of donor MSC in DMT1 receptors. For this, cells were isolated from isogenic mice that constitutively express GFP (MSC^{GFP}), endovenously administered to DMT1 mice and tracked in blood, heart, lung, liver, kidney, pancreas, bone marrow, spleen, inguinal, mesenteric and pancreatic lymph nodes and Peyer's patches. Seven days post-administration, MSC^{GFP} were mainly found into the heart and the lymphoid organs of DMT1 mice. Sixty-five days post-administration, donor MSC were present almost exclusively in Peyer's patches. At days 7 and 65, MSC^{GFP} were under the limit of detection in blood, lung, liver, kidney and pancreas.

Our results show that in DMT1 mice, donor MSC mainly home into lymphoid organs, promote Treg cells augmentation, reduce the activity of reactive T cells and maintain high level of pancreatic protective factors. Hence, the immunomodulation promoted by systemic administration of MSC allows the regeneration of beta-pancreatic islets.

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