TSP-1-Mediated Induction of T Regulatory Cell by Adipose-Derived Mesenchymal Stem Cells: A Mechanism of Immunosuppression

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Adult mesenchymal stem cells (MSC), including adipose-derived stem cells (ASC), have potent immunosuppressive activity in vitro and in mouse models of colitis [1]. Multiple ongoing clinical trials have studied ASC in the treatment of patients with inflammatory bowel diseases (IBD) and other immune-mediated diseases [2, 3]. ASCs are more frequently used for cell-based therapy given their ubiquity, ease of acquisition, and the high yield from adipose tissue. A recent phase III multicenter randomized placebo-controlled trial of allogeneic adipose stem cells injected directly into Crohn's perianal fistulas [4] reported clinical and radiological healing. If MSC therapies are already clinically effective, why study them in mice? Unfortunately, the data from clinical trials using systemically administered MSCs for the treatment of mucosal lesions in IBD have shown good safety but no clear efficacy signal [2]. Although some studies have indicated that T regulatory (Treg) cell induction contributes toward the therapeutic benefits of MSC, the reasons for this are inadequately investigated, requiring additional mechanistic studies conducted in preclinical models to help understand the therapeutic benefits of MSC administration. The study by Takeyama and colleagues in this issue of *Digestive Diseases and Sciences* is important as it reports that transforming growth factor beta (TGF- β) activation by ASC expressing thrombospondin-1 (TSP-1) is a mechanism for Treg cell induction and consequent therapeutic benefit in a murine dextran sulfate sodium (DSS) colitis

model [5]. The authors demonstrate that ASCs administered intraperitoneally (i.p) ameliorated DSS-induced acute colitis and increased the number of Tregs in the colonic lamina propria and mesenteric lymph nodes (MLNs) as assessed by flow cytometry. The increase in Tregs was not accompanied by an increase in CD103+ dendritic cells suggesting the role of an ASC factor that helps CD103+ dendritic cells to induce Tregs. Furthermore, in co-culture assays the authors determined that ASCs do not secrete TGF- β but activate latent TGF- β via TSP-1. Using siRNA to knockdown TSP-1 in ASCs (TSP-1KO), they showed that TSP-1 KO ASCs did not induce Tregs in vivo and failed to ameliorate colitis as compared to mock-treated (nontargeted siRNA control) and untreated ASCs. Using green fluorescent protein-labeled ASCs, the authors showed that ASCs do not migrate to the colon to exert their effect but are rather found in the spleen and in the MLNs. Although their results are congruent with other studies that show limited homing of MSCs to the colon after i.p injection, an elegant study by Sala and colleagues reported that MSCs (including ASCs) formed peritoneal aggregates at the site of injection and did not home to the spleen or to the MLNs [6]. This discordance could be due to the differential expression of chemokine receptors CCR7 and CCR9 between the ASC preparations used in these studies versus deposition of the peritoneal aggregates on the spleen and the MLNs. Future studies using dynamic imaging techniques such as two-photon microscopy are needed to clarify the homing and interactions of MSCs with host cells.

Overall, the important work by Takeyama et al. enhances understanding of the mechanism for induction of T regulatory cells by ASCs that contributes to their therapeutic efficacy. To be able to translate this novel therapy into routine clinical care of inflammatory bowel disease

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patients, continued research with a focus on the mechanism(s) of their efficacy in more disease-relevant and chronic models of intestinal inflammation such as the T cell transfer model of colitis and SAMPI/YitFc model of ileitis is needed.

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