【別紙２】

論文名：Early injection of human adipose tissue-derived mesenchymal stem cell after inflammation ameliorates dextran sulfate sodium-induced colitis in mice through the induction of M2 macrophages and regulatory T cells.

（炎症時のヒト脂肪組織由来間葉系幹細胞の早期投与は、M2 マクロファージおよび制御性 T 細胞の誘導を介することで、マウスのデキストラン硫酸ナトリウム誘導性大腸炎を改善させる。）

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Inflammatory bowel diseases (IBDs) are sometimes refractory to current therapy or associated with severe adverse events during immunosuppressive therapy; thus, new therapies are urgently needed. Recently, mesenchymal stem cells (MSCs) have attracted attention based on their multitude of functions including anti-inflammatory effects. However, proper timing of MSC therapy and the mechanisms underlying the therapeutic effects of MSCs on colitis are not fully elucidated. Human adipose tissue-derived mesenchymal stem cells (hAdMSCs; 1 × 106) were administrated via the tail vein on day 3 (early) or 11 (delayed) using a 7-day dextran sulfate sodium (DSS)-induced mouse model of colitis. The effects were evaluated based on colon length, disease activity index (DAI) and histological score. Cytokine-encoding mRNA levels T cells and macrophages were evaluated by real-time PCR and flow cytometry. Regarding the timing of administration, early (day 3) injection significantly ameliorated DSS-induced colitis in terms of both DAI and histological score, compared to those parameters with delayed (day 11) injection. With early cell injection, the tissue mRNA levels of anti-inflammatory cytokine genes (Il10, Tgfb) increased, whereas those of inflammatory cytokine genes (Il6, Tnfa and Il17a) decreased significantly. Regarding the associated mechanism, hAdMSCs suppressed T cell proliferation and activation in vitro, increased the number of regulatory T cells in vivo and changed the polarity of macrophages (into the anti-inflammatory M2 phenotype) in vitro. Timing of injection is critical for the effective therapeutic effects of hAdMSCs. Furthermore, part of the associated mechanism includes T cell activation and expansion and altered macrophage polarization.