Clinical effect of FMT in SSC measured by the UCLA GIT score

Stackplot of significantly changed relative abundance of fecal bacteria after FMT from week 0 to weeks 4 and 16

Conclusion: FMT of commercially-available ACHIM in patients with SSC appeared safe, effectively reduced lower GI symptoms, altered gut microbiota composition, richness and diversity and appeared to affect the mucosal immune system

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Calming the cytokine storm in children and adults__

OP0328

COMPARISON OF SERUM CYTOKINE PROFILE IN MACROPHAGE ACTIVATION SYNDROME AMONG DIFFERENT BACKGROUND RHEUMATIC DISEASES IN CHILDREN:

Mao Mizuta, Masaki Shimizu, Masaaki Usami, Naoto Sakumura, Hitoshi Irabu, Maiko Takakuwa, Natsumi Inoue, Yasuo Nakagishi, Akihiro Yachie. Graduate School of Medical Sciences, Kanazawa University, Department of Pediatrics, Kanazawa, Japan

Background: Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of pediatric rheumatic diseases. MAS occurs most often in children with systemic juvenile idiopathic arthritis (s-JIA) and less commonly in children with systemic lupus erythematosus (SLE), Kawasaki disease (KD) and juvenile dermatomyositis (JDM). The hallmark of MAS includes uncontrolled and dysfunctional immune responses involving continual activation and expansion of T lymphocytes and macrophages, which in turn lead to marked hypercytokinemia. However, it is still unknown which cytokines play a key role in the pathogenesis of MAS among different backgrounds.

Objectives: This study was aimed to clarify cytokines involved in the development of MAS among different background rheumatic diseases and to identify the serum biomarkers for the diagnosis of MAS.

Methods: Serum neopterin, interleukin (IL)-18, IL-6, tumor necrosis factor (TNF)- α and soluble TNF receptor type I (sTNFR-I) and sTNFR-II levels were determined using enzyme-linked immunosorbent assay in 112 s-JIA patients including 30 with MAS, 8 SLE patients including 3 with MAS, 67 KD patients including 4 with MAS, and 7 JDM patients including 3 with MAS. Cytokine profiles in MAS phase of each disease were compared to those in active phase.

Results: Serum neopterin levels in patients with s-JIA, SLE and KD were significantly elevated in MAS phase compared to those in active phase. Serum neopterin levels in patients with JDM were also elevated in MAS phase compared to those in active phase, although statistically significant. Serum sTNFR-I levels in patients with s-JIA and SLE were significantly elevated in MAS phase compared to those in active phase. Serum sTNFR-I levels in patients with KD and JDM were

also elevated in MAS phase compared to those in active phase, although statistically significant. Serum sTNFR-II levels in patients with s-JIA and KD were significantly elevated in MAS phase compared to those in active phase. Serum sTNFR-II levels in patients with JDM were also elevated in MAS phase compared to those in active phase, although statistically significant. Serum IL-18 levels in patients with s-JIA were significantly elevated in both active and MAS phase compared to those in patients with other diseases. There were no significant differences of serum IL-6 and TNF- α levels among different backgrounds.

Conclusion: The elevation of serum neopterin levels was the common finding in patients with MAS even in different backgrounds. These findings indicate that overproduction of interferon (IFN)- γ might be closely related to the development of MAS. Serum neopterin levels which reflect IFN- γ production might be a promising biomarker for the disease activity of MAS.

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OP0329

PLCGAMMA2/TMEM178 DEPENDENT PATHWAY IN MYELOID CELLS MODULATES THE PATHOGENESIS OF CYTOKINE STORM SYNDROME

Sahil Mahajan¹, Zhengfeng Yang¹, Elisabeth Mellins², Roberta Faccio^{1,3*}.

¹Washington University, Orthopaedics, St. Louis, United States of America;

²Stanford University, San Francisco, United States of America; ³Shriners Hospital for Children, St. Louis, United States of America

Background: Cytokine storm syndrome (CSS) is a life-threatening condition, observed in several rheumatic diseases, and a well-known complication of systemic juvenile idiopathic arthritis (sJIA) (1). Defects in T cell cytotoxicity leading to their excessive activation are major contributors to CSS development. However, dysregulated innate immune responses are also observed (2). The role of monocytes and macrophages as drivers of CSS, regardless of T cells, and the signaling pathways regulating monocyte/macrophage responses, have not been formally investigated.

Objectives: The goal of this study was to determine the contribution of monocytes/macrophages to the development of CSS and analyze the signaling pathways that lead to aberrant monocyte/macrophage pro-inflammatory responses using animal models of the disease and patient samples.

Methods: To study the involvement of monocytes/macrophages in a T cell-dependent model of CSS we treated LCMV-infected Perforin-/- mice with clodronate-liposomes or neutralizing anti-CSF1Ab prior to disease initiation. Similar depletion experiments were performed in a T-cell independent CSS model consisting of five injections of the TLR9 agonist CpG-1826 into WT mice. Myeloid cell contribution to CSS was assessed in mice with LysMCre-driven deletion of Plcy2 or global deletion of Tmem178, a downstream Plcy2 target gene specifically expressed in macrophages. Presence of immune infiltrates in liver and spleen was evaluated by FACS analysis and immunohistochemistry, circulating inflammatory cytokine levels were detected by ELISA, multi-organ damage was evaluated by histology.

Results: Depletion of monocytes/macrophages during early stages of CSS reduces mortality and inflammatory cytokine levels in both T-cell dependent and independent CSS models. Activation of Plcy2 in myeloid cells controls CSS development by driving macrophage pro-inflammatory responses. Intriguingly, the Plcy2 downstream effector Tmem178 acts in a negative feedback loop to restrain inflammatory cytokine production and protect from CSS development. Highlighting the clinical relevance, Tmem178 levels are reduced in macrophages from mice with CSS or exposed to sJIA patient plasma with active disease.

Conclusion: Macrophages are key drivers of CSS initiation. We identified a novel Plcy2/Tmem178 axis as a modulator of inflammatory cytokine production by monocytes/macrophages in CSS. Reduced Tmem178 levels are observed in sJIA and might be responsible for the increased macrophage pro-inflammatory responses.

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