Figure 1: Plasma level of CX3CL1 and CCL26 and expression of CX3CR1 in various subsets of PBMCs. In comparison with HCs, patients with PBC present with following features. (A) A significantly higher plasma level of CX3CL1. (B) An increased tendency of CCL26 level in plasma. (C) A significantly larger percentage of CX3CR1⁺ cells in CD4⁺ T cells. (D) A comparable expression of CX3CR1 in CD8⁺ T cells. (E) A comparable expression of CX3CR1 in NK cells. (F) A significantly larger percentage of CX3CR1⁺ cells in NKT-like cells.

Figure 2: Expression of CX3CL1 and CCL26 in liver tissues and the change of CX3CL1/CCL26-CX3CR1 pathway expression in HIBECs upon stimulation of various cytokines. (A-D) In intrahepatic bile ducts, high expression of CX3CL1 and CCL26, which was indicated by arrows and triangles respectively, was observed in PBC patients. However, only weak expression of CX3CL1 and no expression of CCL26 were found in HCs. (E-F) Weak and no expression of CX3CL1 was revealed in hepatocytes in PBC patients and HCs respectively. (G-H) CCL26 was widely expressed in both PBC patients and HCs. However, in PBC patients, hepatocytes expressed with CCL26 tended to be abundant near portal areas and became scarce in distant regions. This distribution pattern was not observed in HCs. (I) IFN- γ up-regulated the expression of CX3CL1 in HIBEC culture supernatant. (J) IL-4 and IL-13 stimulated the expression of CCL26 in HIBEC culture supernatant. (K) IFN- γ stimulated the expression of CX3CR1 on HIBEC surface.

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AB0082

REDUCED STEROIDOGENIC ACTIVITY OF REPOSITORY CORTICOTROPIN INJECTION (RCI) INDUCES A DISTINCT CYTOKINE RESPONSE FOLLOWING T CELL ACTIVATION IN VIVO

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Background: Melanocortin receptor agonists, such as α MSH have been shown to reduce inflammation in preclinical models, suppressing the production of pro-inflammatory cytokines. Natural and synthetic ACTH analogues remain linked to the induction of corticosteroids as their primary mechanism of action, leading to the anti-inflammatory and immunosuppressive responses. Repository Corticotropin Injection (RCI) is a complex mixture containing purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment for several inflammatory diseases. RCI has been shown to be effective in steroid-refractory autoimmune disease.

Objectives: We hypothesize that Acthar has an immune regulatory response distinct from synthetic ACTH and steroids. These studies sought to explore the differences between RCI and synthetic ACTH on corticosterone levels in rats and cytokine production in a murine T cell activation model.

Methods: RCI (10, 40, or 400 IU/kg) or ACTH (0.6, 1.2, or 2.4 mg/kg) was administered to Sprague Dawley rats, plasma samples collected and analyzed for corticosterone. To determine the effect on T cell cytokine production, Balb/C mice were treated with RCI (10, 40, and 400 U/kg), ACTH (0.6, 1.2, or 2.4 mg/kg) or prednisolone 1 hour prior to the administration of an anti-CD3. Two hours after antibody administration, plasma cytokines were measured using Meso Scale multiplex ELISA.

Results: RCI and ACTH peak corticosterone and area under the curve (AUC) were evaluated. RCI-induced corticosterone rapidly peaked between 2-8 hrs. and was dependent on the dose. ACTH displays a delay in the peak time (8-24 hours) and was not dose dependent. When compared to the high dose ACTH, RCI reduced the AUC by 50.0 $\pm$ 2.6%, 45.5 $\pm$ 5.6% and 27.3 $\pm$ 12.5% respectively for 10, 40, and 400 IU/kg. However, there was no significant reduction between any of the ACTH doses tested.

To further explore functional differences between RCI and ACTH, we examined the effects on T cell activation. In vivo T cell activation with the anti-CD3 antibody (clone, 145-2C11) increased several cytokines, including IL-2, IL-6, IL-10, and IFN γ . Treatment with RCI, ACTH, or prednisolone significantly reduced the production of IL-2, IL-4, IFN γ , and TNF α . Interestingly, RCI showed an inverse dose-response on the production of IL-6 and IL-10. RCI inhibited the production of IL-6 at 74.7 $\pm$ 4.4% and 67.9 $\pm$ 8.5% and IL-10 at 39.1 $\pm$ 7.1% and 26.7 $\pm$ 9.3% for 10 and 40 IU/kg, respectively, whereas 400 IU/kg had no effect. ACTH inhibited the production of IL-6 at a similar level for all doses tested and had no effect on IL-10 production, whereas treatment with prednisolone inhibited all cytokines.

Conclusion: These data show that RCI has a reduced steroidal response compare to synthetic ACTH. RCI has a direct and distinct immunomodulatory response on T cells unique from both synthetic ACTH and steroids. These characteristic effects suggest a mechanism of action for RCI that is steroid-independent and may help explain its benefit in steroid refractory syndromes.

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AB0083

ADIPONECTIN STIMULATES PRO-INFLAMMATORY CYTOKINE PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH EARLY UNTREATED RHEUMATOID ARTHRITIS

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Background: The pathogenesis of rheumatoid arthritis (RA) involves the action of immune cells and fibroblast-like synoviocytes (FLS). Adiponectin, an adipokine produced mainly by adipocytes, is elevated in serum of RA patients compared to healthy controls; moreover, synovial fluid from RA subjects has higher levels of adiponectin compared to controls with osteoarthritis^{1,2}. Adiponectin induces the production of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and IL-8, by