IL-17A AND IL-17F ARE SECRETED BY ENTHESIS T CELLS AND SYNERGIZE WITH TNF TO INDUCE CCL20 FROM ENTHESIAL STROMAL CELLS

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Enthesis is the specialized tissue that connects muscle or tendon to bone. This junction is highly susceptible to inflammation in rheumatoid arthritis (RA) and has been related to synovial pathology. Enthesis inflammation and fibrosis is due to the activity of IL-17A and IL-17F, along with TNF.

Background: Enthesitis or inflammation of tendon/ligament anchors is the cardinal lesion in spondyloarthritides (SpA) [1]. Enthesitis has been associated with the development of SpA. The MAP3K family protein, Apoptosis signal-regulating kinase 1 (ASK1) is a member of the MAP3K family that activates p38 and c-jun and has recently been shown to mediate human RA fibroblast-like synoviocyte (FLS) invasion, proliferation, and migration in vitro. Activity of ASK1 has been shown to modulate human RA fibroblast-like synoviocyte (FLS) invasion, proliferation, and migration in vitro. It is currently unknown whether ASK1 activity is present in entheseal tissues and whether it contributes to the development of enthesis inflammation.

Objectives: To determine if enthesis T cells secrete IL-17A and IL-17F. To study the effect of both IL-17A and IL-17F on CCL20 induction from enthesial stromal cells.

Methods: Normal enthesis tissue was obtained from patients undergoing spinal decompression or surgery for scoliosis correction. Following enzymatic digestion, CD4+ and CD8+ T cells were stimulated with anti CD3/CD28 and IL-17A and IL-17F measured by intracellular FACS.

Results: Enthesial CD4+ T cells secrete IL-17A and IL-17F following stimulation. When used as single agents IL-17A, IL-17F and TNF were able to induce minimal CCL20 from entheseal stromal cells, but great synergy was reported for IL-17A/TNF and IL-17F/TNF. No synergy was shown for TNF and IL-17A or IL-17F and TNF and subsequently CCL20 was measured by an ELISA.

Conclusions: Enthesial CD4+ T cells secrete IL-17A and IL-17F following stimulation. The normal human enthesis contains CCR6+ T cells with an enthesis homoeostasis. IL-17A/F dramatically synergize with TNF to induce CCL20 from enthesis stromal cells, which would be well placed to mediate further migration of IL-17 producing lymphocytes to entheseal tissues.  

REFERENCES:  

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Get the IL-17F outta here!

THU0013

THU0014

TARGETING ACTIVATED ASK1 IN SYNOVIAL FIBROBLASTS IN COMBINATION WITH JAK1 INHIBITION ENHANCES EFFICACY IN RAT CIA

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Background: Despite improved therapy, rheumatoid arthritis (RA) remains an area of unmet medical need. Current therapies have improved disease control by targeting inflammatory pathways. However, treatments rarely induce remission, highlighting the need for new therapies. Filgotinib (FIL) is an orally selective JAK1 inhibitor that has demonstrated clinical efficacy in RA trials. Apoptosis signal-regulating kinase 1 (ASK1) is a member of the MAP3K family that activates p38 and c-jun and has recently been shown to modulate human RA fibroblast-like synoviocyte (FLS) invasion, proliferation, and migration in vitro. We hypothesize that by dual targeting of JAK-dependent inflammatory pathways with FIL and ASK1 signaling in FLS with an ASK1 inhibitor, we can demonstrate an increase in efficacy in a rat collagen-induced arthritis (CIA) model.

Objectives: To evaluate the individual and combination activity of JAK1 and ASK1 inhibition in the rat CIA model by oral dosing with FIL and an ASK1 inhibitor.

Methods: The in vivo efficacy of FIL and an ASK1 inhibitor were tested individually or in combination in a therapeutic rat CIA model. Dosing was initiated at the onset of disease (day 11) and continued until day 18. Efficacy evaluations were based on animal body weights, daily ankle caliber measurements, ankle diameter (expressed as area under the curve), terminal hind paw weights, and histopathology of the ankles and knees.

Results: Administration of FIL individually significantly reduced ankle diameter and final paw weights by 51% and 52%, respectively (p<0.05). There was no change in body weight loss or in histological measurements with treatment. Conversely, ASK1 inhibition did not reduce inflammation as measured by ankle diameter or paw swelling, but resulted in a 48% reduction in ankle histopathological score (p<0.05). The combination of FIL and the ASK1 inhibitor showed significantly greater effects on all measured parameters including paw weight (81% reduction), ankle diameter (78% reduction), and ankle and knee histopathology scores (69% and 87% reduction, respectively) than either agent alone. Body weight loss was also significantly reduced with the combination, and increased toward normal weight gain compared to the monotherapy arms. Body weight loss was also significantly reduced with the combination, and increased toward normal weight gain compared to the monotherapy arms. Conclusion: Combining FIL with ASK1 inhibition significantly improved clinical and histopathology scores, and reduced body weight loss in this model. These data suggest that simultaneously targeting JAK and ASK1 pathways can provide orthogonal activities that can enhance overall disease control.

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