One of the hallmarks of spondyloarthritis (SpA), is the development of enthesitis, most typically of the Achilles tendon and plantar fascia. In this study, we investigated the initiating events leading towards enthesitis development in TNFΔARE mice. These mice are characterized by an enhanced TNF mRNA stability, which in turn leads to the development of several features of SpA, including peripheral and axial arthritis, and Crohn’s like ileitis. One of the striking features of this model is the early appearance of tendinitis/enthesitis of the Achilles tendon. We subjected TNFΔARE mice which had not yet developed signs of inflammation to tail suspension, a biomechanical unloading procedure, thereby prohibiting weight loading on hind paws for 7 days. Western blotting was performed for phosphorylated Erk, one of the mitogen-activated protein kinases on cell lysates from Achilles tendon samples of tail suspended TNFΔARE mice, versus mice that were allowed to walk for 15 minutes after a 7 days period of tail suspension. The effect of small molecular inhibitors of Erk and p38 on enthesitis development was evaluated. In addition, Achilles tendon fibroblasts from TNFΔARE and control mice were subjected to cyclic stretch in a bioreactor, and cytokine and chemokine responses were measured in supernatant. Biomechanical unloading studies indicated that almost no inflammation of the Achilles tendon occurred in unloaded animals compared to weight bearing controls. By contrast, weight bearing front paws exhibited severe inflammation. As early as 15 minutes after initiation of weight bearing, phospho-Erk was upregulated compared to continuously unloaded conditions. Treatment of TNFΔARE mice with small molecular inhibitors of Erk and p38 markedly reduced the extent of Achilles tendon enthesitis. Furthermore, several chemokines were differentially produced insupernatant from stretched TNFΔARE fibroblasts versus controls.

**Conclusion:** These findings provide a novel proof that biomechanical stretch may activate pro-inflammatory signalling pathways, setting off a cascade of events, which in a genetically predisposed host may lead to enthesitis.