Proresolving mediators counter inflammation in stromal cells from patients with Achilles tendon disease

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Introduction

Achilles tendon disorders including tendinopathy and rupture cause pain and disability in athletes and non-athletic individuals. Growing evidence supports the contribution of inflammation to the onset and progression of these injuries, however the processes underpinning resolution of Achilles tendon inflammation are poorly understood.

Materials and Methods

We investigated the bioactive lipid mediator profiles of tendon-derived stromal cells isolated from patients with Achilles tendinopathy (AT) or rupture (AR) under baseline and IL-1β stimulated conditions using LC-MS-MS. RT-qPCR and immunocytochemistry were performed to determine if incubating these cells with two of the mediators produced by tendon-derived stromal cells, 15-epi-LipoxinA_4 (15-epi-LXA_4) or Maresin1 (MaR1), moderated their pro-inflammatory phenotype.

Results

AT cells showed concurrent increased levels of pro-inflammatory eicosanoids and proresolving mediators compared to AR cells. IL-1β treatment induced profound PGE_2 release in AR compared to AT cells. Incubation of IL-1β treated AT/AR tendon-derived stromal cells in 15-epi-LXA_4 or MaR1 reduced pro-inflammatory eicosanoids and potentiated the release of proresolving mediators. 15-epi-LXA_4 or MaR1 also induced SPM biosynthetic enzymes ALOX12, and ALOX15 and upregulated the proresolving receptor ALX compared to vehicle treated cells. 15-epi-LXA_4 or MaR1 also moderated the pro-inflammatory phenotype of AT and AR cells, regulating Podoplanin, CD90, STAT-1, IL-6, IRF5, TLR4 and suppressed JNK1/2/3, Lyn, STAT-3 and STAT-6 phosphokinase signalling.

Discussion

Differences in the bioactive LM profiles between tendon stromal cells isolated from AT and AR patients likely reflect the temporal effects of disease stage. Proresolving mediators including 15-epi-LXA_4 and MaR1 regulate the pro-inflammatory phenotype of patient derived Achilles tendon cells, dampening expression of fibroblast activation markers and regulating PGE_2, STAT-1, IL-6, IRF5, TLR4. These SPM also potentiated the further release of other proresolving mediators in IL-1β stimulated AT and AR cells. In summary, we identify proresolving mediators that are active in Achilles tendinopathy and rupture, and propose SPM including 15-epi-LXA_4 or MaR1 as potential therapeutics to resolve Achilles tendon inflammation.