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THERAPY

Targeting IFN-β to inflamed joints in arthritic mice

Interferon β (IFN-β) has shown therapeutic efficacy in animal models of rheumatoid arthritis (RA), but previous results in humans have been disappointing. It has been suggested that pharmacokinetics underlie this failure, and thus more targeted approaches might improve outcomes. "We decided to harness the pathological events of inflammatory diseases to allow for targeted therapeutic delivery," explains Yuti Chernajovsky, whose new study demonstrates the potential of a latent IFN-β construct that can be activated by aggrecanase-mediated cleavage.

IFN-β is naturally secreted in an active form. By contrast, TGF-β is secreted as a latent cytokine, in complex with latency-associated peptide (LAP). Chernajovsky and colleagues had previously shown that fusing LAP to IFN-β via a cleavage site for matrix metalloproteinases (MMPs), which are highly expressed in arthritic joints, generates a latent form of IFN-β (LAP-mmp-IFN-β) that can be activated by synovial fluid from patients with RA. However, MMPs are also expressed physiologically in many tissues, so to achieve more specific targeting to joints affected by osteoarthritis (OA) or RA, an aggrecanase cleavage site (LAP-agg-IFN-β) was investigated in the new study.

> "LAP-agg-IFN-β ... significantly reduced arthritic scores and paw inflammation..."

The investigators first showed that LAP-mmp-IFN-β and LAP-agg-IFN-β could both be cleaved by synovial fluid from patients with OA, but in these *in vitro* assays the IFN-β activity released from LAP-agg-IFN-β was maintained for longer. Administration of either fusion protein to mice with collagen-induced arthritis significantly reduced arthritic scores and paw inflammation, with a greater clinical improvement observed with LAP-agg-IFN-β. Moreover, proinflammatory cytokine levels, and cartilage and bone destruction, were also decreased by both constructs. By contrast, LAP-IFN-β lacking a cleavage site showed no therapeutic benefits, confirming that cleavage is necessary for efficacy.

Compared with injection of free IFN-β, LAP-agg-IFN-β administration resulted in equivalent levels of IFN-β activity in the inflamed paw, but considerably lower levels at other sites, highlighting the success of this targeting approach. "We believe that targeted delivery of cytokines to sites of disease is a therapeutic area that has not been fully exploited," remarks Chernajovsky. "LAP-mediated delivery is non-toxic and specific to sites of disease. Hence, perhaps higher doses could be used safely to accelerate treatment and reverse the pathological process," he concludes.

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Original article Mullen, L. *et al.* A comparative study of matrix metalloproteinase and aggrecanase mediated release of latent cytokines at arthritic joints. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-203513