INFLAMMATION

Targeting NF-κB in tendinopathy

The nuclear factor-κB (NF-κB) pathway is upregulated in tendon degeneration and injury, but whether this response is a cause or effect of tendon pathology is unclear. The findings of a new study suggest that IKKβ, a kinase that mediates NF-κB activation, contributes to tendinopathy in mice, and that blocking this pathway has therapeutic potential in humans.

"It was unclear from the literature whether inflammation was a good thing or a bad thing for tendinopathy." explains corresponding author Stavros Thomopoulos. "On the one hand, high levels of inflammation can be damaging to the tendons. On the other hand, completing shutting down inflammation with broadly acting anti-inflammatory drugs can also be damaging."

To investigate the underlying processes, Thomopoulos and colleagues focused their attention on the NF-κB pathway. They confirmed that components of this pathway, including IKK complex proteins, were upregulated in the tendons of patients with early-stage tendinopathy, compared with tendons from healthy individuals.

The researchers used a Cre–loxP system to selectively manipulate the expression of IKKβ in the tendon fibroblasts of mice. Constitutive activation of IKKβ lead to degeneration of the rotator cuff tendons (mimicking changes observed in the tendons of patients with rotator cuff disease), whereas deletion of IKKβ partially protected mice from tendinopathy in a chronic overuse-induced model and in a surgical model of tendon injury and repair.

To simulate human inflammatory tendinopathy in vitro, tendon fibroblasts from healthy individuals were incubated with IL-1β. In this model, treatment with an IKKβ inhibitor prevented NF-κB signalling and pro-inflammatory cytokine production.

> "treatment with an IKKβ inhibitor prevented NF-κB signalling and pro-inflammatory cytokine production"

Credit: Matt Olson/Photodisc

"We are currently testing this inhibitor in a rat rotator cuff model," says Thomopoulos. "If successful, we hope to test the efficacy in a large animal model and ultimately in patients."

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OSTEOARTHRITIS

NGF vaccine reduces pain

Biologic antibody therapeutics that target nerve growth factor (NGF) can alleviate osteoarthritis (OA) pain, but would probably be expensive to use clinically. Furthermore, concerns exist that this pain relief method might not be a lasting treatment as a result of the emergence of anti-drug antibodies. New research using the destabilization of the medial meniscus (DMM) model of OA now shows that vaccinating against NGF might be a suitable alternative.

"This work was very much a collaborative project," says Tonia Vincent, corresponding author of the study. "Martin Bachmann's group was engineering a vaccine that would induce mice to make antibodies to their own NGF and meanwhile we were working out how to measure spontaneous pain behaviour in mouse models of knee OA."

Bachmann (who is also a corresponding author on the study) and his group created the vaccine by covalently linking recombinant NGF with a virus-like particle derived from the cucumber mosaic virus.

"It is possible to hoodwink the immune system to making 'self' antibodies by dressing up the antigen on these viral particles," explains Vincent. "This creates a polyclonal antibody response that can be tuned by the interval of further vaccine boosts. As these vaccines do not break tolerance, endogenous NGF is unable to stimulate an antibody response in the absence of the decorated viral particle."

Vincent's group injected this NGF vaccine into mice either before DMM or 10 weeks after DMM plus regular booster injections. Incapacitance testing was then used to assess how the mice distributed their body weight between the destabilized and control limbs. Asymmetrical weight distribution in DMM mice was reversed by vaccination, indicating a reduction in pain experienced by these mice.

"In the next phase we will test how effective the vaccine is in a veterinary setting by treating OA pain in companion animals," says Bachmann. "Animals such as dogs and horses naturally develop OA, so this vaccine could benefit them and showing this treatment works in these animals might support a move to clinical trials in patients with OA."

> "Asymmetrical weight distribution in DMM mice was reversed by vaccination"

Credit: aydinmutlu/E+/Getty

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