Vaccination against nerve growth factor is an effective pain treatment in murine osteoarthritis

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Aims

Pain is the main symptom of osteoarthritis (OA) and can be detected in mice around 8 weeks following surgical destabilisation of the joint. In mice as well as patients, nerve growth factor (NGF) has emerged as a promising target for pain. Neutralising antibodies to NGF significantly suppress OA pain in clinical trials. Here we investigate whether vaccination against NGF could produce endogenous polyclonal anti-NGF antibodies with similar efficacy to antibody therapy but at a lower cost.

Methods

We designed a vaccine targeting NGF by presenting murine NGF on an immune-optimised virus-like particle (VLP) derived from cucumber mosaic virus. At 7 weeks of age, 20 male C57BL6 mice were inoculated with the NGF-VLP construct by subcutaneous injection, while 20 mice received the control-VLP mock vaccine. An additional sentinel cohort of 10 mice was used to assess blood titres of NGF antibodies across the duration of the study. All mice (not including sentinels) underwent partial menisectomy at 10 weeks of age to induce OA. Painful behaviour was assessed daily by a blinded investigator (IvL) for the first 3 days then weekly using weight distribution difference across hind limbs. At conclusion, knees were imaged using micro computed tomography before being harvested for histology (n=24), and ribonucleic acid (RNA) expression (n=16). Bilateral dorsal root ganglia (L3, L4) were collected for RNA expression.

Results

Anti-NGF titres increased in response to NGF-VLP vaccination, with an OD50 of 10^3. Levels of anti-NGF increased with each boost and were maintained for around 3 weeks on each occasion. At high levels of serum anti-NGF immunoglobulin G, NGF-VLP vaccinated animals were significantly protected from painful behaviour in late OA, compared with mock-vaccinated animals. Over time, reduction of anti-NGF titres was associated with return of painful behaviour so that they were indistinguishable from the control group.

Conclusion

We have developed an effective vaccination against NGF that is analgesic in mice with OA-related pain. Vaccination against NGF provides an interesting alternative to blocking NGF using recombinant antibody and is potentially more cost-effective. Given current safety concerns using recombinant anti-NGF therapy, it is unlikely that this approach is ready for development in patients in the near future. However, as autoantigen VLP-vaccines tend not to induce a long-lived plasma cell population, the antibody responses generated are reversible in the absence of booster immunisations and are apparently not stimulated by endogenous NGF. Such therapeutic immune responses can potentially be 'tailored,' to provide control over anti-NGF titres both immediately, after and between vaccine boosts. ■

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