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IMT504 Provides Analgesia by Modulating Cell Infiltrate and Inflammatory Milieu in a Chronic Pain Model

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Abstract

IMT504 is a non-CPG, non-coding synthetic oligodeoxinucleotide (ODN) with immunomodulatory properties and a novel inhibitory role in pain transmission, exerting long-lasting analgesic effects upon multiple systemic administrations. However, its mechanisms of anti-nociceptive action are still poorly understood. In the present study in male adult rats undergoing complete Freund's adjuvant-induced hindpaw inflammation, we focused in the analysis of the immunomodulatory role of IMT504

over the cellular infiltrate, the impact on the inflammatory milieu, and the correlation with its anti-allodynic role. By means of behavioral analysis, we determined that a single subcutaneous administration of 6 mg/kg of IMT504 is sufficient to exert a 6-week-long full reversal of mechanical and cold allodynia, compromising neither acute pain perception nor locomotor activity. Importantly, we found that the anti-nociceptive effects of systemic IMT504, plus quick reductions in hindpaw edema, were associated with a modulatory action upon cellular infiltrate of B-cells, macrophages and $CD8^+$ T-cells populations. Accordingly, we observed a profound downregulation of several inflammatory leukocyte adhesion proteins, chemokines and cytokines, as well as of β-endorphin and an increase in the anti-inflammatory cytokine, interleukin-10. Altogether, we demonstrate that at least part of the anti-nociceptive actions of IMT504 relate to the modulation of the peripheral immune system at the site of injury, favoring a switch from pro- to anti-inflammatory conditions, and provide further support to its use against chronic inflammatory pain. Graphical abstract GA short description - IMT504 systemic Administration. Systemic administration of the non-CpG ODN IMT504 results in a 6-week long blockade of pain-like behavior in association with anti-inflammatory responses at the site of injury. These include modulation of lymphoid and myeloid populations plus downregulated expression levels of multiple pro-inflammatory cytokines and β-endorphin. Nocifensive responses and locomotion remain unaltered.

Keywords: Complete Freund's adjuvant (CFA); Cytokines; IMT504; Lymphocytes; Oligonucleotide; Pain.

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