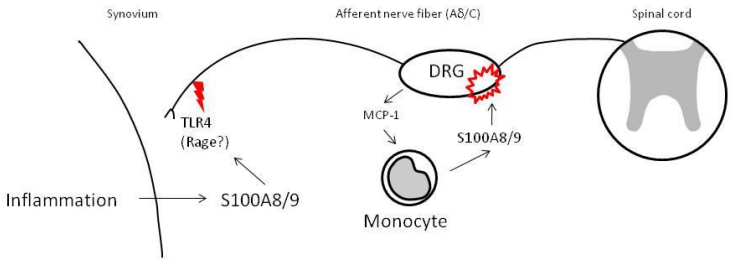
EXPERIMENTAL RHEUMATOLOGY

Title
Alarmins S100A8/9 as targets for pain treatment in Osteoarthritis (OA). How to kill the alarm?

Clinical Relevance
Osteoarthritis (OA) is the most common degenerative and disabling joint disease that affects millions of people worldwide. Its main morphological characteristics are breakdown of the articular cartilage, new-bone formation and prominent changes in the synovium. However, for the patient the main problem is pain. Pain is the most important cause of the disability in OA. So far, no sufficient, long lasting, therapeutic strategy is available to alleviate pain in OA-patients.

Background
Although OA was classically seen as a non-inflammatory disease, it is nowadays well-accepted that a large subset of OA patients show inflammation of the synovium, synovitis. Inflammatory mediators are produced abundantly during this synovitis, among which the alarmins S100A8 and S100A9, that together form the active heterodimer S100A8/9. Apart from a role of this complex in inflammation, it is now recognized that S100A8/9 may be involved in the perception of pain. S100A8/9 is a ligand for Toll-Like Receptor 4 (TLR4), a receptor that has been shown to be involved in nociception. Next to a direct role in nociception, S100A8/9 has been recently suggested to be involved in sensitization of the peripheral nervous system. S100A8/9 can induce cell influx into the dorsal root ganglion (DRG), leading to hyperalgesia or allodynia, signs of sensitization.



Goals
You will study the effect of S100A8/9 on cells from the synovium and DRG regarding mediators relevant for pain. In addition, using specific antibodies, you will determine whether indeed TLR4 is a relevant mediator in this process, or whether a different receptor like RAGE, is important.

We Offer
An internship in a state of the art laboratory on rheumatic diseases. This project includes a broad spectrum of techniques. You will study the effects of S100A8/9 *in vitro* using **cell culture**, after which mechanisms will be studied using **qPCR** to evaluate gene expression and protein levels will be studied using **immunoblotting** and **Luminex**. Furthermore, we will investigate whether S100A8/9 induces expression and production of mediators relevant for pain perception on DRG *ex vivo*. *In vivo* effects of S100A8/9 on the DRG will be studied on **histology** using **immunohistochemistry** to stain for important proteins in pain and nerve injury. This will give you the opportunity to increase your practical skills and increase your scientific knowledge, while adding to the much needed body of knowledge on mechanisms of pain during OA.

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