RHEUMATOID ARTHRITIS

RASFs identified as culprits in the spread of RA

Although rheumatoid arthritis (RA) is known to typically start in a single joint before spreading to nearly all joints of the body, the cells or molecules involved in the dissemination of this disease have, until now, remained unidentified. According to a report in *Nature Medicine*, the finger of blame appears to point at RA synovial fibroblasts (RASFs).

RASFs, as producers of matrix-degrading enzymes, mediate articular cartilage destruction, and these cells have been shown to attach to, invade and degrade cartilage and bone *in vitro*. To investigate whether RASFs can migrate and potentially spread disease *in vivo*, researchers from the Justus Liebig University Giessen, Germany, studied the behavior of these cells in the severe combined immunodeficient (SCID) mouse model of RA. As humoral and cellular immune responses are lacking in these mice, the complete process of RA development cannot be studied, but, as these mice do not reject xenografts, the fate of implants and cells can be investigated over extended periods of time using this model.

Cartilage-sponge complexes from healthy human cartilage were implanted under the skin of SCID mice; on one side these implants contained human RASFs (primary implant) and on the other side (the contralateral flank) they did not. RASFs of human origin were shown not only to invade and degrade cartilage in the

Histology showing RASF invasion (red arrows) and perichondrocytic degradation (blue arrows). © Nature Publishing Group

primary implant, but also to migrate to the contralateral flank, where they invaded and degraded cartilage. As a control, primary implants containing osteoarthritis synovial fibroblasts instead of RASFs were also used; in these implants no or very low levels of invasion were seen.

So, RASFs appear to migrate from the primary implant to healthy contralateral joints, but what route do they take? To answer this question, the authors studied the internal organs of 20 mice at day 60 after implantation. The only organ in which they found RASFs in all mice examined was the spleen, which suggests that the RASFs migrate through the bloodstream to distant cartilage sites.

“The innovative finding is the long-distance migratory potential of RASFs that takes place through the bloodstream,” explains Dr Elena Neumann, one of the

study’s lead researchers. “The migration out of the tissue, through the blood to another site and their ability to transfer their matrix-destructive behavior to the nonaffected region within an organism is new.”

What, if any, are the possible future clinical applications of this work? “The goal of our current research is to inhibit the transmigration and long-distance migration of RASFs. Inhibition of the migratory capacity of RASFs could lead to the protection of nonaffected regions within a joint, but also of unaffected joints of patients with RA,” Neumann concludes.

Jenny Buckland

Original article Lefevre, S. *et al.* Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat. Med.* doi:10.1038/nm.2050