



## Bulletin Board

# Could blocking granulocyte–macrophage colony-stimulating factor action lead to a new treatment for inflammatory diseases?

A study conducted by researchers at the University of Melbourne (Australia) that aimed to determine whether granulocyte–macrophage colony-stimulating factor (GM-CSF) controls inflammatory and/or arthritic pain has found that the protein plays a crucial role in both processes, suggesting that pain alleviation could be achieved from trials evaluating GM-CSF's role in inflammatory/autoimmune conditions.

The research, led by Professor John Hamilton, used experiment models of inflammatory pain (complete Freund's adjuvant footpad), as well as two inflammatory arthritis models, and followed on from the group's discovery that blocking whether GM-CSF function with an antibody suppressed the disease.

The results, published in *Annals of the Rheumatic Diseases*, showed that GM-CSF was required for pain development in both the inflammatory pain and arthritis models, including for IL-1-dependent arthritic pain. Pain in a GM-CSF-driven arthritis model, but not the disease itself, was abolished by the cyclo-oxygenase inhibitor, indomethacin, indicating separate pathways that are operating downstream of GM-CSF for pain and arthritis control.

Commenting on the implications of the study, Hamilton explains that: "Without a doubt, quality of life and to be free from pain are important issues for people suffering with arthritis-related conditions."

Co-author, Andrew Cook concludes: "With our aging population, the more

common condition of osteoarthritis impacts more on our community and medical resources. A new therapy that can block such painful conditions would have massive benefits for health providers and governments in the future."

– Written by Natalie Harrison

### in the news...

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Source: Cook AD, Pobjoy J, Sarros S *et al*. Granulocyte–macrophage colony-stimulating factor is a key mediator in inflammatory and arthritic pain. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2012-201703 (2012) (Epub ahead of print).

## Doctors and patients differ on perception of rheumatoid arthritis activity

Rheumatoid arthritis (RA) is a disease consisting of pain, swelling, inflammation and soreness of the joints. This systemic disease can cause the sufferer to become limited in their daily activities and, in some instances, permanent disability. RA has a worldwide prevalence of 1% and the disease is most common in women in their 20–40s and those situated in developing countries.

Experts recommend premature intervention for the treatment of RA where inflammatory processes can be interfered with as early as possible. Daniel Aletaha (Medical University Vienna, Austria) explained: "Discussion of treatment options by patients and physicians is important in the management of RA." The American College of Rheumatology

and the European League Against Rheumatism have recently standardized the criteria for how disease activity in RA is measured. Currently, patients are asked to evaluate their condition via the patient global assessment (PGA). By contrast, rheumatologists measure the disease using the evaluator global assessment (EGA). Aletaha comments on the differing views this can cause: "Many times there is a discrepancy between patients' and doctors' views of disease activity, with doctors providing a better rating than patients."

The study comprised 646 RA patients from an observational patient database who had begun methotrexate therapy. Patients and physicians completed their respective PGA and EGA assessments. It was these assessments that were used

by the research team to analyze their findings.

The results clarified how the variability in the assessments could be explained by the various measures in RA patients. Pain determines PGA variation by 76%, whilst for EGA assessments swollen joints attribute to 61% of the variability and just 5% by pain. Only 0.5% of PGA variability is a result of swollen joints. In a concluding statement about these findings, the researcher states: "Our study shows pain really drives patient

perception of disease activity, while physicians mostly rely on the number of swollen joints when they interpret a patient's disease activity. The discrepancy of perception between patient and physician were calculated as PGA minus EGA. Pain levels and joint swelling are again explaining these discrepancies to a great deal."

Further understanding the reasons for the differing views on RA disease activity could potentially lead to better decision-making between patients and

their physicians and the subsequent treatment of RA.

– Written by Priti Nagda

Sources: Wiley press room, press releases: <http://eu.wiley.com/WileyCDA/PressRelease/pressReleaseId-104131.html>; Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in the perception of rheumatoid arthritis disease activity. *Arthritis Rheum.* doi:10.1002/art.34543 (2012) (Epub ahead of print).

## Study reveals a DNA methylome signature in rheumatoid arthritis

Researchers at the University of California San Diego (CA, USA) have reported findings suggesting that DNA methylation may have a role in the development of rheumatoid arthritis (RA). It is claimed that methylation may alter genes associated with inflammation and joint damage leading to the disorder. Many genetic associations have been described in RA; however, twin studies have revealed that if one monozygotic twin develops the disorder, the other one only has a 12–15% chance of developing it as well. This led the researchers to consider epigenetic mechanisms as a potential factor in RA progression.

The authors stated that although the methylation of single genes has been reported in autoimmune diseases, no systemic analyses have been reported. Therefore, the authors performed a genome-wide evaluation of DNA methylation loci in fibroblast-like synoviocytes (FLS) isolated from the site of disease in RA. Genomic DNA was isolated from six RA and five osteoarthritis cell lines using

the Illumina® HumanMethylation450 chip. Methylation was confirmed by pyrosequencing and gene expression was determined by quantitative PCR.

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When the DNA from the RA and osteoarthritis samples were compared, it was found that there were 1859 differentially methylated loci between the two. Hypomethylated loci were observed in a number of genes believed to be involved in RA, including *CHI3LI*, *CASP1*, *STAT3*, *MAP3K5*, *MEFV* and *WISP3*. This hypomethylation was associated with increased gene expression. In addition, hypermethylation was seen in the *TGFBR2* and *FOXO1* genes. Grouped analysis revealed 207 methylated genes with multiple differentially methylated

loci, such as *COL1A1*, *MEFV* and *TNF*. The hypomethylation was observed in multiple pathways associated with cell migration, including processes such as focal adhesion, cell adhesion, transendothelial migration and extracellular matrix interactions.

This study revealed that FLS from RA are characterized by a DNA methylome signature that is unique from osteoarthritis and normal FLS. From these findings, the authors concluded that differentially methylated genes could alter FLS gene expression and be a contributing factor to the pathogenesis of RA. Research such as this highlights the important role of epigenetic mechanisms in the development of diseases such as inflammatory arthritis.

– Written by Jonathan Wilkinson

Source: Nakano K, Whitaker JW, Boyle DL, Wang W, Firestein GS. DNA methylome signature in rheumatoid arthritis. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2012-201526 (2012) (Epub ahead of print).

### About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

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## Preventing postinjury arthritis with stem cell therapy

Researchers at Duke University Health System (NC, USA) have discovered a very promising therapeutic approach to post-traumatic arthritis (PTA) – mesenchymal stem cells. The study, which is published in *Cell Transplantation*, provides evidence that intra-articular stem cell therapy can prevent the development of PTA after fracture and has implications for possible clinical interventions after joint injury prior to evidence of significant osteoarthritis.

The researchers, led by Brian Diekman, a postdoctoral researcher in Guilak's laboratory, had hypothesized that the delivery of mesenchymal stem cells would prevent PTA by altering the balance of inflammation and regeneration after fracture of the mouse knee, as these stem cells have beneficial properties in other regions of the body. Indeed, the stem cells were found to prevent PTA.

The second prediction was that a type of mice, bred for their super-healing properties (MRL/MpJ 'superhealer'), would show increased multilineage and therapeutic potential than typical (C57BL/6) mice; however, this was not found to be the case.

"We decided to investigate two therapies for the study," explained Diekman. "We thought that stem cells from so-called superhealer mice would be superior at providing protection, and instead, we found that they were no better than stem cells from typical mice. We thought that maybe it would take stem cells from superhealers to gain an effect as strong as preventing arthritis after a fracture, but we were surprised – and excited – to learn that regular stem cells work just as well."

Explaining the relevance of the findings for clinical

intervention, Farshid Guilak, director of orthopedic research at Duke University Health System and senior author of the study highlights: "Certain people appear to fall into the superhealer category, too. They bounce back quickly and heal well naturally after a fracture, while other people eventually form cases of arthritis at the fractured joint."

He continues: "The ability of the superhealer mice to have superior healing after a fracture may go beyond the properties of their stem cells and be some beneficial factor, like a growth factor, that we don't know about yet."

Unlike a control group that received saline only, the delivery of 10,000 C57BL/6 or MRL/MpJ stem cells to the joint was found to prevent PTA development in mice. Looking at markers of inflammation, the stem cells were found to affect the inflammatory environment of the joint after fracture – by altering the levels of cytokines and the bone healing response.

As the authors point out, one of the challenges in the field is isolating and developing a system for specifically sorting mesenchymal stem cells; in the present study this was overcome by placing the

stem cells in low-oxygen conditions, so that they would grow more rapidly in culture, enabling the researchers to deliver enough of them to make a difference therapeutically.

– Written by Natalie Harrison

Source: Diekman BO, Wu CL, Louer CR *et al.* Intra-articular delivery of purified mesenchymal stem cells from C57BL/6 or MRL/MpJ superhealer mice prevents post-traumatic arthritis. *Cell Transplant.* doi:10.3727/096368912X653264 (2012) (Epub ahead of print).

