Crystallising options for inflammation

Professor Alexander So has been able to identify the IL1β gene as a key inflammatory cytokine in gout and shares why this is one of his most important research findings to date

PROFESSOR ALEXANDER SO

What are the main objectives of your current research efforts?

Our latest project involves the development of a novel model of crystal induced joint inflammation, whereby calcium crystals induce a synovial reaction that resembles what is found in osteoarthritis. We have made extensive use of animal models of osteoarthritis to investigate the genetic influences using knockout mice. Our current research is focused on understanding what the tissue response to calcification is in osteoarthritis. We are looking at whether we can either modify this response or if it is possible to actually inhibit the calcification. The ultimate objective for our current research project is to be able to influence the progression of osteoarthritis.

Could you highlight some of the novel methodologies that have been developed through this work?

For this work we hope to be able to develop more sensitive and reliable techniques for the analysis of crystals in human tissues. Detection and characterisation is a major problem, and for clinical use we need a technique that is rapid as well as reliable. We hope to be able to collaborate with biophysicists and microscopists to develop such techniques. Once we know what the pathogenic role of crystals is, we can try to develop strategies to inhibit and/or modify the crystallisation process.

Can you explain why calcium microcrystals are significant? What potential do they hold for healthcare research?

Calcium crystals are formed in healthy as well as pathological situations. For example, normal healthy calcification takes place during bone remodelling and development, whereas pathological calcification occurs when people suffer from joint, skin and arterial disorders where calcium deposits are found in tissues do not normally calcify. The consequences of this abnormal calcification can be far reaching and severely debilitating, including inflammation, tissue remodelling and the loss of normal function. In joint diseases, we believe that abnormal calcification in the cartilage and the synovium is a factor that aggravates osteoarthritis. If we can interfere with this process or block the downstream events that abnormal calcification induces, then we may have novel therapies to help patients suffering from a range of joint diseases.

What are the processes under which IL-1β influences inflammation and arthritis?

IL1b is produced by two mechanisms in vivo, one that involves the inflammasome, a protein complex which is intensively investigated in a wide range of inflammatory disorders, as it serves as a link between cell stress and the tissue's inflammatory reaction. There is also an inflammasome-independent pathway of IL1β production that is linked to cell death. Both pathways cooperate in an inflammatory state.

What has been learnt about the relationship between IL-1β and joint inflammation when monosodium urate crystals are applied?

The regulation of inflammasome activation by monosodium urate (MSU) crystals is probably finely regulated. We still do not understand what these regulatory factors are, but if we discover these mechanisms, then we can modify the inflammatory reaction in gout as well as other diseases in which the inflammasome is implicated in a therapeutic way. Currently, the use of anti-IL1β as a therapy has gained enormous interest in the management of gout, in particular the use of antibodies that block IL1β in humans. A number of pharmaceutical companies have developed antibodies against IL1β and in the past, they had high hopes that this will be an effective treatment for inflammatory diseases such as rheumatoid arthritis. However clinical trial results in rheumatoid arthritis were disappointing. The re-discovery of IL1β in gouty inflammation led to clinical trials in gout, and so far the results are extremely positive. The question now is not whether the treatment works, but in what situation it should be applied in gout. The proof of concept, that anti-IL1 is effective in an inflammasome-mediated disease, has led to huge interest in the inflammasome and other human diseases, as we have the reagents to inhibit this cytokine.

How important are collaborations with other investigators to help improve your overall work experience and output?

These collaborations are of huge value to us and the creation of the European Crystal Network is a first step towards increased communications between scientists in this field. We hope this collaboration will become truly international and multidisciplinary, as we need new expertise to tackle the questions we are currently researching.