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GENE SIGNATURES AND BIOMARKERS PREDICT ONSET OF RHEUMATOID ARTHRITIS IN AT-RISK INDIVIDUALS

Data may support development of early interventions that can prevent the onset of arthritis

Amsterdam, The Netherlands, 13 June 2018: The results of two studies presented today at the Annual European Congress of Rheumatology (EULAR 2018) provide insight into molecular changes prior to the onset of arthritis which could inform future novel diagnostics and early therapeutic interventions.[1,2]

Rheumatoid arthritis (RA) is characterised by joint inflammation leading to destruction of bone and cartilage. Since structural joint damage is irreversible, early recognition and treatment is a key focus in an effort to halt the progression of the disease.[3] There is a phase before any evidence of RA where specific autoantibodies are present in the body.[4] Individuals who have these antibodies are referred to as RA-risk, however only a subset of these will develop active disease in the short term.[5]

"These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA," said Professor Robert Landewé, Chairperson of the Scientific Programme Committee, EULAR. "This is important because it will contribute to the development of early preventative strategies including potential pharmacological treatment to prevent the onset of disease."

Study reveals synovial tissue gene signatures associated with development of disease in RA-risk individuals[1]

Samples of synovial tissue were taken from the knee joint of 67 RA-risk* individuals who were then followed to see if they went on to develop RA. An explorative genome-wide transcriptional profile study was carried out in 13 individuals to identify gene transcripts with a significant association with arthritis development. These 'gene signatures' were then validated using quantitative real-time PCR† to measure changes in specific genes.

"Our results clearly show molecular changes appearing in the synovial tissue before the onset of arthritis," said Dr. Lisa van Baarsen, Principal Investigator at the Amsterdam Rheumatology and Immunology Center | Academic Medical Center, the Netherlands. "The characterisation of these gene signatures will enable us to better understand the pathophysiology of the pre-clinical phase of the disease and potentially identify novel drug targets for preventive intervention."

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* Defined as individuals with painful joints (arthralgia) but without arthritis but who tested positive for IgM rheumatoid factor (IgM-RF) and/or Anti-citrullinated protein antibody (ACPA)
† Polymerase Chain Reaction

An explorative genome-wide transcriptional profiling study in 13 individuals demonstrated that an increased expression of 3,151 transcripts was associated with a higher risk of arthritis development, and 2,437 transcripts with a lower risk. Further analysis revealed that individuals who developed RA had a higher expression of genes involved in several immune response-related pathways (e.g. T-cell and B-cell receptor pathways, cytokine and chemokine signalling and antigen processing and presentation) and lower expression of genes involved in extracellular matrix receptor interaction, Wnt-mediated signal transduction and lipid metabolism.

Investigators chose 27 differentially expressed genes for validation in the whole study cohort using quantitative real-time PCR. This analysis classified the RA-risk individuals into two groups, where most individuals who developed RA were grouped together ($p=0.03$).

Immunohistochemistry analyses (n=54) of the samples taken at inclusion showed that most individuals already had an abundant expression of chemokine CXCL12 and its receptor CXCR4 which are known to accumulate in the synovium of rheumatoid arthritis patients.[6,7] They also showed that RA-risk individuals that developed arthritis were more likely to show a positive gp38 staining and lower lipid staining.

BCR clones predict imminent onset of rheumatoid arthritis in at-risk patients[2]

Another cohort study in 129 RA-risk individuals validated recent findings[8] that dominant B-cell receptor (BCR) clones in peripheral blood, can accurately predict imminent onset of arthritis in RA-risk individuals.

“Our data support a new biomarker that demonstrates better predictive power compared with other available biomarkers evaluated so far,” said Ms. Anne Musters, MD, Amsterdam Rheumatology and Immunology Center | Academic Medical Center, the Netherlands. “We think that peripheral BCR clones can be used to identify RA-risk individuals that will go on to develop arthritis, which will support the evaluation of early interventions to prevent the onset of disease.”

Results of the study showed that the number of dominant BCR clones was significantly increased in RA-risk individuals who developed arthritis within three years ($p<0.0001$). The optimal cut-off for the test was calculated at five or more dominant BCR clones and applying this test to the study cohort resulted in 45 BCR positive and 84 BCR negative individuals. Over the complete 104 months follow up period, only 13% of BCR-clone negative individuals developed RA compared to 76% of the BCR-clone positive individuals. This resulted in a relative risk of 5.8 (95% CI 3.2-10.3, $p<0.0001$).

By subdividing the individuals further, it was demonstrated that the number of dominant BCR clones significantly correlated with the risk of developing arthritis. Having 10 or more dominant BCR clones corresponded with a positive predictive value of 94% within three years. Within this period none of the 84 BCR negative individuals developed arthritis,

indicating that, based on such test results, these individuals may be reassured concerning imminent RA risk.

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NOTES TO EDITORS
For further information on this study, or to request an interview with the study lead, please do not hesitate to contact the EULAR Press Office:

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About Rheumatic and Musculoskeletal Diseases
Rheumatic and musculoskeletal diseases (RMDs) are a diverse group of diseases that commonly affect the joints, but can also affect the muscles, other tissues and internal organs. There are more than 200 different RMDs, affecting both children and adults. They are usually caused by problems of the immune system, inflammation, infections or gradual deterioration of joints, muscle and bones. Many of these diseases are long term and worsen over time. They are typically painful and limit function. In severe cases, RMDs can result in significant disability, having a major impact on both quality of life and life expectancy.[9]

About 'Don't Delay, Connect Today!'
'Don't Delay, Connect Today!' is a EULAR initiative that unites the voices of its three pillars, patient (PARE) organisations, scientific member societies and health professional associations - as well as its international network - with the goal of highlighting the importance of early diagnosis and access to treatment. In the European Union alone, over 120 million people are currently living with a rheumatic disease (RMD), with many cases undetected.[10] The 'Don't Delay, Connect Today!' campaign aims to highlight that early diagnosis of RMDs and access to treatment can prevent further damage, and also reduce the burden on individual life and society as a whole.

About EULAR
The European League against Rheumatism (EULAR) is the European umbrella organisation representing scientific societies, health professional associations and organisations for people with RMDs. EULAR aims to reduce the burden of RMDs on individuals and society and to improve the treatment, prevention and rehabilitation of RMDs. To this end, EULAR fosters excellence in education and research in the field of rheumatology. It promotes the translation of research advances into daily care and fights for the recognition of the needs of people with RMDs by the EU institutions through advocacy action.

To find out more about the activities of EULAR, visit: www.eular.org.

References

[1] Van Baarsen LG, de Hair MJ, Semmelink JF, *et al*. Synovial tissue profiling in autoantibody positive at risk individuals reveals gene signatures associated with later development of rheumatoid arthritis. EULAR 2018; Amsterdam: Abstract OP0266.

[2] Musters A, van Beers-Tas MH, Doorenspleet ME, *et al.* Dominant B cell receptor clones in peripheral blood predict onset of arthritis in individuals at risk for rheumatoid arthritis – a validation cohort. EULAR 2018; Amsterdam: Abstract OP0204.

[3] Nielen MM, van Schaardenburg D, Reesink HW, *et al.* Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. 2004;50(2):380-6.

[4] Brink M, Hansson M, Mathsson-Alm L *et al.* Rheumatoid factor isotypes in relation to antibodies against citrullinated peptides and carbamylated proteins before the onset of rheumatoid arthritis. *Arthritis Res Ther*. 2016; 18:43.

[5] Bos WH, Wolbink GH, Boers M, *et al.* Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis*. 2010;69(3):490-4.

[6] Buckley CD, Amft N, Bradfield PF, *et al*. Persistent induction of the chemokine receptor CXCR4 by TGF-beta 1 on synovial T cells contributes to their accumulation within the rheumatoid synovium. *J Immunol*. 2000;165(6):3423-9.

[7] Nanki T, Hayashida K, El-Gabalawy HS, *et al*. Stromal cell-derived factor-1-CXC chemokine receptor 4 interactions play a central role in CD4+ T cell accumulation in rheumatoid arthritis synovium. *J Immunol*. 2000;165(11):6590-8.

[8] Tak PP, Doorenspleet ME, de Hair MJH, *et al.* Dominant B cell receptor clones in peripheral blood predict onset of arthritis in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis*. 2017;76:1924-30.

[9] van der Heijde D, *et al.* Common language description of the term rheumatic and musculoskeletal diseases (RMDs) for use in communication with the lay public, healthcare providers and other stakeholders endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). *Annals of the Rheumatic Diseases.* 2018;doi:10.1136/annrheumdis-2017-212565. [Epub ahead of print].

[10] EULAR. 10 things you should know about rheumatic diseases fact sheet. Available at: https://www.eular.org/myUploadData/files/10%20things%20on%20RD.pdf [Last accessed April 2018].