UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 1954

# Insights into the processes preceding the onset of rheumatoid arthritis

**Linda Johansson**

## Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Sal D, Målpunkt T, våning 9, Norrlands Universitetssjukhus, fredag den 27 april, kl. 13:00. Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Assoc.Prof., Felipe Andrade, MD, PhD
Division of Rheumatology, John Hopkins University School of Medicine, Baltimore, USA.

Public Health and Clinical Medicine/Rheumatology

**Organization**
Umeå University
Public Health and Clinical Medicine
Rheumatology

**Document type**
Doctoral thesis

**Date of publication**
6 April 2018

**Author**
Linda Johansson

**Title**
Insights into the processes preceding the onset of rheumatoid arthritis.

## Abstract
Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterized by the production of anti-citrullinated protein antibodies (ACPA) in the majority of all patients and a persistent inflammation in the synovial tissue leading to joint destruction. The aetiology of RA remains to a large extent unknown but is believed to be a complex interplay between genetic, environmental and stochastic factors. Recently, several infectious agents have been shown to have the capacity to induce citrullination of both endogenous and exogenous antigens *e.g.,* Epstein-Barr virus (EBV) and *Porphyromonas gingivalis (P.gingivalis*). Disease progression in patients with RA is suggested to be a longstanding process that begins several years before symptom onset of RA. This hypothesis is supported by studies showing increased antibody levels against ACPA and disease related cytokines/chemokines several years before symptom onset of RA. The presence of ACPA is highly specific for RA and is already used as an indicator of progression and prognosis of the disease. This thesis is aimed to further investigate the origin and role of ACPA and the processes preceding the development of RA. New insights into these processes are of importance in order to be able to prevent the disease onset, achieve better diagnostic methods and treatments in the future.

All of the individuals included in these papers, had attended to the Department of Rheumatology at Umeå University to receive their diagnosis of RA. The register of the patients were thereafter co-analysed with the register of the Medical Biobank of Northern Sweden. Plasma/sera samples were analysed for antibodies and receptor activator of nuclear factor kappa-B ligand (RANKL) using different ELISA techniques from individuals before symptom onset (pre-symptomatic individuals) and at disease onset (patients). Cytokines/chemokines were analysed using Meso Scale Discovery methods. Levels of marginal jawbone loss were measured using dental radiographs from premolar/molar regions. The Larsen score at disease onset was used to grade radiographs of hands and feet.

In ***Paper I*** antibodies against Epstein-Barr virus nuclear antigen (EBNA) 1 and 2 (VCP1 and VCP2) and histone 4 (H4) derived citrullinated peptides (HCP1 and HCP2) were found to predate symptom onset of RA. In ***Paper II***, antibodies against anti-*P.gingivalis* (anti-CPP3 and -RgpB IgG) were significantly increased in pre-symptomatic individuals and were detectable several years before symptom onset of RA. In ***Paper III*** the concentration of RANKL was shown to be increased several years before symptom onset of RA, especially in ACPA/rheumatoid factor (RF)/anti-carbamylated (CarP) antibody positive individuals. Positivity for RANKL was found to appear later in time than both positivity for ACPA, RF and anti-CarP antibodies. The highest Larsen score at disease onset was yielded when combining positivity for RANKL and anti-CarP antibodies. In ***Paper IV*** periodontitis, defined as marginal jawbone loss was significantly higher in pre-symptomatic individuals who never smoked, compared with matched controls. RANKL positive individuals particularly those that were also ACPA positive, had a significantly greater extent of jawbone loss in comparison to those individuals who were RANKL negative.

Antibodies against citrullinated exogenous and endogenous peptides were found to be associated with the symptom onset of RA. No hierarchy among the citrullinated epitopes could be identified. RANKL levels were particular increased in ACPA-positive individuals, and RANKL positivity appeared later in time than the general ACPA response. Periodontitis, defined as marginal jawbone loss was significantly higher in pre-symptomatic individuals, who never smoked.

## Keywords
rheumatoid arthritis, pre-symptomatic individuals, autoantibodies, anti-citrullinated protein/peptides antibodies, Epstein-barr virus, neutrophil extracellular traps, periodontitis, Porphyromonas gingivalis, receptor activator of nuclear factor kappa-B ligand

**Language**
English

**ISBN**
978-91-7601-863-7

**ISSN**
0346-6612

**Number of pages**
62 + 4 papers