Scopus®

Review Article

Endogenous Factor and Pathophysiology of Rheumatoid Arthritis: An Autoimmune Disease from Decades

Lata Kanyal Butola[1], Ashish Anjanker[2], Anjali Vagga[3], Meghali N Kaple[2]

[1]Tutor, Department of Biochemistry, Jawaharlal Nehru Medical College, Wardha, Maharashtra, India; [2]Associate Professor, Department of Biochemistry, Jawaharlal Nehru Medical College, Wardha, Maharashtra, India; [3]Assistant Professor, Department of Biochemistry, Jawaharlal Nehru Medical College, Wardha, Maharashtra, India.

ABSTRACT

Rheumatoid arthritis (RA) is among the most prevalent autoimmune diseases (1-3 % worldwide). RA is a prototypic inflammatory disease, characterized by a changed homeostasis state in which immunological stimulation and unwanted inflammation take precedence. The disordered inflammation has painful and deteriorating immediate effects while causing accumulated tissue damage that could contribute to symmetric polyarthritis leading to lifelong discomfort, impairment and shorter life expectancy. RA is affected by genetic and environmental influences, smoking, diet, obesity, microbiota, and infections were suggested induced illness in individuals genetically prone. The clinical representation of RA is the product of a cascade of responses and close interactions between immune and non-immune cells (e.g., endothelial and fibroblast-like synoviocytes), autoantibodies, soluble mediators such as cytokines and chemokines, and signal transduction pathways of the innate and adaptive immune system. Different immune system players include neutrophils, macrophages, B cells, natural killer (NK) cells, and T cells migrate to the synovial membrane and accumulate in the synovial fluid, resulting in the release of mediators such as cytokines, chemokines, adhesion molecules, matrix metalloproteinases (MMPs) and reactive oxidative species (ROS) which result in joint destruction.

Key Words: Rheumatoid arthritis, Inflammation, Oxidative Stress, Interleukin, Macrophages

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that induces inflammation, stiffness, rigidity, and lack of mobility in the joints and affects the peripheral joint synovial membrane[1]. It has been characterized by erosive synovitis, penetration of inflammatory cells into the synovium or membrane existing in the synovial joints that line the joint capsules and produce synovial fluid for the joints in the hands and feet is the first structure affected. The resulting inflammatory modifications occur in cartilage and bone loss and synovial hyperplasia eventually contributing to bone breakdown as well as articular cartilage and triggering neurological problems, like respiratory, pulmonary, psychiatric, and other skeletal disorders.[2] The health-related quality of life in RA patients is substantially diminished by discomfort, exhaustion and pain. This is often known that mortality is elevated in patients with RA relative to the general population. RA impacts the joints of the shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, thigh, neck, ankle, and metatarsophalangeal.Prevalence is projected at 0.5 to 1 % of the population, primarily of women, with a higher prevalence in the 30-50 year age range.

It is distinguished by local and systemic inflammation with elevated plasma concentrations of proinflammatory cytokines, such as interleukin-6, interleukin 1β, tumour necrosis factor-α, and acute-phase proteins, which constitute an oxidative stress disorder.[3] The major mechanism of cell membrane destruction and cell damage is considered to be lipid peroxidation mediated by free radicals. T-cells and cytokines play a significant role in the treatment of rheumatoid arthritis alongside oxygen radicals such as superoxide and hydrogen peroxide produced by activated macrophages.[4] These reactive oxygen species (ROS) and thus created reactive nitrogen species (RNS) have both beneficial and toxic effect. Oxidative stress is the state under which the ROS and RNS accumulation is deleterious and destroys the cells and biological macromolecules.[5,6] Oxidative stress are

triggered by the disrupted equilibrium between the anti-oxidant processes of the body and the generation of oxidative stress, which plays a significant role in the creation of chronic diseases such as RA, cancer, etc.[7-9]

The term oxidative stress is defined as a pro-oxidant disorder that results in cell damage. Various cells can withstand moderate oxidative stress because they have an antioxidant protection mechanism and a repair program that identifies and eliminates oxidation-damaged molecules like antioxidant enzymes, which are the first safeguard against endogenous reactive oxygen species (EROS) neutralization as well as antioxidants nutrients.[10] Antioxidant compounds are molecules that postpone or reduce the degradation of oxidizable substrates at low concentrations.[11] Zinc, selenium, vitamin A, C, and Ede serve particular consideration among the non-enzymatic antioxidants responsible for lower molecular and cellular oxidative stress.[12] They are capable of destroying cell membrane lipids, connective tissue, and nucleic acids. Free radicals and their by-products are key inflammatory mediators. Because of the chemo-attractive properties of synovial fluid, leukocytes accumulate in the synovial tissue triggering a respiratory burst marked by elevated oxygen intake and anaerobic glycolysis contributing to superoxide, hydroxyl, hypocaloric radicals, etc.[13] It has been shown that neutrophils are involved in the synovial fluid of RA patients, contributing to inflammation and damage.[14,15] The free radicals are produced in mammalian tissues in all physiological environments. A significant element in the tissue harm caused by many pathophysiologies is the unregulated development of free radicals. The shift in the oxidant-antioxidant ratio identified in rheumatic diseases. Oxidant and antioxidant deficiency due to enhanced chemical reaction or inadequate antioxidant protection mechanism contribute to oxidant stress.[16]

Inflammatory Mechanism in Rheumatoid Arthritis

The swelling of the joints suggests the existence of an infection of the synovial membranes triggered by immune system activation. Such infection is consistent with leucocyte proliferation within the synovial cavity. The entire cycle involves the intervention of both the adaptive immune system and the innate immune system, which ultimately would end in the joint destruction. Small joint biopsies along with extensive molecular bases research have contributed to the conclusion that there are many subtypes of synovial participation, including lymphocytic-dominant, fibroid-dominant, and myeloid-dominant. The precise type of detection will lead to better management and treatment response.[17] Advanced mechanisms that involve cytokines and chemokines control this inflammatory process in the joints. Those involve the activating agent of the granulocyte-monocyte group, tumour necrosis factor, and interleukin 6. Certain molecules may be present such as interleukin 1, which are less essential in the

inflammatory cycle. The association between the preceding molecules would induce endothelial cell proliferation and aggregation of cells inside the joint to promote inflammation. Cell aggregation, coupled with fibroblast activity, may contribute to the induction of osteoclast activity by activating RANKL. The influence of cytokines on chondrocytes often affects cartilage tissue. It would result in metalloproteinases and other enzymes destroying the matrix.[18]

Pathogenesis of Rheumatoid Arthritis

RA pathogenesis includes invasion and activation of different communities of cells, and the release of several inflammatory and harmful mediators, including cytokines, prostaglandins, and metalloproteinase. RA pathology has been reported to consist of (i) acute and chronic inflammation, (ii) proliferation of cells, and (iii) destruction/fibrosis of tissues. Natural synovium is a fragile tissue that covers the joint capsule but, in RA, the synovium turns into a violent, tumour-like organ called pannus that invades and erodes the joint.[19] Based on the existence or absence of anti-citrullinated protein antibodies (ACPAs) two main subtypes of RA occur. The calcium-dependent enzyme peptidyl arginine-deiminase (PAD) catalyze citrullination, converting a positively charged arginine into polar yet neutral citrulline as a consequence of a post-translational change. ACPAs can be found in around 67% of RA patients and act as a valuable diagnostic guideline for patients with early, undifferentiated arthritis and as an indicator of the possible development of disease via RA.[20,21] RA's ACPA-positive subset has a more reactive clinical phenotype relative to RA's ACPA-negative subset.[22] It is stated that ACPA-negative RA has distinct patterns of genetic interaction [23] and differentiated responses of the immune cells to citrullinated antigens[24] from those of the ACPA-positive subset. In medication terms,[25-27] less successful methotrexate (MTX) or rituximab therapy reaction has been reported in the ACPA-negative group. This indicates a need for future research on the apparent disparity in pathophysiology between these two subsets. While T cells and macrophage populations dominate the existing pathogenesis hypotheses of RA, there is evidence that B cells and their RF development could also be intrinsic to RA.[28] The probability that RF is involved in disease pathogenesis is increased by the clear finding that 80 % of RA patients have elevated autoantibody serum rates that correlate rheumatoid element is an antibody aimed against the IgG molecule Fc fragment .[29,30] RF can be among all subclasses in RA, but is mainly an IgG antibody that has a strong affinity to macrophage and neutrophil receptors, fixes complement, and may migrate into extravascular space.

RF also demonstrates a large degree of replacement mutations in RA patients suggesting maturation of the affinity.[31] This indicates that RF in patients with RA is generated in response to a somatic mutation mechanism of the immunoglobulin

gene sequence powered by T cells. In comparison, the RF produced by normal individuals in response to infection or immunization is typically IgM, transient, with low affinity, and of the germline, origin indicating that it is part of the innate immune response.[32]Because RF is different in RA patients, it was necessary to figure out how it will lead to inflammation to continue in RA patients.[33]

The earliest in RA pathogenesis is the stimulation of the innate immune response, including the recruitment of dendritic cells by exogenous content and autologous antigens. Antigen-presenting cells, including dendritic cells, macrophages, and activated B cells, present antigens to T cells consistent with arthritis. Concurrently, the synovial membrane is invaded by CD4 + T cells which secrete IL-2 and IFN-g, most RA patients bear the HLA-DRB1 cluster epitope.[34,35] While prevalent associations with the HLA-DRB1 locus were established decades ago, recent research provided new insights into the possible causative variants within both HLA-DRB1 and other HLA loci that lead to the risk of disease. Such alleles share a homologous sequence of amino acids on the HLA-DR b-chain that links different peptides and influences the appearance of antigens in TCRs. HLA-DR alleles associated with the disease can pose arthritis-related peptides, contributing to the activation and expansion of autoantigen-specific T cells in joints and lymph nodes.[34]In addition to the HLADRB1 alleles, genomic stratification through an expression of HLA-DRB4 alleles contributed to the discovery of distinct innate and adaptive immune transcription trends that could anticipate an early RA response, namely methotrexate (MTX). Many important findings on the relationship of HLA loci polymorphisms with RA initiation or therapy reaction have come from research performed in animal models of RA. In collagen-induced arthritis (CIA), the HLA-G2 protein, which is implicated in maternal-fetal immune tolerance, is a valuable mechanism for the treatment of RA, explicitly binding paired Ig-like receptor, expressed only by cells presenting an antigen (APC). B cells lead to RA pathogenesis not only by transmitting antigens but also by developing antibodies, autoantibodies, and cytokines.[35] RF and autoantibodies to the anti-CCP are normal in RA patients. B lymphocytes release proteins of the cell membrane, including immunoglobulin and antigens of differentiation such as CD20 and CD22.[36] More than 100 specific variants of non-HLA loci have been implicated of RA susceptibility, in addition to the HLA loci. For example, in PSORS1C1, PTPN2 and MIR146A genes, polymorphisms in the signalling transducers and transcription activators- (STAT)-4 and interleukin- (IL)-10 genes were associated with a severe disease phenotype in terms of autoantibody status and radiographic damage.[37] Autoantibodies can form broader immune complexes which can further promote the development of pro-inflammatory cytokines, including TNF-α, by supplementing and stimulating Fc-receptors.T- and B-cell activation contributes to

enhanced cytokine and chemokine output, resulting in a feedback loop for additional T-cell, macrophage, and B-cell interactions. Macrophages are active in osteoclastogenesis in addition to receptor presentation and a significant source of cytokines, including TNF-α, IL-1, and IL-6. There is a significant rise in active fibroblast-like synoviocytes inside the synovial membrane, which often releases inflammatory cytokines, PGs and MMPs. Synoviocytes lead to cartilage and bone degradation by secreting MMPs into the SF and by the overt invasion of certain tissues.[34,35]

Macrophages in RA

Macrophages tend to play a crucial role in RA since they are abundant in the inflamed synovial membrane and at the junction of cartilage – pannus. It gives strong signs of activation, such as overexpression of large class II complex histocompatibility molecules, tumour necrosis factor (TNF)-α proinflammatory or regulatory cytokines, and growth factors [eg IL-1, IL-6, IL-10, IL-13, IL-15, IL-18, and granulocyte-macrophage colony-stimulating factor (GM-CSF)], chemokines and chemoattractants [eg IL-8, inflammatory protein macrophage (MIP)-1 and monocyte chemoattractant protein (MCP)-1], metalloproteinases and neopterin.[38-41] Macrophages are unlikely to play a causal role in the pathogenesis of RA other than their work as antigen-presenting cells in the primary autoimmune disease hypothesis.[42]

Factors of tumour necrosis

TNF is a rational part of the immune response of the body to tumour cells, bacteria and viruses. It plays role in both acute and chronic inflammation. Cells release it as they sense a certain compound (an antigen) they have been sensitized to.

Tumour necrosis factor-α

TNF-α arises mainly from monocytes and macrophages, but also B-cells, T-cells, and fibroblasts. This is one of the main cytokine molecules that induce inflammation in RA.[43]It is also an autocrine stimulator and a potent paracrine inducer of certain inflammatory cytokines, namely interleukin-1 (IL-1), IL-6, IL-8, and a granulocyte monocyte-colony stimulating factor (GM-CSF).[44-46] TNF-α is also considered to activate fibroblasts to release molecules of adhesion such as intracellular adhesion molecule (ICAM-1).[47] TNF-α is a pleiotropic cytokine, which enhances the synovial cells' production of cytokines, adhesion proteins, prostaglandin E2, collagenase, and collagen.[48] In RA, TNF-α is mainly developed by macrophages in the synovial membrane and at the junction of cartilage – pannus[49] and is assumed to be a proximal cytokine in the inflammatory cascade. Although an average of around 5 % of synovial cells expresses TNF-α mRNA in vivo[50], the degree of TNF-α expression in synovial tissue tends to be based on the predominant histological configuration [51]TNF-α is a potent cytokine consistent with natural im-

mune and inflammatory response. Individuals with RA have elevated rates of TNF-α in the synovial fluid and it plays a major role in inflammation and joint damage, which are RA hallmarks. Anti-TNF-α therapy induces a cytokine balance change which generates more anti-inflammatory cytokines. Studies have demonstrated a significant increase in synovial inflammation in RA patients after treatment with neutralizing anti-TNF-α Abs or soluble TNF receptors and reduced joint damage after IL-1Ra therapy. Throughout RA synovitis, immunosuppressive and anti-inflammatory cytokines like TGFβ, IL-10, and IL-1Ra are released strongly and stably. Such cytokines have been suggested to indicate attempts by the patient to suppress or regulate inflammation and maintain homeostasis.[52]

Interleukin-6

IL-6 is the most remarkably elevated cytokine in RA, especially in the acute disease synovial fluid.[53] While IL-6 levels in the synovial fluid correlate with the degree of radiological joint injury, and IL-6 and soluble IL-6 receptors promote the production of osteoclasts[54], this cytokine may also protect cartilage in acute disease but also promote excessive bone formation in chronic disease[55]. IL-6 is mainly developed by synovial fibroblasts and only partly by macrophages[56]; two results indicate that the striking growth of IL-6 is a prominent consequence of macrophage activation and the morphological similarity of IL-6-expressing fibroblasts with CD14 + macrophages in RA synovial tissue.[57]

Matrix metalloproteinases

An essential feature of RA synovial fibroblasts and macrophages in the enhanced development of the matrix-degrading enzyme family MMPs. MMPs are a family of zinc-dependent endopeptidases, capable of degrading all major extracellular matrix components. A variety of studies have shown that MMPs are effective mediators in inflammatory tissue and connective diseases such as RA. The gelatinase subfamily of MMPs composed of MMP-2 (gelatinase A) and MMP-9 (gelatinase B) is of great significance in arthritis.[58-60]

Chemokines

Chemokines are chemotactic cytokines, which control immune cell migration in various physiological and pathological processes. We play a key role in homeostasis, in the production of cellular and humoral immune responses, and the involvement of pathologic immune in different diseases. Chemokines consist of a wide family of more than 50 chemokine ligands and receptors, listed in their primary amino acid sequence based on the assembly of cysteine residues.[61]

Chemokine receptors are expressed on all leukocytes and can be divided into two groups:

1. Protein serpentine G – generalized chemokine receptors (GPCRs)
2. Atypical receptors to the chemokine.[62]

Many chemokine ligands may attach to several receptors, whereas some receptors have more ligands, including those involving chemokines in inflammatory processes. Chemokine receptors and ligands were involved in different RA development processes including inflammation and angiogenesis.[63,64] Chemokine activity was documented to differ at various stages of RA. CCL4, CXCL4, CXCL7, and CXCL13 were articulated at an early level, while CCL3 and CCL9 were published at later stages.[65,66] Other chemokines, including CXCL1 and CXCL5, foster inflammation and hence tend to raise their rates by constant inflammation.[67]This should be remembered that citrullination of chemokines (e.g. CXCL5 and CCL2) exists in RA and has been found in RA patients with synovial fluid. Citrulline chemokines have a change in their function that contributes to a decrease in chemotaxis.[68] RA patients have elevated plasma and synovial fluid amounts of CCL2, CCL3, CCL4, and CXCL10. CCL5, on the other hand, indicated a raised plasma volume but a decrease in RA patients' synovial fluid.[69]
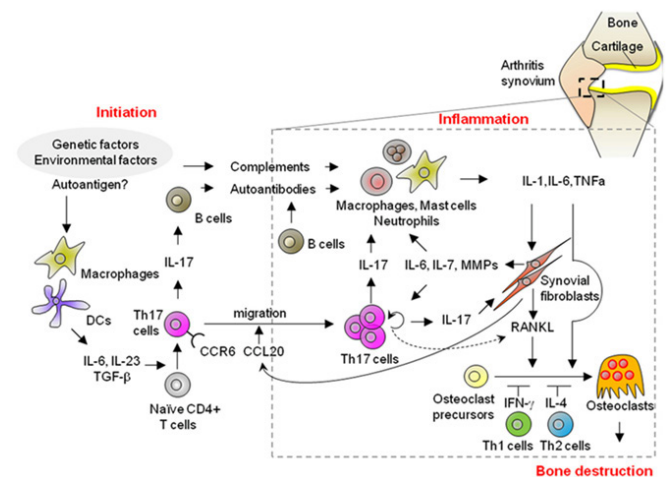

Figure 1: Mechanism of initiation, inflammation and destruction of bone in RA[70]

Different cells including lymphocytes, innate immune cells, osteoclast and synovial fibroblast plays role in the development of RA, through the production of autoantibodies as well as the activation of innate immunity and synovial fibroblast, ultimately leading to bone destruction.[70]

CONCLUSION

RA is a disabling, chronic, inflammatory condition that can cause both joint injury and long-term impairment. The disorder has predominance in women, despite large numbers possessing a healthy family history. To avoid permanent injury

and impairment of vital bodily functions, early detection and action are necessary. The prescribing practitioner will consider adhering to guidelines for the treatment-to-target. Medications such as NSAIDs, opioids, DMARDS, and biological reaction modifications, these medications can target parts of the immune system that trigger inflammation that causes joint and tissue damage. Lifestyle modification is really important for RA patients by performing daily workouts and discovering ways to deal with pain by minimizing tension in life.

REFERENCES

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum. 2006;36(3):182-8.

2. Harris ED. Pathogenesis of rheumatoid arthritis. In: Kelley WN, editor. Textbook of Rheumatology. Philadelphia W. B. Saunders; 1989:905-42.

3. Marques-Neto JF, Gonçalves ET, Langen LF, Cunha MF, Radomski S, Oliveira SD. Multicentric study of the prevalence of adult rheumatoid arthritis in Brazilian population samples. Rev Bras Reumatol. 1993;33(5):169-73.

4. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annual review of immunology. 1996 Apr;14(1):397-440.

5. Jaswal S, Mehta HC, Sood AK, Kaur J. Antioxidant status in rheumatoid arthritis and the role of antioxidant therapy. Clinica Chimica Acta. 2003 Dec 1;338(1-2):123-9.

6. Mahajan A, Tandon VR. Antioxidants and rheumatoid arthritis. J Indian Rheumatol Assoc. 2004;12:139-42.

7. Demirbag R, Yilmaz R, Erel O, Gultekin U, Asci D, Elbasan Z. The relationship between the potency of oxidative stress and severity of dilated cardiomyopathy. Canadian J Cardiol 2005 Aug;21(10):851.

8. Ozgocmen S, Ozyurt H, Sogut S, Akyol O. Current concepts in the pathophysiology of fibromyalgia: the potential role of oxidative stress and nitric oxide. Rheumatol Int 2006;26(7):585-97.

9. Henrotin Y, Kurz B, Aigner T. Oxygen and reactive oxygen species in cartilage degradation: friends or foes? Osteoarthritis Cartilage 2005;13(8):643-54.

10. Zadak Z, Hyspler R, Ticha A, Hronek M, Fikrova P, Rathouska J, Hrnciariková D, Stetina R. Antioxidants and vitamins in clinical conditions. Physiol Res 2009;58(1): S13-17.

11. Halliwell B, Aeschbach R, Löliger J, Aruoma OI. The characterization of antioxidants. Food Chemi Tox 1995;33(7):601-17.

12. Berger MM. Can oxidative damage be treated nutritionally?. Clinical Nutr 2005;24(2):172-83.

13. Bangert SK, Marshall WJ, editors. Clinical biochemistry: metabolic and clinical aspects. Churchill Livingstone; 1995.

14. Vasudevan DM, Sreekumari S. Textbook of Biochemistry for Medical students. 3rd ed. Jaypee Digital Publishers, India, 2001.

15. Nurcombe HL, Bucknall RC, Edwards SW. Activation of the neutrophil myeloperoxidase-H2O2 system by synovial fluid isolated from patients with rheumatoid arthritis. Ann Rheumatic Dis 1991;50(4):237-42.

16. Öztürk HS, Çimen MB, Çimen ÖB, Kacmaz M, Durak I. Oxidant/antioxidant status of plasma samples from patients with rheumatoid arthritis. Rheumatol Int 1999;19(1-2):35-7.

17. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? Curr Opi Rheumatol 2014;26(1):64.

18. Isomäki P, Punnonen J. Pro-and anti-inflammatory cytokines in rheumatoid arthritis. Ann Med 1997;29(6):499-507.

19. Marks M, Marks JL. Viral arthritis. Clin Med 2016;16(2):129.

20. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Internal Med 2007;146(11):797-808.

21. Bizzaro N, Bartoloni E, Morozzi G, Manganelli S, Riccieri V, Sabatini P, et al. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res Ther 2013;15(1): R16.

22. Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat Rev Immunol 2017;17(1):60.

23. Padyukov L, Seielstad M, Ong RT, Ding B, Rönnelid J, Seddighzadeh M, et al. Epidemiological Investigation of Rheumatoid Arthritis (EIRA) Study Group. A genome-wide association study suggests contrasting associations in ACPA-positive versus ACPA-negative rheumatoid arthritis. Ann Rheumatic Dis 2011;70(2):259-65.

24. Schuerwegh AJ, Ioan-Facsinay A, Dorjee AL, Roos J, Bajema IM, Van Der Voort EI, et al. Evidence for a functional role of IgEanticitrullinated protein antibodies in rheumatoid arthritis. PNAS 2010;107(6):2586-91.

25. vanDongen H, vanAken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-32.

26. Sellam J, Hendel-Chavez H, Rouanet S, Abbed K, Combe B, Le Loët X, et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study. Arthritis Rheum 2011;63(4):933-8.

27. Seegobin SD, Ma MH, Dahanayake C, Cope AP, Scott DL, Lewis CM, et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthritis Res Ther 2014;16(1): R13.

28. Mitchison NA, Wedderburn LR. 2000. B cells in autoimmunity. PNAS, 97:8750-1.

29. Edwards JC, Cambridge G, Abrahams VM. Do self-perpetuating B lymphocytes drive human autoimmune disease? Immunology 1999;97(2):188.

30. Sutton B, Corper A, Bonagura V, Taussig M. The structure and origin of rheumatoid factors. Immunology today 2000;21(4):177-83.

31. Randen I, Pascual V, Victor K, Thompson KM, Førre Ø, Capra JD, et al. Synovial IgG rheumatoid factors show evidence of an antigen-driven immune response and a shift in the V gene repertoire compared to IgM rheumatoid factors. Eur J Immunol 1993;23(6):1220-5.

32. Thompson KM, Børretzen M, Randen I, Førre O, Natvig JB. V-gene repertoire and hypermutation of rheumatoid factors produced in rheumatoid synovial inflammation and immunized healthy donors. Ann NY Acad Sci 1995;764:440.

33. Kyburz D, Corr M, Brinson DC, Von Damm A, Tighe H, Carson DA. Human rheumatoid factor production is dependent on

CD40 signalling and autoantigen. J Immunol 1999;163(6):3116-22.

34. Kyburz D, Corr M, Brinson DC, Von Damm A, Tighe H, Carson DA. Human rheumatoid factor production is dependent on CD40 signalling and autoantigen. J Immunol 1999;163(6):3116-22.

35. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Disco 2003;2(6):473-88.

36. Stuhlmüller B, Mans K, Tandon N, Bonin MO, Smiljanovic B, Sörensen TA, et al. Genomic stratification by expression of HLA-DRB4 alleles identifies differential innate and adaptive immune transcriptional patterns-A strategy to detect predictors of methotrexate response in early rheumatoid arthritis. Clin Immunol 2016;171:50-61.

37. Ciccacci C, Conigliaro P, Perricone C, Rufini S, Triggianese P, Politi C, et al. Polymorphisms in STAT-4, IL-10, PSORS1C1, PTPN2 and MIR146A genes are associated differently with prognostic factors in Italian patients affected by rheumatoid arthritis. Clin Exp Immunol 2016;186(2):157-63.

38. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature 2001, 409:860–921.

39. Manolio TA. Genomewide association studies and assessment of the risk of disease. New Eng J Med 2010;363(2):166-76.

40. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis-a comprehensive review. Clin Rev Allergy Immunol 2013;45(2):170-9.

41. Lessard CJ, Ice JA, Adrianto I, Wiley GB, Kelly JA, Gaffney PM, et al. The genomics of autoimmune disease in the era of genome-wide association studies and beyond. Autoimmun Rev 2012;11(4):267-75.

42. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. Rheumatology 1993;32(10):903-7.

43. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. New Eng J Med 2001;344(12):907-16.

44. Butler DM, Maini RN, Feldmann M, Brennan FM. Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti-TNF-alpha antibody with the interleukin-1 receptor antagonist. Eur Cytokine Net 1995;6(4):225-30.

45. Haworth C, Brennan FM, Chantry D, Turner M, Maini RN, Feldmann M. Expression of a granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumour necrosis factor-α. Eur J Immunol 1991;21(10):2575-9.

46. Chin JE, Winterrowd GE, Krzesicki RF, Sanders ME. Role of cytokines in inflammatory synovitis. Arthritis & Rheumatism: Off. J Am Col Rheumatol 1990;33(12):1776-86.

47. Tilders FJ, DeRuk RH, Van Dam AM, Vincent VA, Schotanus K, Persoons JH. Activation of the hypothalamus-pituitary-adrenal axis by bacterial endotoxins: routes and intermediate signals. Psychoneuroendocrinology. 1994;19(2):209-32.

48. Low AS, Symmons DP, Lunt M, Mercer LK, Gale CP, Watson KD, et al. Relationship between exposure to tumour necrosis factor inhibitor therapy and the incidence and severity of myocardial infarction in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76(4):654-60.

49. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, Gizinski A, Yalavarthi S, Knight JS, et al. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med 2013;5(178):178ra40.

50. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti-tumour necrosis factor α therapy and the risk

of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):1754-64.

51. Too CL, Muhamad NA, Ilar A, Padyukov L, Alfredsson L, Klareskog L, et al.. Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case-control study. Ann Rheum Dis 2016;75(6):997-1002.

52. Deon D, Ahmed S, Tai K, Scaletta N, Herrero C, Lee IH, et al. Cross-talk between IL-1 and IL-6 signalling pathways in rheumatoid arthritis synovial fibroblasts. J Immunol 2001;167(9):5395-403.

53. Schatz A, Trankle C, Yassen A, Chipko C, Rajab M, Abouzaki N, Abbate A. Resolution of pericardial constriction with Anakinra in a patient with effusive-constrictive pericarditis secondary to rheumatoid arthritis. Int J Cardiol 2016;223:215-6.

54. Blanco FJ, Möricke R, Dokoupilova E, Codding C, Neal J, Andersson M, et al. Secukinumab in active rheumatoid arthritis: a phase III randomized, double-blind, active comparator–and placebo-controlled study. Arthritis Rheumatol 2017;69(6):1144-53.

55. Smolen JS, Agarwal SK, Ivanova E, Xu XL, Miao Y, Zhuang Y, et al. A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. Ann Rheum Dis 2017;76(5):831-9.

56. Chiu YG, Ritchlin CT. Denosumab: targeting the RANKL pathway to treat rheumatoid arthritis. Expert Opin Bio Ther 2017;17(1):119-28.

57. Schett G, Redlich K, Xu Q, Bizan P, Gröger M, Tohidast-Akrad M, et al. Enhanced expression of heat shock protein 70 (hsp70) and heat shock factor 1 (HSF1) activation in rheumatoid arthritis synovial tissue. Differential regulation of hsp70 expression and hsf1 activation in synovial fibroblasts by proinflammatory cytokines, shear stress, and anti-inflammatory drugs. J Clin Investig 1998;102(2):302-11.

58. Itoh T, Matsuda H, Tanioka M, Kuwabara K, Itohara S, Suzuki R. The role of matrix metalloproteinase-2 and matrix metalloproteinase-9 in antibody-induced arthritis. The J Immunol 2002;169(5):2643-7.

59. Cunnane G, FitzGerald O, Hummel KM, Youssef PP, Gay RE, Gay S, et al. Synovial tissue protease gene expression and joint erosions in early rheumatoid arthritis. Arthritis Rheum 2001;44(8):1744-53.

60. Konttinen YT, Ainola M, Valleala H, Ma J, Ida H, Mandelin J, et al. Analysis of 16 different matrix metalloproteinases (MMP-1 to MMP-20) in the synovial membrane: different profiles in trauma and rheumatoid arthritis. Ann Rheum Dis 1999;58(11):691-7.

61. Hughes CE, Nibbs RJ. A guide to chemokines and their receptors. FEBS J 2018;285(16):2944-71.

62. Griffith JW, Sokol CL, Luster AD. Chemokines and chemokine receptors: positioning cells for host defence and immunity. Annual Rev Immunol 2014;32:659-702.

63. Szekanecz Z, Kim J, Koch AE. Chemokines and chemokine receptors in rheumatoid arthritis. In Seminars in immunology, Academic Press 2003; 15(1): 15-21.

64. Koch AE. Chemokines and their receptors in rheumatoid arthritis: future targets? Arthritis Rheum 2005;52(3):710–721.

65. Greisen SR, Schelde KK, Rasmussen TK, Kragstrup TW, Stengaard-Pedersen K, Hetland ML, et al. CXCL13 predict disease activity in early rheumatoid arthritis and could be an indicator of the therapeutic window of opportunity'. Arthritis Res Ther 2014;16(5):434.

66. Yeo L, Adlard N, Biehl M, Juarez M, Smallie T, Snow M, et al. Expression of chemokines CXCL4 and CXCL7 by synovial macrophages defines an early stage of rheumatoid arthritis. Ann Rheum Dis 2016;75(4):763-71.

67. Chou RC, Kim ND, Sadik CD, Seung E, Lan Y, Byrne MH, et al. Lipid-cytokine-chemokine cascade drives neutrophil recruitment in a murine model of inflammatory arthritis. Immunity 2010;33(2):266-78.

68. Yoshida K, Korchynskyi O, Tak PP, Isozaki T, Ruth JH, Campbell PL, et al. Citrullination of epithelial neutrophil-activating peptide 78/CXCL5 results in a conversion from a non–monocyte-recruiting chemokine to a monocyte-recruiting chemokine. Arthritis Rheum 2014;66(10):2716-27.

69. Sucur A, Jajic Z, Artukovic M, Matijasevic MI, Anic B, Flegar D, et al. Chemokine signals are crucial for enhanced homing and differentiation of circulating osteoclast progenitor cells. Arthritis Res Ther 2017;19(1):1-6.

70. Komatsu N, Takayanagi H. Inflammation and bone destruction in arthritis: synergistic activity of immune and mesenchymal cells in joints. Front Immunol 2012;3:77.