## Special Article

# Rheumatoid Arthritis: A Review of Current Literature

**Danita R. Potter**
**Adjunct Professor, College of Nursing & School of Allied Health, Shreveport, LA. 71101 USA**

**Beatrice K. Launius**
**Assistant Professor, College of Nursing & School of Allied Health, 1800 Line Avenue, Shreveport, LA. 71101 USA**

**Correspondence:** Danita R. Potter, Adjunct Professor, College of Nursing & School of Allied Health, Shreveport, LA. 71101 USA E-mail:drpotter41@yahoo.com

**Abstract**

The purpose of this paper was to review the current literature on Rheumatoid Arthritis (RA) and inflammation in the synovium. The approach utilized studies on Rheumatoid Arthritis (RA) and inflammation in the synovium. Articles published between 2013-2017 in CINAHL, Medline, and PubMed databases were used. The literature was searched via the Watson Library online system which included searched dates from October 2017 to November 2017. One hundred and sixty articles were identified. Results: The resulting abstracts were scrutinized to ensure they met the inclusion criteria: 1) articles published in peer-review journals, 2) no schemata in the article, 3) focus on RA pathophysiology/anatomy/physiology, 4) research article, and 5) no clinical foci. Conclusion: Fourteen identified, seven deemed significant and relevant for inclusion in the review. The articles were not grouped into categories because all articles focused on pathophysiology of RA.

**Keywords:** Rheumatoid Arthritis; synovium; joint inflammation; synovial; and synovitis

## Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that can be functionally debilitating with pain, joint stiffness, and loss of function. It can result in joint damage and deformities, as well as systemic complications including lung disease, coronary artery disease. Permanent disability can occur within first two years of onset. RA affects all nationalities, races, and genders. It affects 1.3 million people in the U. S (more women than men) where the health care costs are greater than $8.4 billion annually and worldwide costs average $39.2 billion a year (Unk & Brasington, 2012). RA, which is complex and difficult to treat, takes considerable time during clinic appointments to discuss the diagnosis, coexisting conditions, treatment options, and developing a plan of care with patient and family (Riley et al., 2017; Unk & Brasington 2012).Methods

**Inclusion & Exclusion Criteria:** Articles reviewed were limited to those published between 2013-2017. CINAHL, Medline, and PubMed databases were used. The literature search utilized the Watson Library online system. The literature search was conducted from October 2017 to November 2017. One hundred and sixty articles were identified. The resulting abstracts were scrutinized to ensure they met the inclusion criteria: 1) articles published in peer-review journals, 2) no schemata in the article, 3) focus on RA pathophysiology/ anatomy/ physiology, 4) research article, and 5) no clinical foci. Overall, fourteen articles were deemed significant and relevant for inclusion in the review. A second analysis resulted in seven research articles for this paper. The articles were not grouped into categories because all articles focused on pathophysiology of RA. The search terms used for the review included Rheumatoid Arthritis, synovium, joint inflammation, synovial, and synovitis. All terms were searched.

## Results

All seven research articles that met the inclusion criteria were included in this paper.

**Review of the Literature:** Wang, et al. (2017) explored the effects of interleukin-34 (IL-34) on RA fibroblast-like synoviocytes (FLS) as a pro-

inflammatory factor and IL-34 stimulated FLS on the production of T-helper (Th17). Il-34 upregulated Th17 production through increased IL-6 expression by rheumatoid FLS. Rheumatoid arthritis (RA) is a progressive systematic disease involving synovial inflammation and articular destruction. In the disease, RA synovial tissue becomes hyperplastic and forms pannus which invades the cartilage and bone.  This eventually leads to restricted movement and disability. When activated, FLS play key roles through the local production of cytokines and proteolytic enzymes leading to degradation of the extracellular matrix and cartilage. Accumulating evidence indicates multiple mediators are involved in the RA-FLS activation including Tumour Necrosis Factor-$x$ (TNF), IL-1, IL-6. These cytokines develop a complex network of autocrine and paracrine regulation modes, which triggers not only proliferation and migration but also increased resistance to apoptosis by FLS. Among cytokines network, there may be undiscovered cytokines whose actions are still unknown. This lends urgency to uncovering the effects and mechanisms of these new cytokines underlying FLS activation. Activation of fibroblast-like synoviocytes is a critical step that promotes disease progression. Wang, et al. found serum IL-34 levels were increased in patients with RA as compared to those of healthy controls.   Additionally, they found positive correlations with C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor and anti-cycle citrullinated peptide antibody.

Treatment with an IL-6R antagonist could attenuate this effect. Their findings support the role of IL-34 in RA inflammatory responses. IL-34 levels of 168 RA patients were compared to those of 85 healthy people.  Those with RA had significantly higher IL-34 levels when compared to healthy controls. IL-34 dramatically promotes IL-6 production of FLS via signalling pathways stimulate cell proliferation.  Several chemokines and their receptors have been implicated in FLS infiltration, macrophages recruitment, and angiogenesis in RA.

Angiolilli et al. (2017) studied whether pro-inflammatory factors present in the inflamed joints of RA patients could regulate histone deacetylase (HDAC) expression and function of FLS. HDAC counteracts HAT activity through targeting histones and on-histone signal transduction proteins and transcription factors. This methodology included protein acetylation in synovial tissue was assessed by immunohistochemistry. Other analyses included synovial tissues gene expression where total RNA was isolated from biopsies of 19 patients using RNA STAT-60 and cleaned with RNeasy columns and DNAse.

The effects of these manipulations were examined using qPCR assays, Findings included synovial class I HDAC expression was associated with local expression of TNF and matrix metalloproteinase-1, while class IIa HDAC5 expression was inversely associated with severity of disease activity. Interleukin-1B or TNF stimulation selectively suppressed HDAC5 expression in RA FLS. Angiolilli, et al. concluded that inflammatory cytokines suppress RA FLS HDAC5 expression, promoting nuclear localization of IRF1 and transcription of a subset of type I interferon respond genes. HDAC5 was identified as a novel inflammatory mediator in RA.

Yoshida and Tanaka (2014) explored current evidence of the pathological role of IL-6 in the development of RA as well as the efficacy and safety profile of Tocilizumab (TCZ) for RA. According to Yoshida and Tanaka (2014), RA is a chronic disease with joint and systemic inflammation resulting from immunological abnormalities. IL-6 has been found to play a key role in the development of the disease. Furthermore, uncontrolled, persistent production of IL-6 may lead to the development of several other immune-mediated diseases. Interleukin-6, a cytokine featuring pleiotropic activity and redundancy, contributes to host defence against infectious agents and tissue injuries by inducing acute phase reaction and immunological and hematopoietic responses.

After binding, the IL-6-IL-6R complex associates with signal-transducing molecule gp130, resulting in the activation of downstream signalling events via Janus kinase (JAK) in target cells. This activation is known as classic signalling pathway. The pathological role of IL-6 in RA contributes to the production of autoantibodies by activating plasma cells. Further, IL-6 has promoted Th cell development which leads to the secretion of IL-21, another B cell differentiation factor. This contributes to local inflammation causing joint destruction through induction of endothelial cells to produce IL-8 and monocyte chemoattractant protein-1 (MCP-1) along with the expression of adhesion

molecules and recruitment of leukocytes to the involved the joints.

Picerno et al. (2015) conducted a systematic review of literature to analyse studies of the pathogenesis of RA over a one-year period. Their review included RA studies focusing on genetic and environmental factors, immunopathogenesis of synovitis, adaptive immune pathways, and burden of RA. In reviewing studies of genetic and environmental factors, Picerno et al. identified new genetic loci associated with RA susceptibility and articular damage progress. They also found detection of genetic polymorphisms involved with RA pathogenesis have increased and identified chromosome 22q12, a single nucleotide polymorphism (SNP), rs1043099, that was previously known to be involved in other autoimmune disease. A relevant role in bone damage progression in RA has been ascribed to genetic loci coding for matrix metalloproteinases (MMP). A correlation was observed between radiographic progression in RA and a cluster of SNPs of SPAG16, a gene expressed in sperm and other tissues.

Olkkonen et al. (2015) investigated the expression of direct clock suppressor DEC1 and DEC2 (BHLHE 40 and 41 proteins) in response to TNFx and investigated their role during inflammation. Clock genes are needed for proper immune cell function. This study hypothesized that the negative regulators in clock DEC1, DEC2 or both are affected by TNFx. Cultured primary fibroblasts were stimulated with TNFx. To study the effect of NF-kB inhibition on DEC2 regulation, IKK-2 inhibitor IMD-0354 was used. The role of NF-kB in DEC2 increase was analyzed using IKK-2 specific inhibitor IMD-0354. Cloned DEC2 was transfected into HEK293 cells to investigate the gene expression effects. Transfections into primary human fibroblasts were used to confirm the results. The presence of DEC2 was analyzed in RA and OA synovial membranes by immunohistochemistry. Results revealed that TNFx increased DEC2 mRNA and DEC2 was mainly detected at nuclei after the stimulus. The effects of TNFx on DEC2 expression were mediated by NF-kB. Overexpression, siRNA and promoter activity studies disclosed that DEC2 directly regulates IL-1B, in both HEK293 cells and primary human fibroblasts. DEC2 was increased in synovial membrane in RA compared in OA patients.

It was hypothesized that DEC2 itself might contribute to the upregulation of IL-B and to test the hypothesis, DEC2 gene was cloned and overexpressed in HEK293 cells (transfected into primary human fibroblasts). TNFx induces the expression of IL-1B both in human fibroblasts and in HEK293 cells. Overexpression of DEC2 in HEK293 cells increased IL-1B mRNA levels in response to TNFx 4-fold. DEC2 also increased TNFx mediated IL-1B promoter activity suggesting that this increase results in part from increased transcription effect in human fibroblasts. Overexpression of DEC2 also in these cells increased IL-1B and CCL8 mRNA levels in response to TNFx. To verify results, Olkkonen et al used silencing of DEC2 siRNA performed which showed a decline in IL-1B increase in response to TNFx in human fibroblasts. Thus, DEC2 protein is abundant in the synovial membrane of RA in comparison to OA. This was evident in the vitro effects of TNFx on upregulation of DEC2, RA, and OA synovial tissues under immunostained for presence of DEC2 where the staining was much more intense with RA synovitis tissue as oppose to OA tissue samplings.

Moret et al. (2013) investigated the phenotypic and functional properties of randomly CD1c myeloid dendritic cells (mDCs) from synovial fluid compared to cells from peripheral blood in RA patients. Myeloid dendritic cells (mDCs) are potent T cell activating antigen-presenting cells that play a critical role in regulation of immune responses in many diseases including RA. CD1c is a major histocompatibility complex class I-like cell surface. The function of CD1c+ mDCs (also referred to as mDCs) from peripheral blood and synovial fluid of RA patients was examined. Methodology included CD1c mDC numbers and expression of costimulatory molecules assessed under fluorescence-activated cell sorting (FACs) analysis in synovial fluid and peripheral blood from patients with RA using a FACS Canto II flow cytometer Cell surface markers expressions on CD1c + mDCs was studied with reagents IgG isotype. Ex vivo secretions of 45 inflammatory mediators by mDCs from SF and peripheral blood of RA patients was delivered by multiplex immunoassay. The capacity of mDCs from synovial fluid to activate autologous CD4+ T cells was measured. Findings of this study showed CD1c +mDC numbers were significantly increased in synovial fluid compared to peripheral blood of patients with RA.

Synovial fluid mDCs secreted higher levels of interferon y-inducible protein-10, monokine induced by interferon y and thymus and activation-regulated chemokine (TARC), but lower macrophage-derived capacity to induce proliferation of CD4+ cells. The mDCs from synovial fluid showed increase expression of antigen-promoting class II, CD1c and costimulatory molecules such as CD 80, CD 86, and CD 40. In summary, Moret et al concluded that the accumulating increased numbers of CD1c+ mDC in synovial fluid of RA patients are involved and contribute to the inflammatory cascade intra-articulating of the secretion of specific T-cell attracting chemokines and the activation of self-reactive T cells.

Kim et al. (2014) investigated the role and mechanism of stromal cell-derived factor (SDF-1) in RA-associated osteoclastogenesis. SDF-1 promotes CD4+ memory T cells recruitment and accumulation migration of monocytes into synovium, and induces pseudoemperipolesis (migration into synovium) both T and B cells. SDF-1 can promote joint destruction by inducing angiogenesis through immobilization of endothelial cells on heparin sulfate molecules and by inducing angiogenesis via activation of chondrocytes an-d osteoblasts through matrix metalloproteinase 3 (MMP-3) and MMP-9. Kim et al asserted that SDF-1 is produced by bone marrow stromal cells, fibroblast-like synoviocytes (FLS), macrophages, and endothelial cells.

The inhibition of SDF-1 protects against the development of collagen-induced arthritis (CIA) and the inhibitor of CXC R4, a unique receptor for SDF-1, reduces the incidence and clinical severity of CIA. SDF-1 may play an important role in the inflammatory response, neovascularization, and joint destruction in the pathogenesis of RA. Outside of its role as a chemokine, SDF-1 is involved in the inflammatory circuit of RA pathogenesis, and its bone destruction of RA is closely associated with osteoclastogenesis and is a major inducer for osteoclasts (RANKL).

Synovial tissue samples were obtained from 8 RA patients and 8 osteoarthritis patients during time of total knee replacements. Synovial fibroblasts were isolated by enzymatic digestion of synovial tissue and reagents included human SDF-1, RANKL, and macrophage colony-stimulatory factor. Under immunofluorescence staining synovial tissue secretion for patients with RA and OA were performed under real time polymerase chain reaction and assessment of RANKL on RNA expression and western blot analysis. Findings revealed that SDF-1 and RANKL were overexpressed in synovial tissue and synovial fluid of patient with RA and showed a significantly positive correlation between SDF-1 and RANKL concentration in synovial fluid compared to OA patients. Abundantly expressed in lining and sublining areas of synovium of RA patients compared to faintly expressed in OA patients. To determine whether SDF-1 induced RANK L expression in CD4+ T cells is affected by pro-inflammatory cytokines, Kim et al investigated whether SDF-1 could induce pro-inflammatory cytokine expression. As result of this analysis, the stimulation of CD4+ T cells with SDF-1 significantly increased TNFx mRNA levels, but IL-1B and IL-6 m RNA levels were unchanged. RANKL mRNA expression induced by SDF-1 was reduced by neutralization of TNFx, but not by neutralization of IL-1B, or IL-6 suggesting that SDF-1 induces the production of TNFx by CD4+ T cells with stimulates RANKL production in both autocrine and paracrine manners. Although, TNFx does not directly induce the production of SDF-1 by RA synovial fibroblasts, it is a major mediator of SDF-1 induced RANKL expression. Both synovial fibroblasts and CD4+ T cells exposed to SDF-1 have a potential to activate and regulate osteoclast differentiation and activation. Thus, SDF-1 play a key role in RANKL and TNFx-mediated osteoclastogenesis targeting jointing destruction in RA patients.

## Discussion

The discussion of the paper highlights the significance of understanding RA in advance practice nursing.

## Significance of RA in Advance Practice

RA continues to be referred as a complex autoimmune disease that impact a large number of patients with multiplex health care demands including physical, biological, spiritual, emotional, and environmental (and more) (Solomon et al. 2015; Riley et al, 2017; Carey, 2015). Nurse practitioners contribute to providing best practices in patients from simple to complex health problems in every day practice. In understanding the pathogenesis of RA, nurse practitioners are in a key and unique

position to expand their roles in engaging in further research in the pathogenesis related to development of RA such as in Yoshida and Tanaka's (2014) where they found that IL-6 plays a key role in the development of this disease.  This can contribute to the nurse practitioner developing specific education sessions for families and patients who have been new diagnosed with RA thus enhancing their understanding of the disease processes.

Knowledgeable of current and the engagement in further research of RA can provide nurse practitioners continuous research to undergird their practice decisions and treatment options for persons who impacted with the diagnosis of RA. For example, in Angiolilli et al.'s study which concluded that inflammatory cytokines suppress RA FLS HDAC5 expression and identified HDAC5 as a novel inflammatory mediator in RA. Moreover, Olkkonen examined the expression of direct clock suppressor DEC1 and DEC2 (BHLHE 40 and 41 proteins) in response to TNF*x* and its role in inflammation. These studies findings can provide an advance practicing nurse with essentials on inflammatory mediators and TNFx role in RA that can directly improve understanding of the inflammatory processes that persons with RA may experience.

Persons who are experiencing pain, loss of function, debilitation and or deformities as a result of RA are in need to be heard, understood, and are in need of education to possibly enhance quality of life. Nurse practitioners are in a pivotal position in the primary settings, hospitals, and urgent care clinics to positively impact the outcomes of care through education, best practices for treatment, proper referrals, and early diagnoses. Such as in Kim et al.'s study which showed that SDF-1 play a key role in RANKL and TNF*x*-mediated osteoclastogenesis targeting jointing destruction in RA patients. This may warrant collaboration with health care providers in oncology and/or genetic specialists for persons with RA.  Moret et al.'s study concluded that myeloid dendritic cells (mDCs) are potent T cell activating antigen-presenting cells that play a critical role in regulation of immune responses in many diseases including RA.

**Table 1: Summary of Literature Review: RA**

| Authors | Purpose | Findings |
|---|---|---|
| Angiolilli et al. (2017) | Studied whether pro-inflammatory factors present in the inflamed joints of RA patients could regulate histone deacetylase (HDAC) expression and function of FLS. | Inflammatory cytokines suppress RA FLS HDAC5 expression and identified HDAC5 as a novel inflammatory mediator in RA. |
| Kim et al. (2014) | Investigated the role and mechanism of stromal cell-derived factor (SDF-1) in RA-associated osteoclastogenesis. SDF-1 promotes CD4+ memory T cells recruitment and accumulation migration of monocytes into synovium, and induces pseudoem-peripolesis (migration into synovium) both T and B cells. | Stimulation of CD4+ T cells with SDF-1 significantly in-creased TNFx mRNA levels, but IL-1B and IL-6 m RNA levels were unchanged. RANKL mRNA expression induced by SDF-1 was reduced by neutralization of TNFx, but not by neutralization of IL-1B, or IL-6 suggesting that SDF-1 induces the production of TNFx by CD4+ T cells with stimulates RANKL production in both autocrine and paracrine manners. |
| Moret et al. (2013) | Investigated the phenotypic and functional properties of randomly CD1c myeloid dendritic | CD1c +mDC numbers were significantly increased in synovial fluid compared to peripheral blood. |

| | | |
|---|---|---|
| | cells (mDCs) from synovial fluid compared to cells from peripheral blood in RA patients. | |
| Olkkonen et al. (2015) | Investigated the expression of direct clock suppressor DEC1 and DEC2 (BHLHE 40 and 41 proteins) in response to TNFx and investigated their role during inflammation. | Overexpression of DEC2 in HEK293 cells increased IL-1B mRNA levels in response to TNFx 4-fold. DEC2 also increased TNFx mediated IL-1B promoter activity suggesting increase results in increased transcription effect in human fibroblasts. |
| Picerno et al. (2015) | Conducted a systematic review of literature to analyze studies of the pathogenesis of RA over a one-year period. | found detection of genetic polymorphisms involved with RA pathogenesis have increased and identified chromosome 22q12, a single nucleotide polymorphism (SNP). |
| Wang et al. (2017) | Explored the effects of interleukin-34 (IL-34) on RA fibroblast-like synoviocytes | Serum IL-34 levels were increased in patients with RA as compared to those of healthy controls.  found positive correlations with C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor and anti-cycle citrullinated peptide antibody. |
| Yoshida & Tanaka (2014) | Explored current evidence of the pathological role of IL-6 in the development of RA as well as the efficacy and safety profile of Tocilizumab (TCZ) for RA | Activation of downstream signaling events via Janus kinase (JAK) in target cells. Pathological role of IL-6 in RA contributes to production of autoantibodies by activating plasma cells.  IL-6 promotes Th cell development leading to the secretion of IL-21, another B cell differentiation factor. |

**Conclusion**

By understanding the pathogenesis of RA, nurse practitioners can provide care that is undergirded by research and data-driven facts whereby care is more comprehensive for patients' and families' and their burdens. Similarly, Picerno et al.'s review which included RA studies focusing on genetic and environmental factors, immunopathogenesis of synovitis, adaptive immune pathways, and burdens of RA. Today, there is an expanding role for advance practice nurses, particularly family and psychiatric nurse practitioners in providing managed care to persons with RA. Advance nurse practitioners are in a unique position to impact care for persons stricken with RA through conducting research to improve practice. By understanding the key pathogenesis processes, nurse practitioners gain the in-depth knowledge of early diagnoses based on key facts. Staying knowledgeable and current with the critical role of regulation of immune responses in RA can

directly contribute to best practices and treatment regimen.

## References

Angiolilli, C., Grabiec, A. M., Ferguson, B. S., Ospelt, C., Fernandez, B. M., van Es, I. E., Baarsen, L. G. M., Gay, S., McKinsey, T. A., Tak, P. P., Baeten, D. L., & Reedquist, K. A. (2017). *Ann Rheum Dis., 75*(2), 430-438.

Carey, S. A. (2015). Women within Rheumatoid arthritis: The unspoken risk factor. *The Journal for Nurse Practitioners, 11*(8), 829-846.

Inglehart, J. K. (2013). Expanding the role of advanced nurse practitioners—Risks and rewards. *New England Journal of Medicine, 368*(20), 1935-1941.

Kim, H. R., Kim, K. W., Kim, B. M., Jung, H. G., Cho, M. L., & Lee, S. H. (2014). Reciprocal activation of CD4 + T ce3lls and synovial fibroblasts by stromal cell-derived factor 1 promotes RANKL expression and osteoclastogenesis in Rheumatoid arthritis. *Arthritis Rheumatology, 66*(3), 538-548.

Moret, F. M., Hack, C. E., Van Der Wurff-Jacobs, K. M. G., de Jager, W., Radstake, T., Lafeber, F. P. J. G., & van Roon, J. A. G. (2013). Intra-articular CD1c-expressing myeloid dendritic cells from rheumatoid arthritis patients express a unique set of T cell-attracting chemokines and spontaneously induce Th1, Th17, and Th2 cell activity. *Arthritis Research & Therapy, 15*(5), 1-10.

Olkkonen, J., Kouri, V., Hynninen, J., Konttinen, Y. T., Mandelin, J. (2015). Differentially expressed in chondrocytes 2 (DEC2) increases the expression of IL-1B and is abundantly present in synovial membrane in Rheumatoid Arthritis. *PLoS One, 10*(12), 1-13.

Picerno, V., Ferro, F., Adinolfi, A., Vaentini, E., Tani, C., & Alunno, A. (2015). One year in review: The pathogenesis of Rheumatoid Arthritis. *Clinical and Experimental Rheumatology, 33*, 551-558.

Riley, L., Harris, C., McKay, M., Gondran, S. E., DeCola, P., & Soonasra, A. (2017). The role of the nurse practitioners in debriefing rheumatology care and services: Results of a U.S. survey. *JAANP, 29*, 673-681.

Solomon, D. H. Fraenkel, L., Lu, B., Brown, E., Tsao, P., Losina, E., & Bitton, E. (2015). Comparison of care provided in practices with nurse practitioners and physician assistants versus subspecialist physician only: A cohort study of rheumatoid arthritis. *Arthritis Care & Research (Hoboken), 67*(12), 1664-1670.

Unk, J. A., & Brasington, R. (2012). *Journal of the American Association of Nurse Practitioner*, doi: 10.1002/2327-6924.12064.

Wang, B., Ma, Z., Wang, M., Sun, X., Tang, Y., Li, M., Zhang, Y., Li, F., & Li, X. (2017). Il-34 upregulated Th17 production through increased IL-6 expression by rheumatoid fibroblast-like synoviocytes. *Mediators of Inflammation, Article ID 1567120*, 1-10.

Yoshida, Y., & Tanaka, T. (2014). Interleukin 6 and Rheumatoid Arthritis. *BioMed Research International, Article ID 698313*, 1-12.