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Original Research Paper

Orthopaedics

CONTEMPORARY UNDERSTANDING OF THE PATHOGENESIS OF RHEUMATOID ARTHRITIS.

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KEYWORDS :

INTRODUCTION:

Rheumatoid Arthritis (RA) is one of the most common rheumatologic conditions. Dell et al (2013) defines RA as a systemic autoimmune polyarticular arthritis, which can also have extra-articular manifestations that can lead to various systemic complications,.

It is more common in women and can present at any age, however, the peak age of onset is the fifth decade.

RA mainly involves the synovial membrane leading to synovial inflammation, proliferation, pannus formation and destruction of the articular cartilage, peri- articular bone and soft tissues.

Clinically, RA can be divided into four phases, a pre-clinical phase with elevated markers of auto-immunity and inflammation, an early inflammatory phase with uncate gorized symptoms and an unconfirmed diagnosis, a destructive phase with joint erosions and progression, and a final phase of irreversible joint damage.

According to serology, patient could be classified into those with positive rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA), those with both positive RF and ACPA, and those with negative serology for either, which is known as seronegative RA (Weisman et al. 2011)

The specificity and sensitivity of both the RF and Anti-CCP are detailed as below:

	RF	Anti-CCP
Specificity	Fair (80%)	Excellent (95%)
Sensitivity	Fair (78%)	Fair (78%)
Frequency in healthy individuals	10–15%	1–2%
Effect of age	Increased levels	None
Presence in other diseases	Infection, other autoimmune diseases, e.g. Sjogren's syndrome, cryoglobulinaemia, lymphoproliferative disorders	Very rare
Association with X-ray damage	Positive	Positive

(1) Figure:Table taken from Adajabeo el al. (2018), ABC of rheumatology.

The present research is focused on a greater understanding of gene-environmental interactions and development of better diagnostic tools for the early inflammatory phase of the disease.

The triad of genetics, environment, and autoimmunity play a huge role in the pathogenesis of RA.

1-The role of genetics in rheumatoid arthritis pathogenesis:

The prevalence of RA in the general population is <1%. However, among siblings, the prevalence increases to 2–4% and in Identical twins, it's 12% to15%.

Genome-wide association studies have identified over 100 genetic loci that are associated with RA.

The largest genetic risk factor for rheumatoid factor positive RA lies within the human leukocyte antigen (HLA) class II region, which encodes the HLA-DRB1 molecule.

The major histocompatibility complex (MHC) antigens or HLA (leucocytes antigen) help to discriminate between such self and foreign antigens. Class II molecule is a heterodimer that consists of alpha and beta chains. It plays an important role in the immune system by presenting antigens to the T helper cells. Class II molecules are expressed on the surface of antigen-presenting cells like dendritic cells.

Any mutation in these genes leads to deregulated immunity leading to autoimmune diseases. The HLA locus on the short arm of chromosome 6 and alleles (gene variations due to mutations) of HLA-DRB1 is associated with susceptibility to RA.

HLA-DR genes act indirectly by regulating the autoantibody production involved in the development and outcome of RA. HLA-DRB1 alleles predispose to ACPA-positive RA whereas alleles of HLA-DR3 predisposes to ACPA negative RA. Seronegative RA patients make up ~30% of the RA population and the genetic susceptibility in this population remains understudied.

Shared epitope" (SE) is a five amino acid sequence part of HLA-DRβ chains encoded by HLA-DRB1. These are associated with severe RA. This amino acid sequence may alter intracellular function contributing to autoimmunity and inflammation in RA, such as NFkB activation, interleukin 6 receptor expressions, and metabolism, increased citrullination of PAD14 receptor, and change in DNA methylation leading to increased inflammation.

2-Environmental factors in rheumatoid arthritis pathogenesis:

Many environmental and lifestyle factors have been studied as potential risk factors for pathogenesis of RA. These include cigarette smoking, excess weight, dietary intake, physical activity, and dental hygiene, all of which are potentially modifiable.

Other factors which are less amenable to modification are, socioeconomic status (e.g., income, education) or female reproductive factors (e.g., parity, breastfeeding, menopause). Despite research showing associations with RA risk, evidence suggests that environmental risk factors in RA may act years before clinical disease manifestations become apparent (Edwards and Cooper 2006).

Cigarette smoking is an established behavioural risk factor for RA and this has been extensively studied. Sparks and Karlson (2016) reported that smoking may exert effects on RA risk throughout all the pathogenesis phases, from preclinical phases of development to clinical RA diagnosis.

The relationship of obesity with pathogenesis of RA and other autoimmune diseases has been investigated. A large Danish cohort study (Linauskas et al., 2018) found that obesity, high body fat percentage and large waist circumference were associated with increased RA risk. This relation was more significant in women.

Beyond tobacco smoke exposure, multiple studies have also

consistently demonstrated an association between exposure to occupational silica dust and ACPA positive RA. There have also been findings linking increased exposure to inhaled particulate air pollution and increased risk for RA. However, the findings have been mixed, perhaps in part because of the complexity of assessing the true exposure to air pollution and accounting for other factors such as specific components of pollution that may vary by locality. In addition, confounders such as lower socio-economic status, a purported risk factor likely affect these findings for RA in individuals who are also exposed to greater amounts of pollution.

Multiple dietary or other factors such as supplements or medications have also been variably linked to RA risk. These include lower intake of vitamin D and antioxidants and higher intake of sugar, sodium, red meats, protein, and iron with increased risk for RA. There have been conflicting reports regarding the effect of Mediterranean diet and prevention of Rheumatoid arthritis. Johansson et al (2018) found that in men and sero-positive RA sub-groups, adherence to Mediterranean diet reduced the risk of RA.

Based on this, they argued that mechanisms and impact of different diets might differ between RA sub-groups. However, in a systematic review, Forsyth et al (2018) state that there is insufficient evidence to support recommendation of this diet regime to prevent RA.

Several other dietary factors and their likely risk for RA have been studied. In their detailed review, Zaccardelli et al (2019) conclude that overall healthier patterns, high fish or omega-3 polyunsaturated fatty acids, and moderate alcohol intake may reduce RA risk, while caffeine and sugar-sweetened soda may increase RA risk.

Liu et al (2019) studied the long-term effects of physical activity and subsequent risk of RA. Their findings showed that in comparison to low physical activity levels, increasing cumulative total hours of physical activity significantly reduced RA risk.

Dental hygiene and periodontal disease have also been implicated as a risk factor for RA. There is evidence that periodontal disease and RA often affect a similar population. However, a causal relationship between gingival disease and RA prevention remains unclear (Arkema et al., 2010).

Researchers have found an inverse association between socioeconomic status measured by education and occupational class and risk of RA. Swedish EIRA study Bengtsson et al (2005) showed that the risk of RA in patients without university degrees was 40% higher compared with those with university degrees. For patients whose occupation required manual labour, the risk for RA was higher than non-manual workers. These associations were found to be stronger for rheumatoid factor positive subgroup of RA.

Because approximately two-thirds of individuals who develop RA are women and a large number of epidemiologic studies point to sex-related factors in RA risk, it has long been considered that there are female-specific factors that influence risk for RA.

The factors include early menopause, the presence of polycystic ovary syndrome, and potentially pre-eclampsia. In addition, across several studies involving diverse populations, the rates of a first diagnosis of RA appear to be increased post-partum, although it is not known whether this phenotype is related to changes in hormone levels such as prolactin or other factors such as transmission of cells/DNA from the foetus to the mother (microchimerism).

Protective factors include breast-feeding and, variably, use of hormone replacement therapy and oral contraception, with greater protection seen with longer-term use (e.g., >7 years).

3- Immunological factors in the rheumatoid arthritis pathogenesis:

RA is strongly associated with various immune cells and each of the cell type contributes differently to the disease pathogenesis. B-cells, T-cells and macrophage play critical roles in the pathogenesis of RA. These cells reside in synovium or circulate in peripheral blood:

B-cells:

According to Adebajo et al (2018), in RA, B cells are the source of the inflammatory cytokines, antibodies (RF and anti CCP antibodies), they also contribute to T cell activation and antigen presentation.

Repairing mechanisms either during the progression from early immature to immature B-cells in the bone marrow, or before the B-cells become mature naïve B-cells normally eliminates autoreactive B-cells. Both processes are highly regulated by two immune checkpoints.

In RA patients, both checkpoints are usually defective, leading to the large production of autoreactive mature naïve B-cells (Yap, 2018)

Autoreactive B-cells can also act as an antigen presenting cell (APC) in stimulating T-cells maturation and differentiation into memory CD4+ T-cell.

In addition, B-cells mediate T-cells activation through expression of costimulatory molecules.

B cells do also contribute to the elevation of RANKL production in the peripheral blood synovial fluid and the tissues of RA.

According to Geusens (2012), RANKL binds to the RANK receptor of pre-osteoclasts and mature osteoclasts and stimulates their activation and differentiation.

In rheumatoid arthritis (RA), bone erosions are the result of osteoclastic bone resorption at the sites of synovitis, where RANKL expression is also found.

T-cells:

According to Yap et al (2018), T-cells can be activated by various cell types including B-cell, macrophages and dendritic cells (DCs). Although the exact role of T-cells in RA remains unclear, there are convincing evidences supporting that CD4+ T-cells contribute significantly to the chronic autoimmune response of RA. During activation of T-cells, CD4+ T-cells interact with human leukocyte antigen (HLA) or major histocompatibility class II (MHC-II) molecules as well as co-stimulating molecules such as CD28 that are expressed on the surface of APC.

This interaction then leads to the onset of downstream PI3K signalling pathway leading to the maturation of Cd4+. Subsequently, it results in the antigenic activation of naive CD8+ T-cells that promote inflammation.

It has been reported that CD4+/CD28null correlated with systemic morbidities associated with RA such as vasculitis and acute coronary syndrome.

In addition to cell-to-cell interaction, current evidences also suggest that CD4+ T-helper (Th) cells mainly contribute to the pathogenesis of RA through the secretion of cytokines and chemokines to support the inflammation in the joint. T–cells activate macrophages and fibroblasts and transform them into tissue-destructive cells.

Macrophages:

They are found in both the intimal and subintimal regions of normal synovium. However, macrophages make up a minority of cells in the normal intima, while the numbers in inflammatory arthritis increase dramatically.

In RA synovial tissue the number of macrophages accounts for up to 80% of the intimal layer. In an inflamed joint, the macrophages regulate the secretion of pro-inflammatory cytokines and damaging enzymes that are associated with inflammatory responses and subsequently leading to joint destruction. Other than producing cytokines and enzymes, macrophages also mediate multiple RA-related biological processes such as recruitment of lymphocytes, cartilage damage, joint erosion, angiogenesis and fibroblast proliferation.

Cytokines:

McInnes (2007) states that an immune response to an inflammatory process is led by a cytokine reaction. In the early pathogenesis of RA, the predominant cytokines that are secreted from T-cells and stromal cells are IL-13, IL-14 and IL-15. These cytokines result in the inflammatory response and contribute to the chronic inflammation Other cytokines such as IL-6 and tumour necrosis factor alpha (TNF-□) have also been reported to promote RA by stimulating the activation of both chondrocytes and osteoclasts and produce MMPs that degrade the matrix of articular cartilage leading to bone resorption in RA.

There are several potential mechanisms of immunologic activity that may be related to hormones including glycosylation of autoantibodies and alterations of T and B cell function, and these may be important in early development of RA and in established classified disease.

Cytokine	Role in the disease process
TNF alpha	***Local effects:*** • Increased monocyte activation, cytokine release, PG release • Increased polymorphonuclear leucocyte priming, apoptosis and oxidative burst • T-cell apoptosis, clonal regulation, TCR dysfunction • Increased endothelial cell adhesion molecule expression, cytokine release • Decreased synovial fibroblast proliferation, collagen synthesis • Increased MMP and cytokine release ***Systemic effects:*** • Acute-phase protein production • HPA axis dysregulation (fatigue and depression) • CVD promotion

(2) Figure: Table summarising the role of TNF alpha in the pathogenesis of rheumatoid arthritis.

Antibodies:

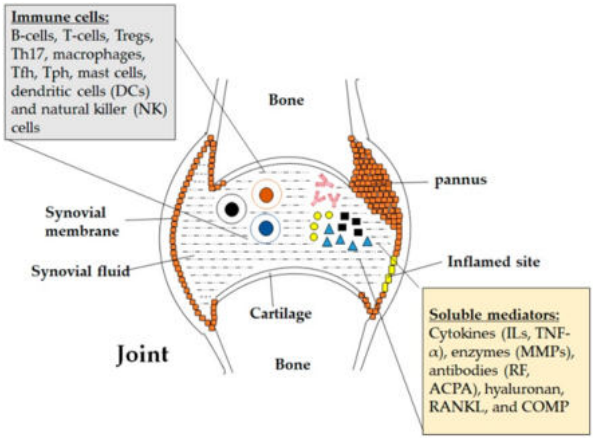
When immune dysregulation occurs, the body's antibodies attack their own antigens.

RF is an autoantibody that targets the Fc portion of immunoglobulin G. Another antibody that is highly pertinent in RA is ACPA (also known as anti-CCP). ACPA is a family of antibodies with overlapping specificities. These antibodies recognize a range of citrullinated proteins such as filaggrin, fibrinogen, vimentin, collagen II, enolase and histone.

Other immune cells such as mast cell, dendritic cells and natural killer (NK) cells have also been reported to mediate RA pathophysiology via diverse mechanisms.

Tyrosine kinase:

Signalling through PDGFRs promotes the proliferation and migration of FLSs, contributing to the formation of a pannus. Migration of endothelial cells to form blood vessels through angiogenesis is promoted by signalling through VEGFRs and regulated by TIE1 and TIE2. Activation of T cells and B cells through T-cell receptors and B-cell receptors, respectively, requires a variety of tyrosine kinases, including Lck, Btk and Syk. Several routes, such as binding of SCF to KIT, can activate mast cells, which produce numerous inflammatory and degradative factors in the synovium. M-CSF binding CSF1R promotes the maturation of monocytes into macrophages and subsequent osteoclast formation, which results in bone erosion. Sawson et al (2009)



(3) Figure: Host immune cells and soluble mediators in rheumatoid arthritis pathogenesis, NCBI, Yap et al (2018)

In addition to that there are several potential mechanisms of immunologic activity that may be related to hormones including glycosylation of autoantibodies and alterations of T and B cell function, and these may be important in early development of RA and in established classified disease.

DISCUSSION:

Genetic, environmental and immunological factors play different roles during the pathogenies of rheumatoid arthritis, which despite its heterogeneous nature, shares a common clinical phenotype. Guo et al. (2018) have differentiated the development of RA progression into four stages, which might occur sequentially or overlap.

Triggering:

The appearance of ACPA has been linked to the interaction between certain genetic and environmental factors. The strongest genetic factors associated with ACPA- positive RA known as shared epitope are found in HLA-DR1 and HLA-DR4. However, a genome-wide association study by Padyukov et al. (2011) found a distinct genetic aetiology of ACPA-positive and ACPA-negative RA which is mainly confined to the HLA region and that result in differential immune response to citrullinated antigens.

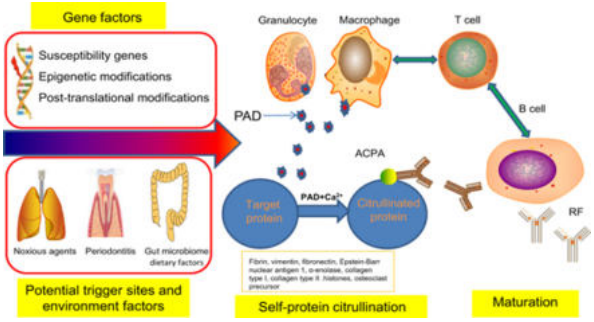
Several environmental factors trigger the production of ACPA in RA with epigenetic factors regulating the gene-environment interaction. Smoking, periodontitis, and gut microbiome have been implicated in stimulating citrullination of self-proteins, leading to the creation of new antigenic epitopes 'neoantigens' with the production of autoantibodies against these citrullinated peptides. Interestingly, a study by Hensvold et al. (2015) investigated the role of genetic and environmental factors in the development of ACPA and ACPA-positive RA in a cohort of 12590 twins revealed that environment, lifestyle and stochastic factors may be more important than genetics in determining which individuals develop ACPA; however,

genetic factors, particularly shared epitope, may have a relatively larger role in determining which ACPA-positive individuals will ultimately develop arthritis.

Maturation:

Immunological factors play an integral role in this stage of pathogenesis which is also called 'loss of tolerance'. ACPA represents abnormal antibody response to a range of citrullinated proteins distributed in the whole body (fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1, α-enolase, type II collagen, and histones); in addition, many citrullination neoantigens would stimulate MHC class II-dependent T cells that in turn would help B cells produce more ACPA resulting in pain, bone loss and inflammation in RA.

The following figure by Guo et al (2018), clearly demonstrate triggering and maturation stages of RA.



(4) Figure: Triggering and maturation stages of RA.

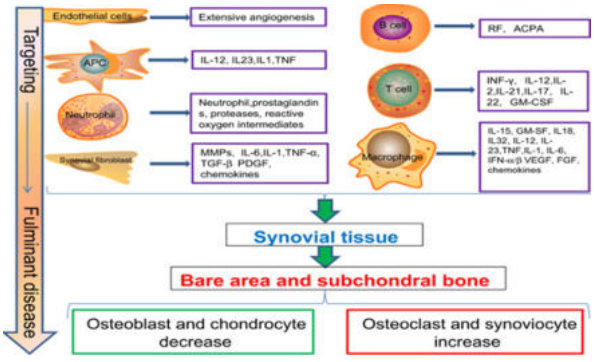
Targeting stage:

Immunological derangements result in the targeting stage where the synovium is infiltrated by leukocytes and the synovial fluid is filled with pro-inflammatory cytokines. Fibroblast-like synoviocytes interact with the disordered innate immunity and adaptive immunity, with failure to resolve inflammation and ultimately leading to chronic synovitis. Endothelial cells contribute to angiogenesis, and the imbalance between pro-inflammatory M1 and anti-inflammatory M2 macrophages contributes further to the pathogenesis.

Fulminant stage:

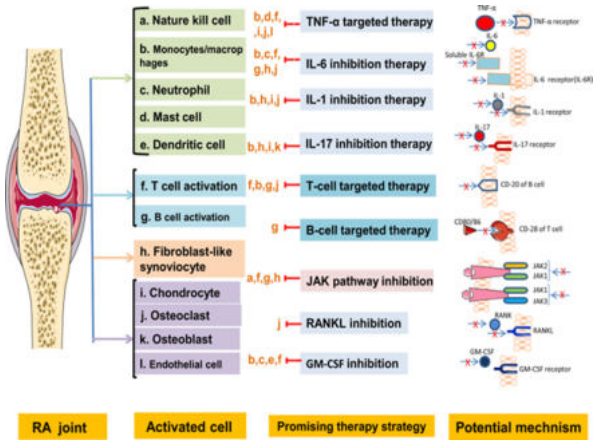
Hyperplastic synovium, cartilage damage, bone erosion, and systemic consequence are all manifestations of the fulminant stage where inflammatory cytokines and proteinases lead to abnormal proliferation of fibrocyte-like synoviocytes. Bone erosions occur at the spots where the synovial membrane inserts into the periosteum, and subchondral bone destruction results in articular cartilage degeneration as the result of a decrease in osteoblasts and an increase in osteoclasts and synoviocytes.

The following figure by Guo et al. (2018) explain the targeting and fulminant stages of RA.



(5) Figure: Targeting and fulminant stages of RA.

This deeper understanding of RA resulted in innovation in the medical therapeutics that target this complex pathology at several points which led to better outcomes and prognosis; the breakthrough implementation of biological agents in RA treatment is the best example for that. Brumester (2019) summarised the action of biological agents in RA and other autoimmune disease into those interfering with cytokine function, signal transduction or production, agents that inhibit the "second signal" required for T-cell activation and those which deplete B cells. These agents gave "a lease on life" for patients who were resistant to previously used medications (Fan and Leong 2007), and improved the health-related quality of life in patients with active RA (Strand and Singh 2012). Guo et al. (2018) have clearly described theses targets in the following diagram.



(6) Figure: Cells and key receptors/pathways targeted by current therapy strategies. RANKL receptor activator of nuclear factor-KB ligand, JAK Janus kinase/signal transducers.

Prevention of RA is another interesting area of research that started to prosper after deeper understanding of RA pathogenesis, several studies have had investigated different therapeutics' effects in patients with high risk for RA, although with inconclusive results.

CONCLUSION:

The pathogenesis of rheumatoid arthritis is a complex process, with variable contributions from genetic, environmental and immunological factors. This is reflected in a wide range of clinical presentation and complications, and at the same time it opens the doors for diverse treatment and preventive modalities. Taking this complicity in consideration, treatment decisions should be individualized. Promoting healthy lifestyle and exercise, well balanced diet, smoking cessation and oral hygiene may each play a favourable role in patients with or at high risk for RA. Determining patient's specific HLA type and other genetic factors might be useful with predicting prognosis and guiding treatment in patients with RA; however, this role is still investigational and further research is needed to establish evidence-based guidelines for treatment and prevention of RA.

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