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Review Article

A Review on Pathogenesis and Treatment of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a multisystem, chronic inflammatory disease with autoimmune characteristics that has no known ethology. It is characterised by distinctive joint abnormalities and a higher death rate. Several cytokines, particularly interleukin-1 and tumour necrosis factor-a, are significantly involved in the induction and maintenance of the chronic inflammatory process of the joints in RA as well as in the systemic manifestations of the disease, suggesting that a number of factors contribute to the pathogenesis of this serious disease. The degeneration of the rheumatoid joint may also be influenced by other elements including metalloproteinase and reactive oxygen species. Despite the best usage of existing ant rheumatic drugs, many RA patients experience discomfort, significant functional loss, and early mortality. This is because present therapies for RA are insufficient since they only partially manage established RA. The necessity for novel therapeutic regimens with the potential to effectively regulate the inflammatory process in the rheumatoid joint and to generate long-term remission or perhaps cure is underscored by the recent statistics about the prognosis of RA with the use of the present medicines. The primary treatment objective is to regulate the production and activity of the factors involved in the pathophysiology of the illness. Neutralising one or a few of the many variables that contribute to the pathophysiology of RA may not have much of an impact. Because it inhibits the majority of the major factors involved in the pathophysiology of the illness rather than being restricted by its inhibitory actions to a single component, interleukin 4 may be a very promising drug for a successful therapy of RA in this regard. Controlled long-term clinical trials should be conducted to demonstrate the validity and efficacy of this potential method, even if recent studies clearly support it when used with interleukin-4

INTRODUCTION

A systemic autoimmune disease that causes progressive joint deterioration, rheumatoid arthritis (RA) is characterised by symmetric synovial joint inflammation. The etiology and pathophysiology of RA remain poorly understood

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despite the disease's significant research. However, it is evident that cytokines are a major factor in activating synovial cells, which causes inflammation and joint degeneration in arthritic joints[1]. Based on their various contributions to the development of the illness, it is commonly accepted that the cytokines TNF-a, IL-1, and IL-6 are the key actors in the pathogenesis of RA. In order to treat RA, anti-TNF-a and anti-IL-1 medicines are now available. TNF-a and IL-1 have thus been specifically targeted in the development of RA therapy. However, not all RA patients respond well to these medications. Additionally, the use of presently available biologics, particularly anti-TNF-a medications, has drawn criticism due to the elevated risk of infection in patients on cytokine antagonist therapy. As a result, research into novel cytokines and other RA treatment options is ongoing. Immunology research has made significant discoveries on a cytokine called IL-17, which is generated by TH17 cells. Evidence suggests that the cytokine IL-17 has potent pro-inflammatory effects and can increase inflammation brought on by other cytokines, including TNF. Additionally, IL-17 may encourage bone and joint deterioration by activating osteoclasts and matrix metalloproteinases. Inhibition of IL-17 slows the progression of inflammation and joint damage in various animal models of RA. A novel member of the type I cytokine superfamily, IL-21 binds to a composite receptor made up of the common cytokine receptor chain and the private IL-21R receptor. T cells from a patient with RA's peripheral blood or synovial fluid released a lot of cytokines after being stimulated by IL-21, however blocking IL-21 greatly reduced the amount of inflammatory cytokine production in RA synovial cell cultures. Additionally, it has been demonstrated that inhibiting the IL-21/IL-21R pathway improves illness in RA animal models[2].

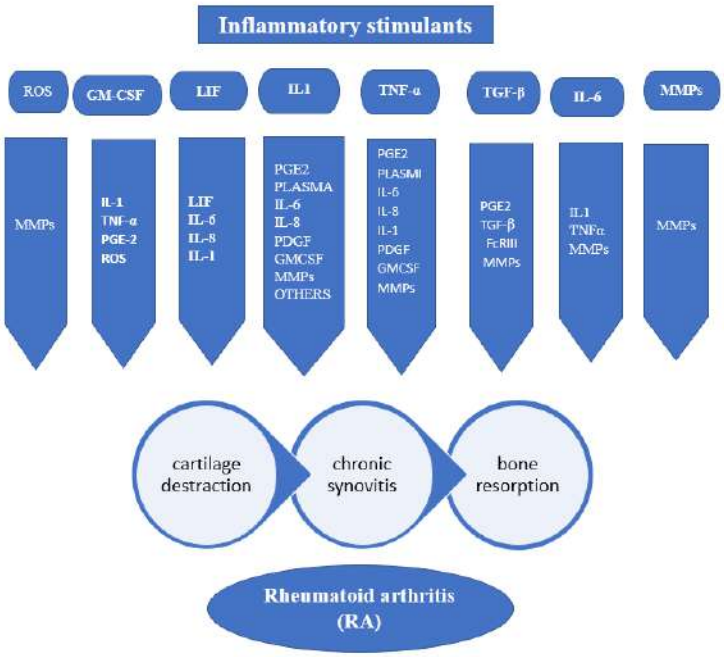

Fig: Diagram showing the roles played by cytokines and other elements in the development of RA.

PATHOGENETIC ASPECTS OF RA

Although a genetic basis involving the MHC II complex has been suggested, the exact cause of RA remains unknown. RA is more likely to develop in people with the HLA-DR4 haplotype, and extra-articular involvement and a more severe course of the illness are more common in people with the "shared epitope" allele. A connection

between bacterial and viral infections and polyarthritis in vulnerable individuals has also been suggested. In fact, viral illnesses such the parvovirus and rubella can cause arthritis that resembles RA. As with lyme disease, persistent bacterial infection can also cause arthritis. with animal models, chronic arthritis can also be brought on by bacterial cell wall fragments. However, no infectious agent responsible for the disease has ever been identified from RA patients. Despite the fact that the precise relationship between the immune system and synovial inflammation is still unknown, research on animal models of RA has made substantial progress in identifying its pathogenetic components. An damage to the synovial vasculature is observed after the RA starting event, which is followed by an influx of T lymphocytes, primarily of the CD4 memory type[3]. Antigen-presenting cells in the synovium then further activate these cells in response to (unknown) (auto) antigens. These CD4+ cells are unmistakably of the Th1 subtype; they generate interferon (IFN), interleukin-2 (IL-2), tumour necrosis factor (TNF), and interleukin-17 (IL-17), which in turn activates monocytes, macrophages, and fibroblasts through cell-cell interaction and the release of these cytokines. By producing IL-8, the latter cells draw in and stimulate neutrophil granulocytes[4]. Neutrophils are present at the cartilage junction zone, but a far greater number of cells aggregate there and generate a variety of cartilage-degrading enzymes, including metalloproteases. Within the synovial membrane, B cells, dendritic cells, T cells, and macrophages create different autoantibodies in the form of lymphoid follicle-like structures. such as autoantibodies that target the Fc fragment of IgG, or rheumatoid factor. Patients with RA may deposit these autoantibodies in their cartilage in the form of immune complexes[5]. It is unclear whether the onset of autoimmunity is a lone primary, a coprimary, or a secondary event, but it is at least believed to have an impact on the continuation of the inflammatory cascade since immune complexes can trigger macrophages to secrete proinflammatory cytokines[4]. As the condition progresses, a variety of cells, including B cells, macrophages, fibroblasts, neutrophil granulocytes, dendritic cells, and many more, severely enter the normally relatively avascular synovium. Up to 30 cell layers of synovial lining can form, most likely as a result of macrophage infiltration and synovial fibroblast growth. In particular, TNF, IL-1, and IL-6 are highly produced by the latter. The illness is further fueled by the presence of several additional cytokines, including chemokines, angiogenic molecules, and others like IL-17, IL-18, and IL-15 in the inflamed synovial membrane. These pro inflammatory cytokines then stimulate signalling pathways and transcription factors, which in turn regulate cytokine transcription[6].

Role of synovial fibroblasts

Synovial fibroblasts in RA pathogenesis

As the illness worsens, synovial tissue in RA experiences considerable synovial fibroblast growth and infiltration into surrounding tissues, which regulates tissue homeostasis, modifies the inflammatory response, and mediates tissue damage. The activation, differentiation, and proliferation of RA synovial fibroblasts are significantly influenced by a number of transcription factors, including nuclear factor-kappa B (NF-B) and activator protein 1. The production and activation of matrix-degrading enzymes, such as matrix metalloproteinases, aggrecanase, and cysteine pro teases, which are important enzymes in joint degeneration, are regulated by these transcription factors. In a rat model of pristane-induced arthritis and the synovial tissue of RA patients, an endoplasmic reticulum stress-related protein was shown to be increased, and intra-articular injection of si-Derl3 relieved the condition. In synovial fibroblasts from

RA patients, serum amyloid A protein stimulates the synthesis of IL-6 and chemokine (C-C motif) ligand 20 through the activation of NF-B and mitogen-activated protein kinases (p38 and JNK1/ JNK2). As discussed before, synovial fibroblasts support the ongoing inflammation that causes RA joints to deteriorate. The subgroups of fibroblasts have been found in recent transcriptome investigations, including single-cell RNA sequencing (scRNA-seq). These pathogenic fibroblasts localise near blood vessels in the inflamed synovium, secrete proinflammatory cytokines such as IL-6, C-X-C motif chemokine ligand 12, and C-C motif chemokine ligand 2, are proliferative, and have a phenotype typical of invasive cells in vitro. Similarly, multiomics analysis, including scRNA-seq, revealed that this subset, which is characteristic. These HLA-DRAhi sublining fibroblast-expressed genes have a connection to the presentation of the major histocompatibility complex class II and the interferon gamma-mediated signalling pathway linked to increased expressions of the IL6 and CXCL12 genes[7].

B cells in RA pathogenesis When it comes to the development of antibodies, notably RF and anticyclic citrullinated peptide antibodies (ACPA), B cells play a crucial role in the pathogenesis of RA. Comparatively to RA patients who are seronegative, those with persistently positive RF and/or ACPA are more likely to experience decreasing function, increasing erosions of the bones and joints, and extra-articular symptoms. Additionally, early in the course of the disease, B cells begin to produce the RA-specific antibodies ACPA and anticarbamylated peptide antibodies. As a result, the positive effects of B lymphocyte reduction on joint inflammation seen in clinical studies further corroborate the significance of B lymphocytes in RA aetiology. Citrullinated proteins play a crucial role in the pathophysiology of RA. Additionally, peptidylarginine deiminases on -enolase, vimentin, fibrin, fibrinogen, and many other proteins catalyse the citrullination of arginine residues, which takes place as a result of the delimitation of these residues in rheumatoid joints. Recent years have seen the publication of studies examining the possible diagnostic utility of synthetic peptides containing citrullinated epitopes, which are regarded to be crucial in the diagnosis of RA. The measurement of Cit-ME-vimentin peptides may have an advantage over commercially available kits for the diagnosis of RA, according to a study that compared the enzyme-linked immunosorbent assay measurements of three citrullinated peptides (CCP3, Cit-ME-vimentin, and Cit-ME-enolase) with sera from patients with RA. According to a cohort study evaluating the clinical effectiveness of anti-cetrullinated alpha-enolase peptide-1 (CEP-1) antibodies in Chinese RA patients, those with anti-CEP-1 positivity had significantly more disease activity and bone destruction than those with anti-CEP-1 negativity8,9.

T cells in RA pathogenesis T cells have a crucial role in immunological RA responses. About 50% of RA synovial cells are activated T cells, which are important in the stimulation of adaptive immune responses. These are mostly memory CD4 T lymphocytes with strong HLADR antigen expression. The T helper 1 (Th1) and Th17 subsets of T cells are the predominant T cell subsets, but Th2 and regulatory T cells do not seem to be present. Additionally, it has been discovered that RA patients have much more programmed cell death-1 (PD-1)hiCXCR5 CD4+ T cells in their synovium. These cells seem to encourage B cell responses and antibody production in the inflamed synovium. T cells' effector activity is mediated by cytokines and is dependent on their level of differentiation. For instance, interferongamma, which is crucial for activating macrophages and enhancing phagocytic activity, is secreted by Th1

cells. IL-17A, IL-17F, IL-21, and IL-22 are the main effector cytokines produced by Th17 cells. They are involved in cell recruitment, the production of pro-inflammatory cytokines and chemokines, the stimulation of B cell differentiation, and the activation of natural killer cells. For the treatment of RA, biological treatments that target IL-17 have exhibited very minimal clinical success. Additionally, there is evidence that IL-17A blockers are more clinically effective than placebo in treating RA patients, albeit some clinical trials did not achieve their main objectives. Several IL-17A blockers are widely accessible for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis, in contrast to the failure of IL-17 inhibition for RA. Maximum T cell responses require a second signal, and costimulation is a critical component of T cell activation throughout the RA immune response. CD28 and CD40 ligands are two examples of molecules for which such signals are made available. Both have a high level of synovial T cell expression in RA. Abatacept, also known as CTLA4-Ig, is a B7 (CD80/CD86)-binding molecule that has been fused to cytotoxic T lymphocyte-associated protein 4 (CTLA4-Ig), which has been used to treat RA patients and appears to be more successful in those with RF and/or ACPA positivity than in those who do not. The costimulatory receptor PD-1 plays a crucial role in the upkeep of immunological tolerance and imparts peripheral tolerance to ward against autoimmunity[10,11,12]. Metabolism and signaling in RA pathogenesis Growing evidence points to the significance of cellular metabolism in controlling immune cell activity. Cellular metabolism has been recognised as a possible therapeutic target in the treatment of RA in recent mechanistic investigations. Hexokinase 2 (HK2), which is highly expressed by fibroblast-like synoviocytes and drives their invasive nature, is hyperglycolytic, and HK2 inhibition is a new therapeutic approach. Furthermore, endothelial cell angiogenesis and inflammatory cell infiltration depend on succinate signalling linked to hypoxia-inducible factor-1. Additionally, it has a tight connection to the metabolic circumstances, T cell activation, proliferation, and differentiation. Furthermore, GLUT1 inhibition by T cell-specific deletion or small-molecule GLUT1/ glycolytic inhibitors improved the phenotype of several autoimmune disease models, including graft-versus-host disease, arthritis, lupus, and psoriasis. This is because CD4 cells are particularly crucial for glucose metabolism [70]. Initiating intracellular signalling, cytokines and cell surface molecules interact to their respective receptors or ligands to control the expression of target genes. Tyrosine kinases, transcription factors, and other molecules have all been found to participate in this extracellular to intracellular inflammatory signalling. Additionally, the protein tyrosine phosphatase N22 (PTPN22) gene has a single nucleotide polymorphism that is one of the most significant non major histocompatibility complex genes in the etiology of autoimmune disorders, including RA. Additionally, PTPN22 has a significant role in T-cell receptor-initiated signalling in T cells and is essential for the formation of regulatory T cells in the thymus and The 17 cell differentiation[13,14,15].

Targeting the cytokines

TUMOR NECROSIS FACTOR- α

The type 1 TNF receptor (p55) and the type 2 TNF receptor (p75) are the two receptors that TNF, which was identified in the 1970s, interacts to. Mesenchymal cells (fibroblasts, osteoblasts), monocytes, T and B cells, as well as both of their receptors, may all generate TNF. Cytokines, endotoxins, heat stress, neoplastic transformation, viral agents, and other events can all cause TNF expression. TNF itself promotes osteoclastogenesis, slows collagen synthesis, activates polymorphonuclear leukocytes, natural

killer cells, and cytotoxic T cells, and increases cartilage degradation. TNF's proapoptotic actions are mostly mediated by the p75 receptor (TNF-RII), whereas its proinflammatory effects are primarily mediated by the p55 receptor (TNF-RI). TNF is substantially expressed in the synovium and synovial fluid of people with RA. In the presence of RANKL, a crucial component in osteoclastogenesis, it is very effective in causing monocyte differentiation into osteoclasts. Additionally, synovial fibroblasts produce more proinflammatory cytokines and metalloproteases as a result of TNF, while chondrocytes produce less proteoglycan. The significance of TNF in joint inflammation has been demonstrated in animal studies. Mice with systemic TNF overexpression experience symmetric erosive polyarticular arthritis. Additionally, these mice experience systemic bone loss comparable to that in RA patients. Animal studies showing that TNF inhibition effectively reduces synovial inflammation, cartilage deterioration, and bone erosio are consistent with our findings[16,17].

IL-1 (INTERLEUKIN-1)

Two types of IL-1 are currently recognised: IL-1 is a nonsecreted locally acting version and is detectable in the serum of individuals with an active immune system. IL-1 was first identified as a fever-inducing humoral factor. The type I IL-1 receptor (IL-1R1) is where IL-1 acts, as opposed to the type II IL-1 receptor (IL-1R2), which does not transmit signalling. IL-1 is expelled from cell membranes by the interleukin-converting enzyme (ICE). A naturally occurring counterregulatory cytokine is called IL-1 receptor antagonist (IL-1ra). Signal transmission and activation are prevented by IL-1ra binding to the IL-1 receptor. IL-1 engages the IL-1RI intracytoplasmically, activating Myd88 and TRAF-6 before phosphorylating I-B and releasing NF-B, a proinflammatory transcription factor. Like TNF, IL-1 is generated by a variety of cells, but when there is inflammation, monocytes and macrophages make the most of it. TNF, IL-1, IL-6, and other cytokines are produced by IL-1, and it also stimulates osteoclastogenesis, promotes the development of metalloproteases that break down cartilage and matrix, increases chemokine production, and contributes to neoangiogenesis[18,19,20]. The significance of IL-1 in joint inflammation was suggested by animal models. In the collagen-induced arthritis (CIA) model, injection of IL-1 causes joint inflammation in the knee joints, and suppression of IL-1 by administration of either IL1ra or antibodies against IL-1 significantly reduces joint inflammation, cartilage loss, and bone erosion. Furthermore, RA-like illness with erosive polyarthritis manifests in IL-1ra deletion animals. Inhibition of IL-1 is substantially less effective in TNF-driven RA models, such as adjuvant-induced arthritis (AIA) and TNF transgenic mice. IL-1 levels in synovial fluid samples and rarely in blood from RA patients are correlated with disease activity. In RA synovial tissues, increased IL-1 expression and reduced IL-1ra production have been found, pointing to an unbalanced IL-1/IL-1ra ratio. The ability of IL-1 to degrade cartilage was revealed in ex vivo investigations using synovial fibroblasts[21].

IL-6 (INTERLEUKIN-6)

IL-6 was first identified in 1982 as a marker of B cell development. It is a member of the helical-structured cytokine family that includes IL-11, oncostatin M, cardiotrophin-1, and ciliary neurotrophic factor as well as the leukaemia inhibitory factor. In order to attach to gp130, which serves as the IL-6 family of cytokines' common signal transducer, IL-6 first binds to the membrane-bound IL-6 receptor (gp80). As an alternative, IL-6 can bind to soluble IL-6R and subsequently bind to membrane-bound gp130 to provide signal transduction. Numerous different types of cells, such as T cells, B cells, macrophages, fibroblasts, endothelial cells, and

tumour cells, release IL-6. Additionally, it causes macrophages to terminally differentiate and functions as a growth factor for both T and B cells. It is also a stem cell growth factor and improves megakaryocyte differentiation into platelets. Mice that are IL-6 transgenic provide more proof of the hormone's physiological significance in vivo. These mice experience a variety of side effects, including increased megakaryopoiesis, polyclonal plasmocytosis with autoantibody production, elevated fibrinogen levels and decreased serum albumin, and eventually, mesangial proliferative glomerulonephritis and lymphocytic interstitial lung disease. Anti-IL-6R antibody therapy improves illness in these animals[22].

IL-15 (INTERLEUKIN-15)

IL-15, which functions similarly to IL-2, was initially reported in 1994.90 Although it also needs its own receptor chain, IL-15 utilises parts of the IL-2 receptor. It is macrophages that largely generate IL15. Production of IL-15 is stimulated by infectious agents (BCG), TNF, IL-1, and cell-cell interactions (T cell-macrophage). Because many human organs only express IL-15 mRNA and not the protein, IL-15 is carefully controlled. Both the transcriptional level and the post-transcriptional level are regulated. In both in vitro and in vivo settings, IL-15 promotes T cell migration and proliferation. By stimulating the production of IFN-, IL-15 directs naïve T cells in a Th1-type direction. Furthermore, recombinant human (rh)IL-15 can cause a local inflammatory infiltrate with just one intradermal injection. CD3+ T cells make up the majority of these cell clusters.93 Additionally, IL-15 causes toxicity in natural killer cells.94 Additionally, IL-15 attaches to macrophages and triggers the production of TNF, IL-1, and IL-6. IL-15 increases the expression of the osteoclast lineage markers calcitonin receptor and TRAP and stimulates the differentiation of bone marrow mononuclear cells into osteoclast precursors.

The inquiry into IL-15 expression in RA was prompted by IL-15's pro-inflammatory effects. The presence of IL-15 in RA synovial tissue has been known since 1996, although it is much less frequently found in reactive arthritis or osteoarthritis (OA) synovial samples. The bulk of the IL-15-positive cells were macrophages and fibroblasts, which were seen in the synovial lining layer, sublining layer, and perivascular aggregates. Additionally, soluble (s)IL-15 was found in RA synovial fluid samples but not in those from OA patients, and sIL15 levels linked with TNF levels in synovial fluid[23].

NEW STRATEGIES FOR THE TREATMENT OF RA

The inability of current therapeutic agents to completely cure RA or even to induce long-term remission highlights the need for new therapeutic regimens that are capable of effectively controlling the inflammatory process in the rheumatoid joint. A key treatment objective is to regulate the synthesis and activity of the components implicated in the pathophysiology of the synovitis in RA. Since many factors play a role in the pathogenesis of this autoimmune disease, removing one or more of the factors may only have a limited positive effect. This necessitates the use of a variety of antagonising agents in combination to eliminate all or the majority of the effects of the dominant mediators involved in the pathogenesis of RA. However, the use of numerous medications in combination may result in lower compliance and a higher incidence of adverse effects. Therefore, the best strategy for developing an effective therapy for RA is to look for a single medication that has the capacity to successfully antagonise the majority, if not all, of the primary disease mediators. One such substance may be interleukin 4 (IL-4). A tiny soluble glycoprotein called IL-4 is released by mast cells, basophils, and activated T lymphocytes. It works in concert with other cytokines to regulate the immune response

and the proliferation and differentiation of hematopoietic cells. It also affects nonhematopoietic cells in a number of different ways. Recent research has shown that IL-4 is a potent anti-inflammatory compound. The secretion of IL-1, TNF-a, and IL-6 by activated monocytes was shown to be significantly inhibited by this cytokine, and this suppression happened, at least in part, at the level of mRNA. In an ex vivo model of persistent RA synovitis, IL-4 was also shown to inhibit these cytokine outputs from rheumatoid synovial explants. Long-lasting and active at low quantities, IL-4 inhibited all three cytokines. Additionally, since anti-IL-4 antibody could stop IL-4-induced suppression of cytokine production, the observed inhibition was specific for IL-4. Additionally, a recent study using an ex vivo model of bone resorption in RA showed that IL-4 inhibits bone resorption. This suppression occurred as a result of IL-4 inhibiting osteoclast activity and survival as well as proinflammatory cytokine release. Furthermore, it has recently been demonstrated that IL-4 is a powerful inhibitor of the harm to articular cartilage caused by TNF-a, IL-1, and synovial inflammatory cells[24].

Myelomonocytic cells respond to IL-1 through the IL-1 type I receptor (IL1R I), whereas IL-1R II suppresses IL-1 activity by serving as a dummy target for IL-1. It has recently been shown that IL-4 inhibits the synthesis of IL-1 as well as the activity of IL-1 by causing the development and release of a soluble version of IL-1R II. A naturally occurring IL-1 inhibitor has also been demonstrated to decrease IL-1 activity by challenging IL-1 for occupancy of the type I receptor. It has been demonstrated that the naturally occurring antagonist, known as IL-1 receptor antagonist, is upregulated by IL-4. Both in vitro and in vivo, the lifespan of human polymorphonuclear leukocytes is constrained. These cells are greatly encouraged to survive by IL-1, which might exacerbate the inflammatory response in the rheumatoid synovium. The impact of IL-1 in promoting the survival of these cells is nearly entirely reversed by IL-4. These IL-1 activity-inhibiting processes might be some of the means by which IL-4 works as an anti-inflammatory[25]. A type of receptors known as Fc RIII (CD16) can be found on mature tissue macrophages or on monocytes directed to inflammatory areas. The up-regulation of these receptors results in respiratory burst activity and the production of the oxygen free radical superoxide anion. They may play a significant role in triggering immunophagocytosis. These outcomes might exacerbate tissue damage in persistent inflammatory lesions, including RA. TGF-6, which is abundant in the RA synovial fluid, has the ability to efficiently up-regulate the expression of CD16 on the mononuclear leukocytes that make up the synovial fluid, which might lead to the induction of respiratory burst activity and the production of superoxide radical. It has recently been demonstrated that IL-4 effectively reduces TGF-6's capacity to stimulate CD16 expression. Since it has the potential to down-regulate, IL-4 is the only factor that accounts for the observed inhibition. Following treatment with polyclonal IL-4 antibodies, CD16 expression is entirely suppressed[26].

Despite the many T cells that infiltrate the rheumatoid synovium, IL-4 is essentially undetectable in RA synovial fluids. These fluids include substances that prevent both normal lymphocytes from producing IL-4 and from using IL-4 to stimulate T cell development. It indicates that TGF-B contributes to the inhibition of IL-4 production.

CONCLUSION:

It is still unknown what causes RA to begin. Infections, generalised inflammation, and injuries are some of the potential triggers for the condition. However, other factors may have an impact on the disease's pattern and course. It is obvious that

different HLA-DRB1*04 allelic variations affect the development of RA and the severity of the clinical symptoms. Strong data suggests that T cells are crucial to RA. They play a significant role at several disease checkpoints. T-cell helper activity is crucial for the development of complex lymphoid structures in the synovial membrane, which affects how devastating synovitis is. However, the joint is not the only location of aberrant T-cell immunity in RA. Massive T-cell pool abnormalities that are seen in RA point to a root cause of T-cell homeostasis dysfunction. A rheumatoid T-cell compartment has a restricted diversity due to the formation of sizable clonal T-cell populations, in contrast to a normal T-cell compartment that is very diverse and contains a vast spectrum of various T cells. Patients with RA who have expanded T-cell clonotypes have functional traits that make them potentially tissue-damaging effector cells. Therefore, novel therapeutic strategies for RA should T cells in RA pathogenesis 7 aim to prevent T-cell activation in the synovial membrane and attempt to restore the diversity of the T-cell compartment by preventing the spread of T-cell clonotypes and by encouraging the generation of new T-cells.

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