

REVIEW ARTICLE

Role of Cytokines in Pathogenesis of Rheumatoid Arthritis-A Review

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ABSTRACT

Introduction-Cytokines are polypeptides autacoids produced by phagocytes and some other cells. A large number of cytokines are active in the joints of patients with rheumatoid arthritis (RA). It has been evidently proved that cytokines play fundamental role in bone reabsorption and connective tissue destruction and also in complications associated with RA. **Aim**-By knowing the sinister role of cytokines to induce rheumatoid arthritis in patient, the present study is focused on the review of different cytokines which involve in the pathogenesis of the disease.

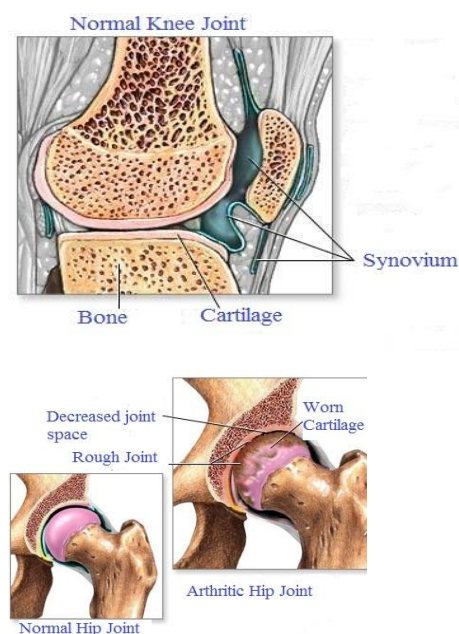
Result-From the literature available from different article on cytokines it is clear that cytokines like Tumor necrosis factor (TNF- α), chemokines and Interleukins (IL) are responsible for the pathogenesis of rheumatoid arthritis.

Conclusion-from the previous literature it was concluded that Cytokines are responsible for the pathogenesis of rheumatoid arthritis. Safe intervention can be evaluated by understanding this fact.

Introduction (Greek *cyto-*, cell; and *-kinos*, movement) [1]- Cytokines are known to be pivotal mediators in the RA process. Cytokines are polypeptide substances produced by activated lymphocytes (lymphokines) and activated monocytes (monokines) may act on self cell producing them or on other cells [2]. These polypeptides are known to mediate some aspect or other of the inflammatory process. The effector phase of both natural and acquired immunity are in large part mediated by cytokines [3] Cytokines are diverse meaning and are not alike. Different types of cytokines are produced by cells like i) colony stimulating factor which stimulate production of blood cells ii) Growth and differentiation factor which function primarily in development and immunoregulatory and proinflammatory cytokines Cytokines include interleukins, interferon and TNF- α that function in immune system[4]. Cytokines interact with cells of the immune system in order to regulate the body's response to disease and infection. Cytokines also mediate normal cellular processes in the body. Cytokines serve as molecular messenger between cells, with regard to arthritis, cytokines regulate various inflammatory responses [4] Overproduction or inappropriate production of certain cytokines by the body result in arthritis. For example, it has been found that interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) are produced in excess in rheumatoid arthritis where they are involved in inflammation and tissue destruction. Cytokines act in the response of injury where it helps to exert innate immune response. The innate immune system which act as double edged sword for the host [5]

Many pro-inflammatory cytokines including TNF- α , chemokines and growth factors are expressed in diseased joints. Rheumatoid arthritis joint synovial membrane infiltration and cartilage degeneration whereas a normal joint show a normal cartilage and proper shape of synovial membrane. Proinflammatory cytokines like TNF- α and IL-1 β are meant mostly to be involved in the rheumatoid arthritis. Single cytokine is alone able to exert its pleiotropic activity and different cytokines combinely shows redundancy [6] like TNF- α alone can induce inflammation, fever, sleep anorexia and alteration in neuroendocrine system whereas the overproduction of TNF- α , IL-1, IL-6, IL-17, IL-18 and so many other interleukins shows their action to induce RA. The Fig1&2 depicted below are showing a normal knee joint and arthritic joint.

Fig1&2[7]



Proinflammatory cytokines like TNF- α , IL-1, IL-6, GM-CSF and chemokines like IL-8 play a pivotal role in the pathogenesis of Rheumatoid arthritis [8]. It is now accepted that TNF- α and IL-1 play a major role in RA [9]. Cytokines are a group

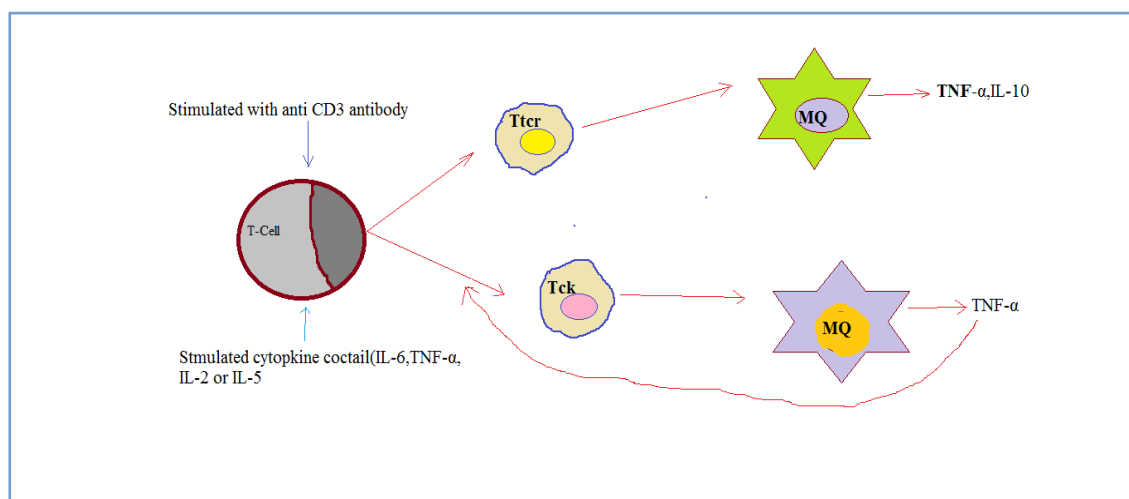
of chemicals like Tumor necrosis factors (TNF) and Interleukins (IL). The member of tumor necrosis factor involve TNF- α , TNF- β and TNF- γ whereas interleukines involve IL-1, IL-2, IL-6 and IL-23 and many more. The most involving cytokines in the RA are TNF- α , IL-1; IL-6 and IL-2. Several researchers have reported the role of these cytokines in the pathogenesis of RA. Present study is therefore focused on the review on the role of cytokines (TNF- α and IL-1 to IL-10) in RA.

Material

TumorNecrosisFactor (TNF)

TNF- α was identified in 1975 as the factor in serum isolated from endotoxin treated mice [10,11] It is a pleiotropic, pro-inflammatory, pro-apoptotic cytokine that regulates the activity of neutrophils, eosinophils, and T & B lymphocytes and modulates the properties of the vascular endothelium.

Tumor necrosis



factor (TNF), cachexin or cachectin formerly known as tumor necrosis factor alpha or TNF- α is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction [12]. It is produced chiefly by activated macrophages, although it can be produced by other cell types as well. The primary role of TNF is in the regulation of immune cells.

Being an endogenous pyrogen, TNF is able to induce fever, induce inflammation, to induce apoptotic cell death, to induce cachexia, to induce sepsis (through IL1 & IL6 production), and to inhibit tumorigenesis and viral replication. The primary role of TNF is in the regulation of immune cells. It has been found that dysregulation of TNF production leads to induce variety of human diseases, including Alzheimer's disease,[13] inflammatory bowel disease (IBD)[14], cancer [15] and major depression[16] .

Role in pathogenesis of arthritis. The actions of TNF- α is important in the pathogenesis of RA include its ability to induce the production of other proinflammatory cytokines, including IL-1 and IL-6, together with its ability to induce the production and release of chemokines. TNF- α is a pleiotropic, proinflammatory mediator which is

produced in response to infection to confer immunity to the host. It is now accepted that TNF and IL-1 produced locally in the inflamed synovial joint contribute directly or indirectly to the pathogenesis of rheumatoid arthritis(RA)[17,18]. The effect of the TNF- α in infection is beneficial but tight regulation of TNF- α production is required to protect the host from its detrimental

activities. Deregulated production of TNF- α is thought to play pivotal role in pathogenesis of RA. T-cells are found responsible for the secretion of TNF by direct contact mediated interaction. Histological studies of synovium in RA have indicated that this tissue is very cellular and that several different cell type including macrophages and T-cells are in close proximity[19] Direct contact mediated interaction using transformed T-cells and monocytes have been found to play a major role in inducing the release of TNF- α , IL10 and metalloproteinase [20-21] specific surface interaction molecule that are reported to mediate induction of monocyte cytokine synthesis includes CD69, IFA1[20,25,26] CD44[27] CD40[28], membrane TNF[29] and signaling lymphocytic activation molecule[30].

Fig3.Figer is showing cytokine dis equilibrium induced by cytokine stimulated T-cell (Tck), monocytes(MQ),monocytes(Tcr) cell receptor dependent stimulated T cells.

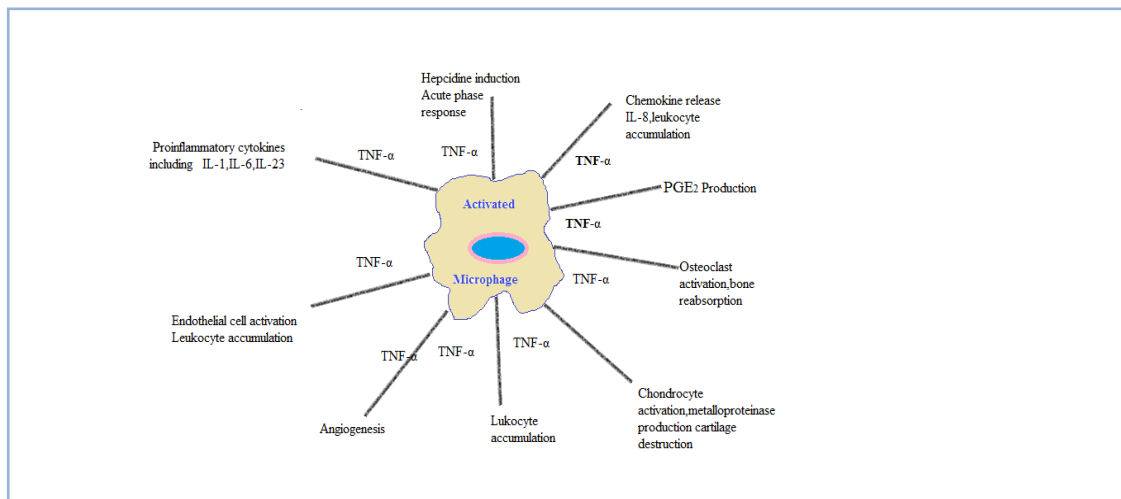
Evidences for the role of TNF- α in the pathogenesis of RA has been reported by showing its presence in synovial fluid [29,30]. The role of TNF- α in early joint swelling in RA has found [30].

The presence of TNF- α in rheumatoid arthritic serum and synovial fluid has been presented by using several experimental models for rheumatoid arthritis. Significant concentrations of TNF- α and IL-1 has been reported in arthritic joints of experimental antigen induced arthritic rabbit [31].

In one of the study TNF- α has been reported to be secreted by activated mast cells. Mast cells are equipped with F_C receptors for binding to autoantibodies and the receptor for binding to complement usually in the form of antibody compliment complex. Mast cell produces large amount of TNF- α and IL-1 cytokines that play a critical role in perpetuating the inflammation. Mast cell might have received the signal when bound by autoantibodies and complement fragments and release TNF- α and IL-1, contributing to the pathology in the synovium that result in erosive arthritis [32]

Mechanism of TNF- α to lead inflammation to RA has explained by one more way as TNF- α is responsible to trigger the release of other cytokines like proinflammatory cytokines (IL-1,IL-6,IL-23 and GM) together with its ability to induce the production and release of chemokines (IL-8) that attract leukocytes from the blood into inflamed tissue. This process is facilitated by upregulation of key integrins and adhesion molecules on endothelium which finally causes the destruction of proteolytic and metalloproteinase enzyme which bring about the destruction of subchondrial bone [25] (fig-4).

Fig-4



Control on overproduction of TNF- α .

Overproduction of TNF- α is regulated by using TNF- α inhibitors and also called TNF- blockers. These blockers bind to TNF- α and prevent TNF- α attaching to cell surface receptors. Enbrel (Etanercept), remicad (Infliximab) and humiradalimumab are TNF blockers [1]

Interlukines-(inter-in;lukine-leukocytes).

Interlukines are the another member of cytokines which are meant play a major role in the pathogenesis of RA. The role of different interlukines in the pathogenesis of RA is discussed here one by one.

Interleukin -1(IL-1)- Role of IL -1 cytokine in the pathogenesis of RA has been implicated by significant experimental evidences. To understand the role of cytokines in RA the different cells involved should be discussed. The pathogenesis of RA depends upon a number of cell types (Fig-4). Macrophage after activation express HLA-Class II molecule. Because of their proximity to T-cell they may function as antigen presenting cell and perpetuate immunological response within the joint. Chondrocytes get involved in these

properties and have the ability to produce cartilage specific antigen. In RA chondrocytes release degredative enzyme and reduces its capacity to synthesize new matrix components. T-cells in the rheumatoid joints have a memory CD4+ phenotype which express various activation markers and are found in close proximity to antigen presenting cells[33,34]. β -Cells are also found in large number in the rheumatoid joints[35] β -Cells are responsible to produce immunoglobulines and autoantibodies i.e. rheumatoids factor and anticholagen antibodies which form immune complexes that can local inflammation as well as IL-1 and TNF- α released by macrophage. Another type of cell which plays a role in pathogenesis of RA is synoviocytes and endothelial cells. These cell express specific cell adhesion molecule (CAM) on their surface along with intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin which control the infiltration of inflammatory cells into the joint. The fibroblast like synoviocytes predominates into the pannus[33] IL-1 and TNF- α upregulates the expression of CAMs on endothelial cell their by directing emigration of blood cells from circulation into the synovium[36,37]. These

cytokines also stimulate synoviocytes and chondrocytes to release MMPs and other proteanase that degrade cartilage. They upgrade the expression of proinflammatory genes

including cyclooxygenase II and nitrous oxide synthase which in turn lead to increase in the release of PGE2 and nitrous oxide[36] (Fig-5)

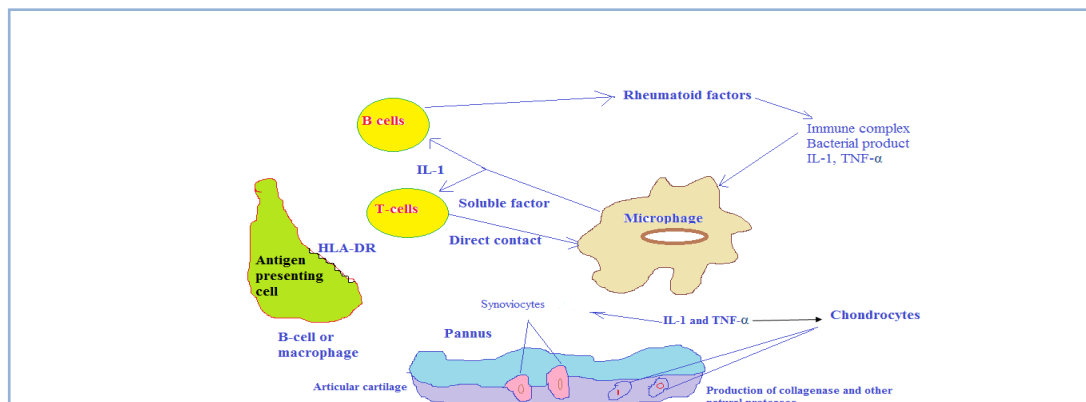


Fig-5.figure is showing the role of IL-1 and cells involve in the Pathogenesis of RA.

IL-1 Family consist of three members viz IL-1 α , IL1 β produce the biological effects attributed to the cytokines and IL-1 receptor antagonist(IL-1Ra) is an endogenous inhibitor that block the action of the other two members [36-40]. The three dimensional structure of the family members are related.Each member in the family has a distinct amino acid sequence. IL-1 α , and IL-1 β are produced as 31kDa precursor protein and termed as pro IL-1 α and pro IL-1 β . Both IL-1 α is generally retained within the cell or expressed on the cell surface which is believed to act as autocrine messenger. IL-1 β is secreted then and act on other cell to produce its biological action.IL-Ra is synthesized and secreted as 17kDa

proteins by the same cell. Each members of IL-1 binds with high affinity to specific receptor located on the surface of the target cell. Binding of IL-1 α or IL-1 β to type 1 IL-1 receptor (IL-1R1) which is enhanced by an accessory protein IL-1R-AcP leads to intracellular signals transduction and regulation of gene expression and as a result cellular responses (Fig-5) Begning to the type II IL-1 receptor (IL-1RII) on these cells does not cause cell activation because the receptor contain very short cytoplasmic domain that is unable to signal transducer signal following IL-binding. Therefore IL-1R-II receptor acts as decoy receptor. Il-1Ra binds to both IL-1RIand IL-1RII and does not induce signal transduction. Instead,it competitively antagonize the binding of IL-1 α and IL-1 β and thereby reducing the effect of these cytokines.(Fig-6)

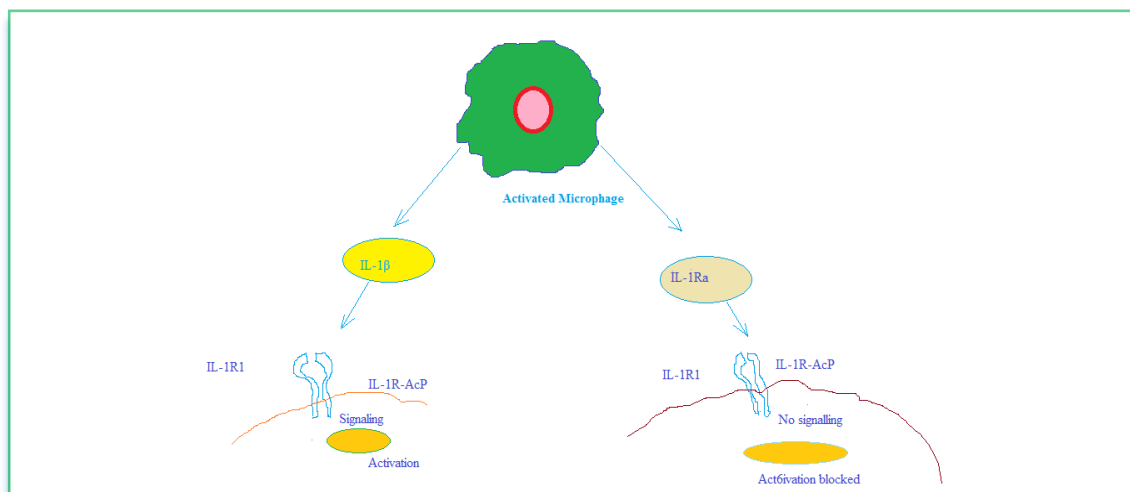


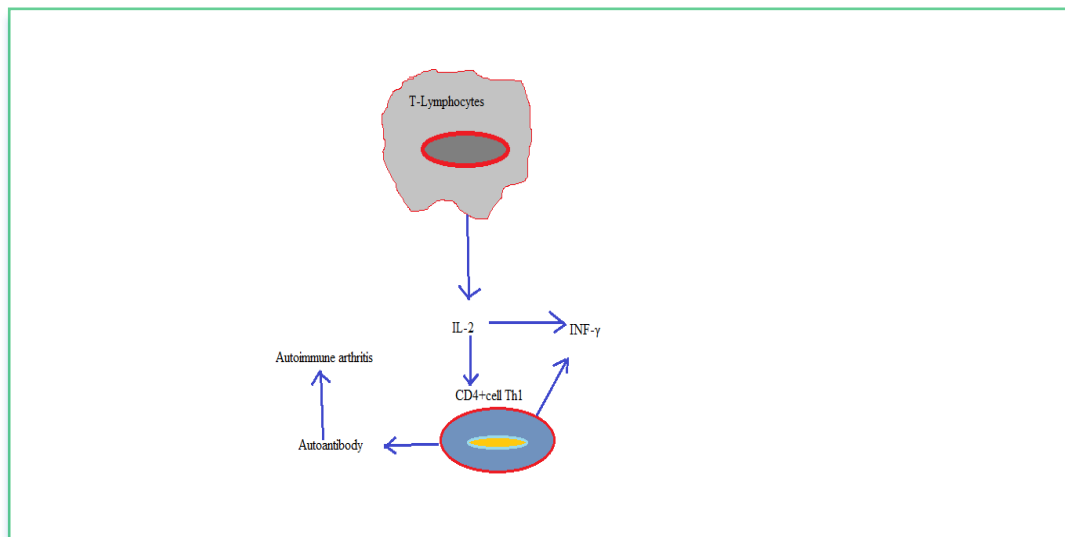
Fig-6- showing the role of IL- 1 β and IL-1Ra in the progression of RA.

The production of IL- 1 β and IL-1Ra has been evaluated in tissue culture using synovial cells from RA patient [36].

3.0 Interlukine-2(IL-2) - IL-2 T-cell growth factors produced by activated helper, is an important immunoregulatory molecule required for normal lymphocyte function[41].The synthesis of IL-2 leads to production of interferon gama (IFN- γ) by T-cell[42-44]. The synthesis of IL-2 is generally consider as a proinflammatory cytokine that exacerbate Th-1 mediated disease states such as autoimmune arthritis[45]. A growing body of evidence from both animal model of arthritis and human rheumatoid arthritis suggest that Th-2 type cytokines such as IL-4 and IL-10 can protect against arthritis whereas Th-1 type cytokine such as IL-2 and IFN- γ can be proinflammatory[46-55]. Number of observations support for this concept. The RA synovium is infiltrated with CD4+T cell Th-1 phenotype [56]. In murine collagen induced arthritis (CIA) a model of RA Abs can inhibit disease onset [57]. It is surprising that most studies in cytokine has failed to detect IL-1

protein, in RA synovial fluid [58]. Few evidences has been proved experimentally for the presence of IL-2 The failure of detection of IL-2 may relate to the timing of synovial sampling. In a study the serial sampling of synovium of RA patient was avoided because of difficulty. The experiment was tested on murine collagen-induced arthritis model to analyze mRNA cytokine pattern at various stages of autoimmune arthritis. These studies demonstrated that IL-2 mRNA decline during the chronic stage of the disease [59]. Further support for this fact comes from the record demonstrated that IL-2 protein is significantly increased in peripheral blood mononuclear cells from patient with early but not late RA [60]. In order to characterize T-lymphocyte function in RA the production of IL-2 employing T-cells from synovial fluid(SF)Synovial tissue and peripheral blood(PB) of patient with RA. Total nineteen patient 15 female and 4 male with definite or classical RA were studied. SF was obtained from 15 and ST from IL-2 assay and IL-2 activity was detected using murine IL-2 dependent cytotoxic T-cell line (CTLI-2).

Fig-7 is showing role of IL-2 in RA.



4. Interleukin-3 (IL-3). The synthesis of IL-3 is regulated by CD4+ cell [61]. An amount of IL-3 has been reported in synovial fluid by using CIA mice model. IL-3 is known to be a potent growth promoting cytokine and is found to be associated with neurologic disorders. IL-3 is primarily produced by activated T-cells, stimulates growth and differentiation of monocytes, basophils and other leukocytes population from the bone marrow in an immune response. It has been demonstrated that IL-3 plays an important role in the onset of RA, an autoimmune disease [62]. Along with its growth regulatory action, IL-3 also induces the release of IL-6 and IL-4. But the release of IL-4 is 3 times less than IL-6. This fact has been proved in CIA induced arthritis in mice. In the same model, an amount of IL-3 was found [61]. The recombinant IL-3 induces histamine release from human basophils, also leads to some aggressive form of inflammation [62].

5. Interleukin-4 (IL-4). Is an anti-inflammatory cytokine and helps to control proinflammatory cytokines. IL-4 is a member of CD132 dependent cytokine which also comprises IL-2, 7, 9, 15 and

21 [63]. IL-4 has two receptors: Type 1, which is composed of IL-4R α and CD132 (IL-2 R γ or γ c), and Type II receptor, composed of IL-4R α and IL-13R α chain [64]. IL-4 has largely been associated with anti-inflammatory since it decreases monocytes and macrophages functions [65, 66] and induces Th2 type responses. IL-4 also has been reported to possess proinflammatory functions such as recruitment of inflammatory cells on the endothelial cell surface [67] and increasing eosinophils, macrophages and B cell chemoattraction [68-70]. This dual nature of IL-4 confirms its anti and proinflammatory activity. Several members of the CD132-dependent cytokines include IL-2, IL-4, IL-7, IL-9 and IL-21 are involved in diverse inflammatory disorders. Among these, IL-4 is best known for its anti-inflammatory activity. IL-4 has been found to induce IL-1 receptor antagonist in neutrophils [71]. In one more study by using the murine air pouch model, it has been reported that IL-4 possesses proinflammatory activity *in vivo* based on its ability to attract leukocytes including neutrophils. By analyzing two polymorphs of IL-4 and four

polymorph of IL-4RA genes in patient with RA, the role of IL-4 in this disease has been reported.

6.Interlukin-5(IL-5).Is produced by T-helper 2 cells which stimulate B-cell growth and increase immunoglobulin secretion. IL-5 Th2 cytokine that is a part of homopoetic family. Being a hematopoietic cytokine, IL-5 plays a key role in the differentiation, maturation, and survival of eosinophils derived from bone marrow precursors [72, 73]. The link between IL-5 and eosinophils is highly conserved in mammals [74,75] which suggest a selective pressure for maintenance of this function in the immune repertoire. In one of the study mouse strains with genetically altered IL-5 expression have been used to understand what changes occur to the immune system as a result of its dysregulation. Depending on the transgenic construct, IL-5 overexpression has been shown to cause moderate [76] to massive eosinophilia, lower bowel inflammation, and enhanced autoantibody production [77, 78]. IL-5 has been shown to be essential for eosinophils maturation and survival [72-73]. Over all the action of IL-5 by activating Th1 receptor shows its anti-inflammatory action. But its role in the production of auto-antibody also shows its role in autoimmune disease.

Interlukines-6(IL-6). IL-6 was identified in 1986 as a B cell regulatory factor and is now recognized as mediating as pleiotropic functions which include effect on the maturation and activation of B and T cells macrophages, osteoclasts, chondrocytes and endothelial cells and broad effect on haematopoiesis in the bone marrow. IL-6 is produced by a variety of cell types in response to infection, trauma, and immunologic challenge

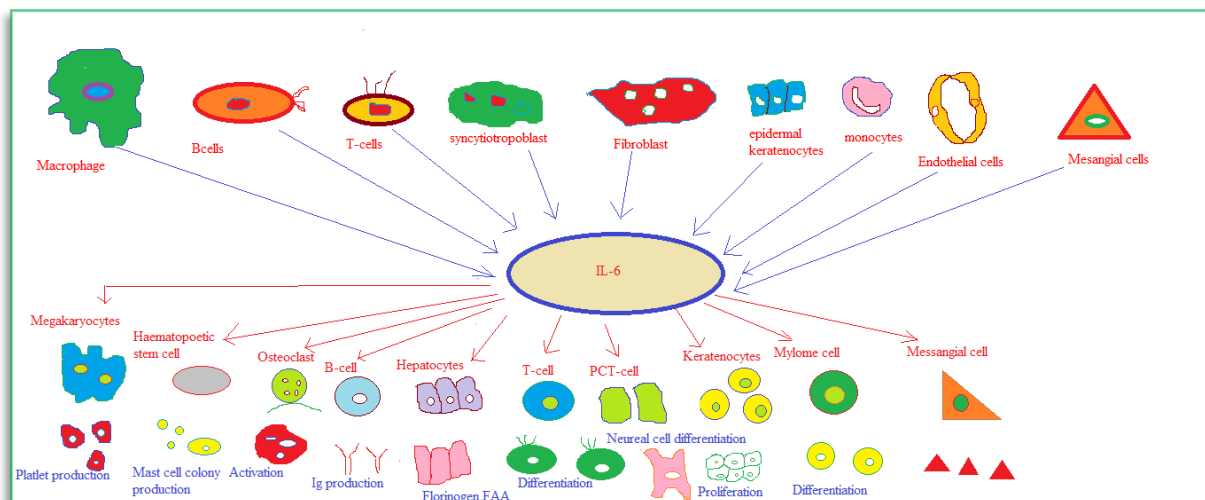
[79]. IL-6 plays a prominent role in disease processes and has both proinflammatory and anti-inflammatory characteristics. It promotes inflammatory events through the expansion and activation of T cells and the differentiation of B cells (fig.-8). IL-6 has also demonstrated a protective role in disease processes. For example, in a septic shock model, IL-6 protected mice against death by suppressing acute neutrophils accumulation caused by intratracheal administration of endotoxin[80]. IL-6 produces many other effects throughout the human body, both locally and systemically. IL-6 is relevant to several disease such as diabetes[81], Atherosclerosis [82], depression[83], Alzheimer disease[81], systemic lupus erythromatous [82] and Rheumatoid arthritis[83]

Interleukin 6 (IL-6) plays a pivotal role in the pathophysiology of rheumatoid arthritis (RA). It is found in abundance in the synovial fluid and serum of patients with RA and the level correlates with the disease activity and joint destruction. IL-6 can promote synovitis and joint destruction by stimulating neutrophils migration, osteoclasts maturation and vascular endothelial growth factor (VEGF)-stimulated pannus proliferation. Concentrations of IL-6 have been reported in synovial fluid and serum/plasma from patients with rheumatoid arthritis [84].

Several studies have confirmed that excessive amounts of IL-6 and soluble IL-6R are produced in the joints of patients with RA, particularly the synovium, which is a thin tissue layer covering the joint from the inside. These increases contribute to inflammation, swelling, joint damage and destruction associated with RA because of IL-6.

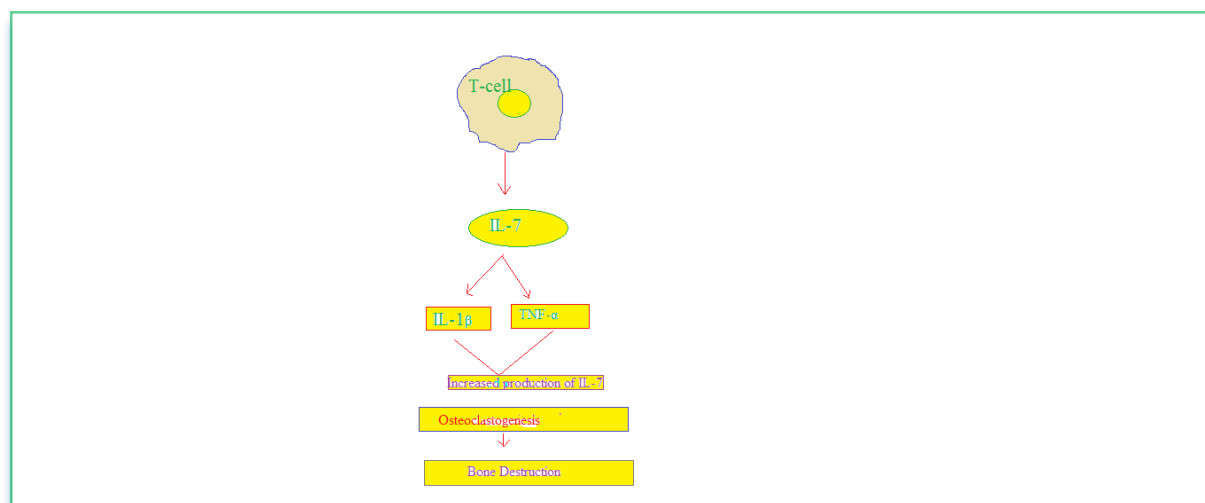
Fig.8. shows the release of IL-6 from different cells which further stimulate other cells to

stimulate their activities.



Interlukine-7(IL-7)-IL-7 is secreted by T-cells. IL-7 is a T-cell growth factor and regulator of Th1 and Th2 cytokines production IL-7 and IL-7 related cytokine thymic stromal lymphopoietin (TSLP) stimulate inflammatory responses that can aggravate rheumatoid arthritis. IL-7 activity is dependent on signaling through the IL7R. In joints IL-7 is known to have a more sinister role contributing to a vicious cycle perpetuating inflammation. Typically, IL-1 β and TNF- α increase the stromal production of TNF- α by

macrophages. Most importantly, IL-7 and in turn IL-7 upregulates the production of osteoclastogenic cytokines by T-cells, leading to maturation of osteoclasts and therefore bone destruction. The high level of IL-7 in RA joints has been demonstrated. Increased IL-7R has been reported in RA synovial tissue. CD4+Tcells from RA synovial fluid and tissue strongly expressed IL-7R as well as a percentage of B-cells and macrophages[85-86]. Several other studies have cleared the fact that IL-7 plays a pivotal role in the pathogenesis of RA[88]. (Fig-9)



Interlukin-8(IL-8)-IL-8 is a polypeptide leukocyte chemotactic cytokine of 72 amino acid

with a molecular mass of 8KD in its mature form [85]. IL-8 is released from variety of cells like monocytes/macrophages, fibroblast and endothelial cell in the presence of lipopolysaccharides, IL-1 and TNF- α at the site of inflammation [86-91]. The prolonged effect of IL-8 thus increases the severity inflammation which can lead to an autoimmune disease. The role of IL-8 in RA has been proved experimentally. The concentration of IL-8 in joint synovial fluid has been observed [92-93].

Interlukin-9(IL-9)-Interleukin-9 is a cytokine produced by Th2 cells. IL-9 was first identified as a mouse T cell growth factor [99] but using in vitro assay systems it has also been demonstrated to modulate B cell maturation [100-101] and to lymphopromote proliferation and differentiation of mast cells [102] and hematopoietic progenitors [103]. IL-9 was originally described as a mast cell growth factor for its ability to enhance the survival of primary mast cells and to induce their production of the inflammatory cytokine IL-6 [104-106] thus indirectly plays a role in the progress of RA. IL-9 also stimulates the production of mast cell proteases and the high-affinity IgE receptor, suggesting that IL-9 primes mast cells to respond to allergen via increased cell surface expression of the high-affinity IgE receptor and the production of inflammatory mediators including IL-6 and several proteases [107].

Interleukin-10 (IL-10). Interleukin-10 functions as an effective immunomodulatory molecule based on two important functions viz. inhibition of cytokine synthesis and down regulation of antigen presenting cells [108-111]. IL-10 has been

described as murine Th2 cell product [108]. Role of IL-10 in arthritis has been reported by taking the peripheral blood sample from RA patient [112] and from synovial joint fluid [113]. The anti-arthritic activity of IL-10 has been given experimentally by using human and CIA mice model with the observation that anti-IL-10 helps in the enhancement of arthritic condition more in both models whereas injected exogenous IL-10 lower the severity of the disease [114]. The action of IL-10 is correlated with that of IL-4. Instead of the anti-inflammatory activity IL-10 are also meant to release some proinflammatory cytokines.

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