Asian Journal of Immunology

4(2): 37-46, 2020; Article no.AJI.57314

Role of Inflammatory Cytokines in the Pathogenesis of Rheumatoid Arthritis and Novel Therapeutic Targets

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS designed and supervised the study. Author AUK wrote the first draft of the manuscript, outline the protocol and performed the statistical analysis while authors UA and DCS managed the literature search and analyses of the study. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Jaffu Othniel Chilongola, Tumaini University, Tanzania.
Reviewers:
(1) S. Tripathy, Sri Vasavi Institute of Pharmaceutical Sciences, India.
(2) Ingrid Patricia, Dávalos Rodríguez, México.
Complete Peer review History: http://www.sdiarticle4.com/review-history/57314

Review Article

Received 06 April 2020
Accepted 12 June 2020
Published 29 June 2020

ABSTRACT

Cytokines are low molecular weight secreted proteins that mediate and regulate immune responses, inflammation and hematopoiesis; they act by autocrine, paracrine, endocrine and antagonistic mode of actions. cytokines have strong correlation with autoimmune disease, the most prominent among others is rheumatoid arthritis (RA) which targets synovial joints, and often accompanied by an array of extra-articular manifestations which are ultimately major predictors of increased morbidity and mortality, RA affect about 1% of the world population and about 0.6% of the American population with annual incidence estimated to about 40 per 100,000 individuals and mostly women. Persistent inflammation endorsed by major pro-inflammatory cytokines such as Interleukins (IL-1, IL-6) and tumor necrosis factors (TNF-α) and imbalance between the pro-inflammatory and anti-inflammatory cytokines is the main pathogenesis of RA. Evidence suggests that interaction between antigen-presenting cells and CD4+ T helper cells is involved in the induction of inflammation in RA. Continuous recruitment and activation of macrophages and

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monocytes occur with the recruitment of pro-inflammatory cytokines, specifically TNF-α, IL-1 and IL-6 into the synovial cavity resulting to loss of cartilage and bone erosion. These activated immune cells stimulate angiogenesis, which explains increased vascularity found in the synovium of patients with RA. Novel therapeutic targets are developed to minimize the morbidity rate, the use of TNF-α blockade drugs such as Adalimumab, Etanercept and Infliximab is widely approved globally with more precise therapeutic effect on inflammation. As the IL-1 plays a critical role in joint damage by facilitating the degradation of cartilage which leads to RA, the use of interleukin-1 receptor antagonist drugs such as Anakinra suppresses RA by inhibiting the release of IL-1, likewise, the use of anti-IL-6 receptor agent such as tocilizumab has become a major resource for the treatment of RA.

Keywords: Interleukins; rheumatoid arthritis; tumor necrosis factor; therapeutics.

1. INTRODUCTION

The concept of cytokines was described in 1974 after the discovery of interferon for the first time. Cytokines are small secreted proteins with a molecular weight less than 30 kDa (<200 amino acids) that mediate and regulate immune responses, inflammation, and hematopoiesis they are released by varieties of cells such as leukocytes, produced *de novo*(starting from the beginning) in response to an immune stimulus and act by binding to the surface membranes of target cells to evoke a cascade of responsive reactions [1-2]. They bind to specific receptors on target cells, triggering signal-transduction pathways that ultimately alter gene expression in these cells to produce cytokines that are involved in innate, adaptive immunity, the gene products (proteins) participate in the cell proliferation, differentiation, migration, and apoptosis activities [3-4].

To be more precise, cytokines regulate the intensity and duration of the immune response by stimulating or inhibiting proliferation, differentiation, trafficking or emigration of lymphocytes all the while acting as a messenger for both arms of the immune system [5]. Cytokines either stimulate or suppress the responses of various cells involved in host immune mechanisms, they assist such cells to interact or convey the essential messages for the proper functioning of defense systems against numerous pathogens or disease conditions. Cytokines and their receptors exhibit very high affinity for each other as a result they can exert their biological effects even at very low concentrations [6].

According to the secretion of cytokines, they are classified in Table 1.

2. MATERIALS AND METHODS

This literature review titled 'role of inflammatory cytokines in the pathogenesis of rheumatoid arthritis and novel therapeutic targets'' was conducted using online database of scientific collections, key articles used were retrieved precisely from NCBI (PMC, PUBMED), Google Scholar, using the terms 'Rheumatoid arthritis, cytokines, and therapeutics of rheumatoid arthritis as keywords for our search. We included scientific publications from December 2004 to November 2018. Articles focusing on clinical characteristics, epidemiology, pathogenesis, and treatments for rheumatoid arthritis were eligible for inclusion.

2.1 Mode of Cytokines Action

A particular cytokine might bind to receptors on the membrane of the same cell that secreted it and exert its biological effect, a condition which is referred as autocrine action [8].It can also bind to receptors on a target cell nearby and exert its biological effect which is known as paracrine

Table 1. Shows different classes of cytokine and their function

Chemokine	Function	Ref.
Lymphokines	cytokines that are secreted by T cells and regulate the immune response	[7]
Proinflammatory	cytokines that amplify and perpetuate the inflammatory process	[7]
Anti-inflammatory	cytokines that negatively modulate the inflammatory response	[7]
Growth factors	cytokines that promote cell survival and result in structural changes in the airways	[7]
Chemokine	cytokines which are chemotactic for inflammatory cells	[7]

action [8]. Besides, those cytokines which bind to target cells in distant locations and exert their biological effect are known to exert endocrine mode of action [8]. However the synergistic effect is seen when the combined effect of two or more cytokines is greater than the additive effect of individual cytokine [9].

Another mode of action exhibit by cytokine is their ability to activate multiple signaling pathways thereby affecting the activity of multiple cells which is known as pleiotropic mode of action [9]. Besides, redundant mode of action is also seen when multiple cytokines have the ability to exert similar function [9]. Under some circumstance two or more cytokines may act on one cell and the effect of one cytokine inhibit or offset the effects of another cytokine [10].

2.2 Pro-inflammatory Cytokines

Pro-inflammatory cytokines or simply inflammatory cytokines are special types of signaling molecules that are excreted from immune cells like T helper cells and macrophages and certain other cells that promote inflammation [11]. The most prominent among them are interleukins (IL-1, IL-6) and tumor necrosis factor (TNF-α and TNF-β) which play an important role in mediating immune response, excess production of inflammatory cytokines contributes to inflammatory diseases [11]. Inflammatory cytokines are proved to be beneficial for their bactericidal capacity of phagocytes, recruit additional innate cell populations to sites of infection, induce dendritic cell maturation and direct the subsequent specific immune response to the invading microbes [12]. Three pro-inflammatory cytokines, interleukin-1, interleukin-6, and tumor necrosis factor-α, appear to have a central role in tissue destruction and are secreted by a variety of cell types comprising monocytes, macrophages, dendritic cells, epithelial cells, keratinocytes and fibroblasts [12].

Interleukin-1 (IL-1) is one of the primary inflammatory cytokines that mediate many local and systemic features of inflammation, they are made mainly by monocytes and macrophages in response to a range of stimuli including various microbial products, viruses, immune complexes, activated T cells and combine the action of other cytokines such as interleukin-2 and interferon-gamma [13]. IL-1 exist in two isoformIL-1 α and β both of which are prototypic pro-inflammatory cytokines that exert pleiotropic effects on a variety of cells and play key roles in acute and chronic inflammatory and autoimmune disorders [13]. IL-1α is a regulator of intracellular events and a local inflammatory mediator, while IL-1β is primarily an extracellular protein released from cells [13]. IL-1 also stimulates the proliferation of keratinocytes, fibroblasts and endothelial cells of the tissues, therefore IL-1 is a critical component in the homeostasis of tissues and its unrestricted production may lead to tissue damage [14]. IL-6 is produced locally in the inflamed tissues following cellular activation by bacterial lipopolysaccharide or other cytokines such as IL-1β or TNF- α [14].

There are two IL-1 receptors, IL-1RI and IL-1RII. IL-1α and IL-1β signal through IL-1RI, binding to IL-1RII does not lead to cell signaling and is therefore considered as a decoy receptor, upon binding of IL-1 to IL-1RI, a second receptor termed IL-1 receptor accessory protein (IL-1RAcP) gets recruited at the cell membrane to form a high-affinity binding receptor complex leading to intracellular signalling [15]. A third IL-1 family member, IL-1 receptor antagonist (IL-1Ra), binds to IL-1 receptors and prevents the interaction of IL-1 with its receptors, acting as a natural IL-1 inhibitor.IL-1β has important homeostatic functions in the normal organism, such as regulation of feeding, sleep, and temperature, however, overproduction of IL-1β is implicated in the pathophysiological changes that occur during different disease states such as rheumatoid arthritis, neuropathic pain, inflammatory bowel disease, osteoarthritis, vascular diseases, multiple sclerosis, and Alzheimer's disease [15].

Tumor necrosis factor- α (TNF- α): Is a pro-inflammatory cytokine that possesses a wide range of immune regulatory functions and has the potential to stimulate the production of secondary mediators, including chemokine or cyclooxygenase products, which amplifies the degree of inflammation [16]. TNF-α was cloned over 2 decades ago and its identification in part led to the discovery of a superfamily of tumor necrosis factor (TNFs) and their receptors [17]. Macrophages are major producers of TNFα and interestingly are also highly responsive to TNFα, it signals through two transmembrane receptors, TNFR1 and TNFR2 and regulate several critical cell functions including cell proliferation, survival, differentiation and apoptosis [17].

Aberrant TNFα production and TNFα receptor signaling have been associated with the pathogenesis of several diseases, including rheumatoid arthritis, Crohn's disease,

atherosclerosis, psoriasis, sepsis, diabetes and obesity [18]. TNFα has been shown to play a pivotal role in orchestrating the cytokine cascade in many inflammatory diseases and because of this role as a "master regulator" of inflammatory cytokine production, it has been proposed as a therapeutic target for several diseases [19]. Indeed, anti-TNFα drugs are now licensed for treating certain inflammatory diseases including rheumatoid arthritis and inflammatory bowel disease [20].

Interleukin 6 (IL-6): Is a pleiotropic inflammatory cytokine synthesized by a variety of cells such as T lymphocytes, macrophages, monocytes, and synovial fibroblasts [21]. IL-6 was initially discovered and referred as B-cell differentiation factor identified in tissue culture supernatants which induce B cells to produce immune globulins and involved in diverse biological functions, such as T lymphocytes activation, induction of acute-phase response, growth stimulation, differentiation of hematopoietic precursor cells and proliferation of synovial fibroblasts [22]. IL-6 is among the major cytokines which contribute to the progression of many chronic inflammatory diseases and a well-established target for pharmacological intervention [23-24].

Mammalian IL-6 exerts its biological effects by binding to two cell surface receptors, IL-6Rα and glycoprotein 130 receptors [25-27] The assembly of the IL-6·IL-6Rα·gp130 on the cell surface forming a complex activates the JAK family of tyrosine kinases and the downstream STAT3 transcription factor [28-30]. In cells that express IL-6Rα, IL-6-dependent activation of the signal-transducing gp130 receptor is mediated by membrane-bound IL-6Rα. alternatively; IL-6 in a complex with soluble IL-6Rα (sIL-6Rα) can activate gp130 in cells [31].

2.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joint. Autoimmune diseases are illnesses that occur when the immune system mistakenly attacks the body [32]. The immune system contains a complex organization of cells and antibodies design to protect the body against infections, one of the most prominent among autoimmune diseases is rheumatoid arthritis; also refer to as systemic illness or rheumatoid disease [33].

The other type of Rheumatoid arthritis is juvenile idiopathic arthritis which manifests in individuals less than 16 years of age [33]. When tissue inflammation occurs, the disease is active (relapsed) and the symptoms include fatigue, loss of appetite, muscle and joint pain, joint redness, joint swelling joint tenderness rheumatoid nodules and finally if the symptoms persist it lead to loss of joint function [33]. When tissue inflammation subsides, the disease is inactive (remission), remission may occur spontaneously with treatment and can last for weeks, month and years [33].

RA targets synovial joints and is often accompanied by an array of extra-articular manifestations which are ultimately major predictors of increased morbidity and mortality [34]. It was discovered that joint damage occurs very early in RA, and after 2 years, approximately 50% of patients will exhibit bone erosions [35]. Early management of rheumatoid arthritis with disease-modifying antirheumatic drugs (DMARDs) is well recognized in regulating the disease severity, until recently, treatment options were limited to single or combination therapy with a relatively restricted therapeutic armament [36]. These comprise of immunosuppressive and DMARDs such as azathioprine, prednisolone sulfasalazine, and methotrexate [37]. Many of these medications reduce disease activity and block the radiological progression of bone erosion, judging by the clinical experience they are regarded to be suitable in many patients [38].

2.4 Prevalence of Rheumatoid Arthritis Globally and in the US

RA is a common disease that affects about 1% of the world population and about 0.6% of the American population, many adults are impacted by the condition with prevalence of 0·8–1·0% and the disease continues to cause significant morbidity and premature mortality [39]. The annual incidence of RA has been estimated to about 40 per 100,000 individuals, this shows that in each 100,000 individuals 40 new cases of RA are been diagnosed [40]. RA often initially impacts many children and individuals between 30-50 years of age, surprisingly, about three-quarters of all the individuals with RA are women [41].

2.5 Pathogenesis of Rheumatoid Arthritis

In the synovial joint, there is an imbalance between pro-inflammatory cytokines and anti-

inflammatory cytokines [42]. T lymphocytes play an essential role by the production of various cytokines with different properties which facilitate the process of inflammation at the disease state [42]. Interestingly, the T-helper cells which have two main phenotypes are characterized by two distinct cytokine profiles namely Th1 and Th2 along with the third subset called Th0 which is found to be the precursor of the two subsets [42]. Th0 cytokine profile is intermediate, hence Th1 cells significantly intercede the cell-mediated immune response (CMI) while the Th2 cells intercede the humoral immune response, and these crucial steps determine whether the acquired immune response is dominated by activation of macrophage, cell - mediated immune response, pro-inflammatory activity of humoral immune response and anti-inflammatory activity [42].

T cell-induced in the presence of TNF α, IFN-γ, and IL-12 develop into Th-1 type of phenotype whereas those induced in the presence of IL-4, IL-6 and IL-10develops into Th-2 phenotype [43]. Evidence suggests that interaction between an unknown exogenous or endogenous antigen via antigen-presenting cells and CD4+ T helper cells are involved in the induction of inflammation in RA [43]. Continuous recruitment and activation of macrophages and monocytes occur with the recruitment of pro-inflammatory cytokines, specifically TNF-α and IL-1 and IL-6 into the synovial cavity, the release of these cytokines mediates tissue destruction by activation of chondrocytes and fibroblasts which release collagenases and metalloproteinase with resultant cartilage loss and bone erosion [44]. These activated macrophages, monocytes, lymphocytes and fibroblasts, as well as their product, also stimulate angiogenesis, which explains increased vascularity found in the synovium of patients with RA [44].

3. THERAPEUTIC TARGET

TNF-α blockade: TNF-αis a potent cytokine that promotes inflammation by stimulating fibroblasts to express intercellular adhesion molecules that play a substantial role in inflammation, immune response and intracellular signalling event [46]. Interaction of these adhesion molecules with their respective ligands on the surface of leukocytes results in increased transport of leukocytes to inflammatory sites, including the joints in patients with rheumatoid arthritis [45].

TNF-αindirectly down-regulates inflammation by stimulating the release of the corticotrophin-releasing hormone, this hormone stimulates the adrenal cortex to release cortisol, which inhibits inflammation [46]. As an inflammatory cytokine, TNF-αhas an important role in rheumatoid synovitis as studied in the culture of synovial cells from patients with rheumatoid arthritis, by blocking the TNF-αwith antibodies significantly

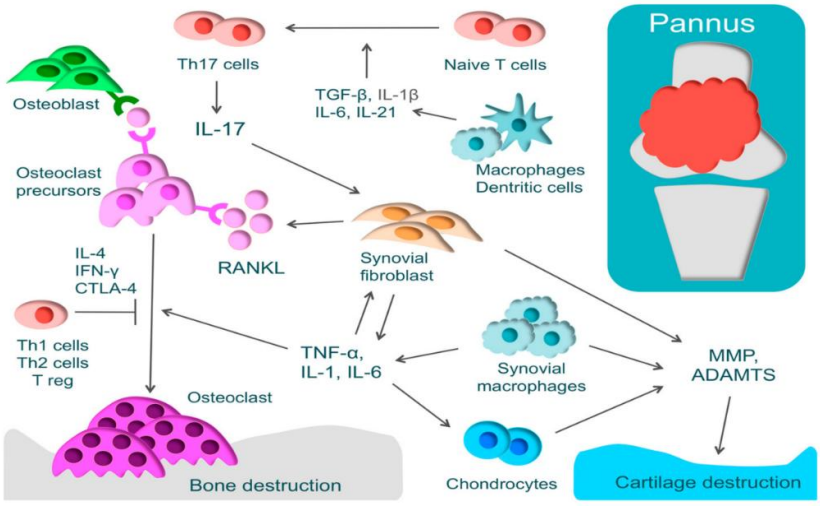

Fig. 1. RA is characterized by proliferative synovium (pannus) and an excessive immune response of T-cells. Pannus comprises T-cells, synovial fibroblasts, and macrophages that produce inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), IL-6, and IL-17. These inflammatory cytokines activate osteoclasts, leading to bone destruction [45]

reduced the production of interleukin-1, interleukin-6, interleukin-8, and granulocyte–monocyte colony-stimulating factor [47]. Thus, the blockade of TNF-αhas a more precise effect on inflammation than the blockade of other cytokines present in high concentrations in the synovial membrane, such as interleukin-1 [48].

The result of studies in the animal model shows the importance of TNF-αin rheumatoid arthritis, in transgenic mice that expressed a deregulated human TNF-αgene, there is the spontaneous development of polyarthritis which is another form of arthritis that affects many joints, and however first aid treatment of these animals with a monoclonal antibody against TNF-αprevents the development of RA [49].

Interleukin-1 receptor antagonist: The IL-1 receptor antagonist (IL-1RA) is an endogenous ligand that binds the interleukin-1 receptor (IL-1R) without recruiting the interleukin-1 receptor accessory protein (IL1-RAcP) to hinder the activation of the receptor, IL-1RA has a higher affinity for the IL-1R than IL-1α or IL-1β and serves to regulate the signaling of IL-1 by preventing the binding of other active cytokines [51].

Deficiency of IL-1RA results in a reduction of regulatory function and can lead to severe inflammation and auto inflammatory disorders such as arthritis, vasculitis, and skin lesions in humans [52]. IL-1 binds to two types of cell-surface receptors, type I receptors are found on many cells in trace amount, they have a cytoplasmic tail and are capable of intracellular signaling, while type II receptors are expressed primarily on neutrophils, monocytes and B cells, they are decoy receptors which bind circulating IL-1 without delivering any intracellular signal [53].

Soluble forms of both types of IL-1R compete with cell surface receptors thereby decreasing IL-1 mediated activation of cells [54]. IL-1RA, binds the type I receptor with high affinity without triggering a signal, therefore providing another mechanism for inhibiting the IL-1 activity [55]. IL-1 plays a critical role in joint damage by facilitating the degradation of cartilage which leads to rheumatoid arthritis, whereas the injection of antibodies against IL-1 suppresses collagen-induced arthritis in mice and decreases the damage to the cartilage [56].

Anti-interleukin 6 receptor: Interleukin-6 (IL-6) is a major pro-inflammatory cytokine with pleiotropic functions, IL-6 plays a key role in immune activation and inflammation in RA, thus, inhibition of IL-6 is a good strategy in controlling RA [57]. IL-6 has diverse and protein effects on many cell types, involved in both homeostatic and inflammatory pathways, however anti-IL-6 receptor agent tocilizumab (TCZ) has become a major resource for the treatment of RA [58].

In patients with RA, TCZ has a dramatic effect on B lineage cells, with decreases in levels of circulating switched and unswitched memory B cells and with overall decreases in measured levels of antibody gene hypermutation in blood B cells [59]. A humanized IL-6R antibody, tocilizumab (TCZ), was developed by a research team from Chugai Pharmaceutical Company and Osaka University in Japan [59]. After several randomized clinical trials (RCTs), an intravenous formulation of TCZ (TCZ-IV) was approved for RA treatment in Japan in 2008, in Europe in 2009, and in the USA in 2010 [58].

Recently, a subcutaneous formulation of TCZ (TCZ-SC) was developed in consideration of patients' preferences after a non-inferiority trial of TCZSC and TCZ-IV, TCZ-SC was approved in Japan and the USA in 2013 and Europe in 2014 [60]. TCZ displays a good efficacy in patients with RA, including disease-modifying anti-rheumatic drug (DMARD) naïve patients and patients with an inadequate response to conventional synthetic DMARDs (csDMARDs), methotrexate (MTX), or TNF inhibitors (TNFi) [60].

Table 2. Showing TNF-α blockers as the first therapeutic agents approved for the treatment of rheumatoid arthritis*;* TNF-α blockade has become a central strategy of targeted anti-inflammatory therapy in the disease

Agent	Class	Target	Structure	Ref.
Adalimumab	Cytokine inhibitor	TNF-α	Human monoclonal Antibody	[50]
Certolizumab	Cytokine inhibitor	TNF-α	Pegylated humanized Faḃ fragment of an anti–TNF-α monoclonal antibody	[50]
Etanercept	Cytokine inhibitor	TNF-α	TNF-α receptor–Fc fusion	[50]
Golimumab	Cytokine inhibitor	TNF-α	Human monoclonal Antibody	[50]
Infliximab	Cytokine inhibitor	TNF-α	Chimeric monoclonal Antibody	[50]

Table 3. This therapeutic agent is considered one of the cytokine blockades in rheumatoid arthritis; it has profound effects on systemic features, acute phase response and synovitis

Agent	Class	Target	Structure	Ref
Anakinra	Cytokine inhibitor	Interleukin-1	Interleukin-1 receptor antagonist	[57]

Table 4. This therapeutic agent is considered to be one of the cytokine blockades in rheumatoid arthritis; it has profound effects on systemic features, acute phase response and synovitis

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Agent	Class	Target	Structure	Ref
Tocilizumab	Cytokine inhibitor	Interleukin-6 receptor	Human monoclonal antibodies	[63]

The overall efficacy including clinical responses and the radiographic damage progression of TCZ was comparable to that of other biological DMARDs such as TNFi [61]. IL-6 was found to affects psychosomatic functioning, sleep-related symptoms, and fatigue, while on the other hand, TCZ improves sleep quality and fatigue [62].

4. CONCLUSION

This review has summarized the critical role played by the cytokines in the pathogenesis of RA. Persistent recruitment and activation of macrophages and monocytes occur with the recruitment of pro-inflammatory cytokines, specifically TNF-α and IL-1 and IL-6 into the synovial cavity which leads to tissue destruction by activation of chondrocytes and fibroblasts thereby releasing collagenases and metalloproteinase with resultant cartilage loss and bone erosion. However, due to the increase morbidity and premature mortality of RA in the world population, many therapeutic strategies are adopted to overcome the disease. The novel therapeutic approaches to RA that are aimed at restoring this cytokines imbalance include the use of monoclonal antibodies to TNF-α as mentioned in (Table 2) which mainly inhibit the proinflammatory cytokine activity, IL-1R-antagonist such as Anakinra which suppresses collagen-induced arthritis thereby decreasing the damage to cartilage and the use of Tocilizumab which displays a good efficacy in patients with RA, including disease-modifying anti-rheumatic drug naïve patients and patients with an inadequate response to conventional synthetic DMARDs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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