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REVIEW ARTICLE

Emerging Therapeutic Targets: Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis involves a range of various intricate pathophysiologic facets that contribute to synovitis, synovial hyperplasia, autoantibodies generation as well as cartilage and bone damage leading to functional impairment. Although current therapeutic modalities including NSAIDs, corticosteroids, DMARDs and biologic response modifiers target various contributory factors but still not effectual in the apt management of rheumatoid arthritis, thus pointing towards the investigation of new prospects to not only manage but cure this perplexing disorder. Hence, Tumor necrosis factor-α converting enzyme (TACE/ADAM17), Toll like receptor 5 (TLR5), Citrullinated immunoglobulin binding protein (citBiP), anti-BRAF autoantibodies, Perforin and membrane attack complex (MAC), Migration inhibitory factor of macrophages (MIF), Mucin (MUCs), IL-1β, NLRP3 inflammasome signaling, NETosis, Hepatocyte growth factor (HGF), progranulin, PTPN22, iRHOM2, immune mediated immunolytic pathways, tenascin-C and various chemokines are intriguing areas, which in future might be more beneficial in the treatment and management of arthritis in majority of populace with minimum risks.

Keywords: Rheumatoid arthritis, therapeutics, innovative targets.

INTRODUCTION

Arthritis by and large denotes more than 100 rheumatic diseases, which are characterized by pain, inflammation and stiffness in musculoskeletal system and ranges from localized, self-limiting disorders to systemic, autoimmune processes [1]. Rheumatoid arthritis (RA) is a chronic systemic inflammation, also called “immortal cancer”, described by permeation of inflammatory cells and proliferation of synovial tissue, escorted by bone and cartilage annihilation. It can briskly evolve into multisystem inflammation with irreversible joint damage consequently initiating disability, untimely mortality and compromised quality of life [2]. Autoimmunity and chronic inflammation are actuated by a disparity amongst pro- and anti-inflammatory cytokines, thus instigating joint mutilation in RA [1]. T cells, B cells, fibroblasts, macrophages and pro-inflammatory cytokines are allied with the pathogenesis of arthritis that involves articular cartilage hyperplasia [3]. Arthritis follows in all age groups and peaks between the ages of 35 and 50, disturbing approximately 0.5-1% population worldwide, with women being affected two to three times more recurrently than men [4].

Treatment of RA by non-steroidal drugs, steroidal agents, anti-rheumatic drugs, biologics and immuno-suppressants is common but these drugs are notorious for some unsolicited effects like gastrointestinal disorders, immunodeficiency and humoral disturbances [5]. Hence, targeted drug discovery is the hallmark in research era today. Its aim is controlling the target activity while delivering the potential therapeutics for treatment of RA. During this process, target identification and its substantiation plays a major role in drug discovery project’s accomplishment [6]. Hence, aim of present review is to highlight new pathological targets and investigation areas for RA (Figure **1**) so, that additional work will improve the lead generation

paradigm and create target based drug discovery platforms that will eventually influence future drug development.

Figure 1. Novel therapeutic targets for Rheumatoid arthritis.

INTRIGUING RESEARCH AREAS IN RHEUMATOID ARTHRITIS

Tumor Necrosis Factor-α Converting Enzyme (TACE)

TACE is largely distinguished as metalloproteinase 17 (ADAM17). This enzyme belongs to ectodomain family. It sheds proteases adept to control biologically distinct pathways. Instigation of cell surface proteins comprising cytokines such as TNF-α, ligands of ErbB (*e.g*. TGF-α, amphiregulin), cytokine receptors (IL-6 R and TNF-R) and adhesion proteins (L selectin and ICAM-1) can excite immune reactions as, they are pro inflammatory. As, TNF-α is targeted by anti-inflammatory drugs, hence speculation can be made that inhibition of ADAM17 can be a therapeutic target for treating inflammatory and immune associated complaints. On the other hand, for tumor growth and during wound healing, the stimulation of ErbB pathway via trans-activation and Notch1 cleavage is crucial. *In-vivo* studies have discovered that stimulation of ADAM17 directs a range of pro- and anti-inflammatory reactions. This orchestrating role avowed that involvement of ADAM17 in lashing inflammatory cancers is triggered by perpetual immune system activation and it frequently ends up in extreme involvement of ErbB family members in the growth of many tumors. Hence, it is notable that loss of ADAM17 activity results in loss of ErbB signaling hence, pointing to alternative substances that block ErbB directly. However, problem may arise in blockade of this enzyme owing to many physiologic activities of ADAM17. Moreover, tissue-specific deletion, or hypomorphic knock-in of ADAM17 demonstrates an *in-vivo* role in controlling inflammation and tissue regeneration. So, blockade of ADAM17 could be a potential strategy for treating inflammation and cancers. Therefore, new data on cellular trafficking of ADAM17 might open up an avenue of a more cell specific inhibition of this key enzyme [7, 8].

Toll Like Receptor 5 (TLR 5)

Rheumatoid arthritis is an incessant immune arbitrated disorder in which TLR initiated innate immunity plays an imperative part. In RA, ligation of TLR2 and 4 by EDA fibronectin, HSP60, 70 and 96 as well as fibrinogen ensues in generation of chemokines, pro-inflammatory cytokines and destructive matrix metalloproteinases whereas, proangiogenic factors persuade leukocyte migration, angiogenesis and bone erosion. Recently, it has been established that raised expression of TLR5 in rheumatoid and osteoarthritis, paralleled to myeloid and endothelial cells of normal synovial tissue can uphold the production of numerous proinflammatory elements. Besides, TLR5 ligation prompts endothelial chemotaxis and tube formation via instigation of PI3K/AKT1 pathway. More so, differentiation of TH-17 cells and production of joint IL-17 is correlated with TLR5 interceded angiogenesis. In conclusion, interference with TLR5 function may overturn RA pathogenesis by subduing neovascularization, TH-17 polarization, IL-17 intervened angiogenesis and TNF-α prompted osteoclast maturation. Thus, from preclinical evidence, loss of function of TLR5 highlights it as a novel therapeutic target regarding RA therapy [9, 10].

Mucins (MUCs)

Mucins have got imperative function in pathogenesis of certain illnesses. They are high molecular weight glycoproteins, which take part in protection and lubrication of surfaces of articular cartilage and gastrointestinal tract epithelium. Mucins, comprising MUC-1 derived from RA synovial fluid incite IL-6 generation on peripheral blood mononuclear cells. Even though, additional investigation regarding biochemical properties of this mucin on immunocompetent cells and synovial cells is still desired. Therefore, MUC-1 could be a new target specific for joint inflammation in treating RA [11].

Migration Inhibitory Factor of Macrophages (MIF)

It is accredited as multifunctional cytokine in inflammatory disorders including RA, contributing in a variety of pathological events such as T-cell activation, leukocyte infiltration/adhesion, cytokine expression, liberation of inflammatory intermediaries and stimulation of mitogen-activated protein kinase. It also modulates p53 expression and inhibits apoptosis as well as, discharge matrix metalloproteinases. Consequently, MIF has been allied with pro-inflammatory events in numerous ailments, like RA and atherosclerosis. More so, MIF has been designated as a soluble factor, expressed by T cells in delayed-type of hypersensitivity reactions and various pathological conditions. Thus, MIF inhibitor would epitomize a novel orally active direct anti-cytokine therapy in RA and atherosclerosis in which use of biological treatment targeted against cytokines is very costly. Moreover, substantial efforts are underway towards achieving the goal whether such compounds can be developed or not, but MIF is still a probable treatment target for small molecules or treatment based on antibody [12, 13].

Anti-BRAF Autoantibodies

BRAF (v-raf murine sarcoma viral oncogene homolog B1) is accountable for pro-inflammatory cytokine production through a process known as mitogen-activated protein kinase (MAPK) signaling pathway. It has been reported that purified anti-BRAF autoantibodies isolated from RA patients stimulated BRAF kinase activity in *in-vitro* phosphorylation assay of MEK1 (mitogen extracellular regulated kinase), a major BRAF substrate. Hence, autoantibodies against BRAF might be a therapeutic target for narrative anti-rheumatic therapies [14].

Citrullinated Immunoglobulin Binding Protein (citBiP)

RA is characterized by the presence of autoantibodies known as Anti-citrullinated protein/peptide antibodies (ACPAs) directed against body proteins including fibrinogen, alpha-enolase and vimentin. In addition to these proteins, citBiP having pro-inflammatory role in arthritis has newly been identified as another ACPA target in RA patients. Hence, it can be concluded that citBiP is allied with pathogenesis of inflammatory arthritis and could be a new diagnostic and therapeutic target for RA [15].

NETosis

In RA, neutrophils exhibit more extracellular trap formation (NETs) that externalizes autoantigens and immunostimulatory molecules, which perpetuate pathogenic mechanisms and upholds aberrant adaptive and innate immune response in joint. NETosis, in rheumatoid arthritis neutrophils is induced by inflammatory cytokines i.e., IL-17A and TNF-α. As a result, expansion of inflammatory responses occur such as induction of IL-6, chemokines, IL-8 and adhesion molecules. Besides, ACPA concentration and systemic inflammation are augmented owing to this phenomenon. Moreover, ACPAs and rheumatoid factor perpetuate NET production, conserving tailored autoantigen supply to immune system. As a consequence, role of NETosis in RA pathogenesis might offer new potential targets for treating RA and its allied complications [16].

Hepatocyte Growth Factor (HGF)

In RA synovium, the c-Met receptor (tyrosine-protein kinase Met or hepatocyte growth factor receptor) and HGF are over expressed. HGF being heterodimeric protein is composed of one α-chain consisting of four kringle domains with a β-chain. The α-chain has high affinity to interact with c-Met and β-chain is accountable for c-Met instigation. In order to deter HGF, researchers have created an antagonist of HGF, termed as NK4 (contains four HGF domains of α-chain). Subsequently, high affinity attachment of NK4 to c-Met occurs without its triggering. NK4 constrains cancer associated metastasis, its growth and also angiogenesis. Similarly, in both preventive and therapeutic models of RA, inflammation together with joint impairment was subdued by NK4 gene therapy. Hence, biological or pharmacological therapies targeted against HGF and NK4 gene therapy could be effective therapeutic options in combating RA [17].

Perforin and Membrane Attack Complex (MAC) Activity in Protein Citrullination

Protein citrullination is a process involving modification of peptidyl arginine residues to citrulline, mediated by peptidyl arginine deiminases (PADs). Till now, five isoenzymes have been recognized in human body which are PAD1 to PAD4 and PAD6. Many physiological and biochemical processes are connected with protein citrullination e.g., regulation of genes, moisturization of skin and formation of hair

follicles. In addition, involvement of citrullination is also seen in the formation of NETs and regulation of chemokines. However, in RA, two immune regulated membranolytic pathways are persuaded by discernible hypercitrullination, which are interceded by MAC and perforin. Moreover, a profile of citrullinated autoantigens is generated by the activity of MAC and perforin on neutrophils, which is characteristic of RA. During complement and perforin activity, activation of PADs may be pivotal to production of citrullinated autoantigens in RA and hence, these pathways might serve as new targets for monitoring and therapeutic modulation for development of new drugs [18].

Interleukin (IL)-1β and NLRP3 Inflammasomes

In RA, IL-1β is a main mediator of bone and cartilage destruction but our knowledge regarding IL-1β generation is still deficient due to lack of apposite mouse models in which inflammasomes carve up disease. Increased activation of NLRP3 inflammasome leads to secretion of caspase-1, pyroptosis and IL-1β thus, leading to *in-vivo* pathogenesis of RA. Hence, removal of NLRP3, caspase-1 and IL-1 receptors noticeably guard against inflammations and cartilage destruction [19]. The mechanism of inflammation in many hereditary and non-hereditary auto-inflammatory diseases is still unknown, but clinically the response of IL1 inhibitor suggests that inflammasome dysfunction play an obvious role in pathogenesis. Thence, multiple and non-redundant negative regulators of NLRP3 inflammasome would provide multiple checkpoints to ascertain appropriate immune responses. But such regulators are not found hitherto and relative importance of these regulators needs to be explored in upcoming days [20]. Hereinafter, controlling of inflammasome might open new viewpoints for understanding the underlying pathology and its treatment in future research era [21].

Immune-Mediated Membranolytic/Pore Forming Pathways

It has been found that anomalous citrullination of proteins has pathogenic role in RA, but that specific role is indistinct. It is indefinite whether citrullination reveals continuing inflammation or whether it is allied with onset of RA pathogenesis. It has been formerly established that cellular hypercitrullination existing in synovial fluid (SF) cells in RA may be the outcome of immune related membranolytic pathways that actuate a family of calcium-dependent PADs in joint inflammatory cells. MAC and perforin persuade citrullination of various auto-antigens in RA as, formerly described. The researchers used anti-modified citrulline immunoblotting to recognize cellular citrullination and defined perforin and MAC-induced **"**citrullinome" by mass spectrometry (MS) and matched it with citrullinome found in rheumatoid arthritis SF cells. So, using MS, scientists were able to validate the activation of perforin and MAC pathways for RA joint. Perforin and MAC pathways stimulate intracellular PADs and persuade increased citrullination present in RA target tissue. This array of cellular hypercitrullination triggered via two immune-interceded membranolytic paths is dependable with a preferred rheumatoid arthritis model, which proposes that immune responses to citrullinated proteins are a result of infectious or inflammatory measures. Based upon existing knowledge, there are links among immune related membranolytic pathways and instigation of PAD enzymes in rheumatoid arthritis. So, it is suggested that these interactions may be novel targets for rheumatoid arthritis treatment [18].

Tenascin-C (Tnc)

With the introduction of biological agents, there have been incredible developments in RA treatment, nonetheless mechanisms initiating cytokine synthesis and withstanding disease chronicity is still unidentified. Tnc is a glycoprotein present in extracellular matrix precisely noticed at regions of tissue damage and inflammation of rheumatoid joints. Earlier, it was demonstrated that acute joint inflammation was promptly resolved in mice that did not express Tnc and remained arthritis free. However, the joint inflammation is upholded by injection of Tnc in mice joints, and cytokine production is persuaded by supplementation of exogenous Tnc in explant cultures of inflammatory synovium of patients suffering from rheumatoid arthritis. Besides, Tnc tempts pro-inflammatory cytokines synthesis (*i.e*., TNF-a, IL-6 and IL-8 in primary human macrophages and IL-6 in synovial fibroblasts), through activation of Toll-like receptor 4 (TLR4) dependent signaling pathways. Thus, Tnc is identified as innovative activator of TLR4 intervened immune process, which arbitrates tenacious tissue destruction and synovial inflammation in arthritis patients. Collectively, above-mentioned data direct a potential role of Tnc in RA pathogenesis, where a continuous destructive cycle is generated by its stimulation upon tissue injury. By

understanding the mechanism through which Tnc mediates persistent inflammation, this erroneous inflammation can be suppressed by designing a Tnc targeted drug delivery system while, maintaining signals necessary for host defense against bacterial infection [22].

Tnc may tempt the production of factors explicit for polarization of Th17 by stimulating receptors on bone marrow-derived dendritic cell surface. Also, signaling pathway is initiated, which ensue in cytokine secretion and their de novo synthesis. For Th17 cell polarization, a network of transcription factors is also essential that work in combination with master regulator (RORγt) of Th17 polarization to facilitate IL-17 synthesis. Tnc activates TLR-4 on which murine IL-17 dependent arthritis essentially develops. IL-1α and IL-6 manifestation is also kindled by Tnc in murine macrophages through activation of α9 integrins. This signifies that numerous receptors may intervene Tnc-induced production of cytokine, independently or collectively. Nevertheless, IL-17 has a pivotal role in immune response and if inhibited, may convene adverse effects, such as neutrophil suppression, increased infection etc. The stimuli which are disease-specific initiate the synthesis of IL-17 in RA, which target pathologic joint inflammation without compromising physiological host defenses [23].

Chemokines

a. Chemokines and Chemokine Receptors

Numerous inflammatory intermediaries comprising matrix-degrading enzymes, cytokines and chemokines are produced by fibroblasts and leukocytes in synovial tissue. Chemotactic action is employed by chemokines on neutrophils, monocytes and lymphocytes. In synovitis and tissue destruction in chronic synovial inflammation, chemokines and chemokine receptors play an important role by positioning and recruiting the cells of immunity to the point of inflammation [24]. Formation of ectopic germinal center is also due to the involvement of chemokines and chemokine receptors and by unrestrained increase in immune cells within the joint. In the preceding era, most work have been done on the pathophysiology of these receptors in RA. By using a pharmacological approach to inhibit these receptors will have a definite success, basing on the current concepts of agonists and antagonists to be targeted against chemokines and their receptors [25]. Recent evidence suggests that to identify the inhibitors which directly target chemokines or their receptors might have a promising strategy in treating RA.

b. Regulation of Chemokine-Induced Synovial Angiogenesis

The synovial neovascularization relies on imbalance among angiogenic intermediaries and inhibitors of angiogenesis. There are numerous interactive mechanisms comprising inflammatory mediators in rheumatoid arthritis synovium. Various pro-inflammatory cytokines may directly arouse angiogenesis or indirectly by augmenting angiogenic chemokines synthesis. Chemokines play vital part in arthritis accompanying angiogenesis. Indeed, TNF-α and IL-1 stimulate the release of chemokines by rheumatoid arthritis synovial fibroblasts. The promptness in angiogenic secretion of SDF-1/CXCL12 and MCP-1/CCL2 in rheumatoid arthritis synovial tissue fibroblasts occur by the employment of pro-inflammatory and angiogenic properties of IL-18. In RA, macrophage migration inhibitory factor (MIF) is a pro-inflammatory and angiogenic cytokine. MIF also excites the secretion of IL-8/CX CL8. A lot of CXC chemokines, in addition to some CC and CX3C chemokines might get implicated in angiogenic, as well as inflammatory processes linked with RA. For defining rheumatoid arthritis progression in arthritic synovium, the determination of synovial vascularity and angiogenic chemokines manifestation might have some value. Anti-angiogenesis targeting using chemokine or chemokine receptor inhibitors may control synovial inflammation. In a recent research, IL-13 gene transfer in rat adjuvant-induced arthritis stemmed in angiogenesis suppression that was connected with down regulation of angiogenic chemokines ENA-78/CXCL5 and groα/CXCL1 [26].

Inactive Rhomboid Protein 2 (iRHOM2)

TNF-α convertase (TACE) is regulated by iRHOM2. It belongs to Rhomboid intramembrane proteinase family. For discharging TNF-α and for triggering epidermal growth factor receptor (EGFR), TACE is very vital [27]. The main drug target for RA is the cytokine TNF-α. To target TACE, a protease which releases TNF-α from cells can be another method. Nevertheless, in immune cells, tissue-specific inhibition of TACE, seems vital as it splits other proteins involved in development and cancer. An additional function for iRHOM2, *i.e*., facilitating TNF-α

release from macrophages has also been seen in three recent studies. In the endoplasmic reticulum, the iRHOM2 functions as a shipment receptor which binds TACE (also known as ADAM17). It splits membrane bound TNF-α precursor aiding TACE to reach the plasma membrane, ensuing in the release of TNF-α cytokine. Accordingly, at macrophages cell surface, genetic inactivation of iRHOM2 hampers TACE activity and other cells of immunity, thus preventing release of TNF-α. Hence, in rheumatoid arthritis, TNF-α acts as vital pathological player but its requirement in innate immunity is also there. All in all, inactivating iRHOM2 is a sophisticated way by which tissue-specific TACE inactivation in immune cells can be obtained while, perpetuating critical TACE functions in other organs. This makes iRHOM2 a striking drug target for rheumatoid arthritis [28].

Progranulin (PGRN)

It is a growth factor which has been involved in tissue repair, tumorigenesis, embryonic development and inflammation. The PGRN intrude TNFα-TNFR interaction by attaching directly to tumor necrosis factor receptors (TNFRs). Earlier study described that collagen induced arthritis was seen in mice having PGRN-deficiency whereas, PGRN administration withdrew inflammatory arthritis. Selective TNFR binding is seen with Atsttrin, which is an engineered protein (comprising 3 PGRN fragments). In multiple arthritis mouse models, inflammation was prevented by PGRN and Atsttrin and they both reduced TNF-α triggered intracellular signaling. Together, these discoveries prove that PGRN is an antagonist of TNF-α signaling and plays a pivotal role in pathogenesis of arthritis. PGRN being key inflammation regulator might employ its anti-inflammatory properties by hampering attachment of TNF to its receptors. However, in inflammatory process, macrophages and neutrophils release proteases that condenses PGRN into distinct 6-kD granulin units, which are pro-inflammatory and may counteract anti-inflammatory effects of intact PGRN. PGRN's anti-inflammatory actions are conserved by its binding proteins (secretory leukocyte protease inhibitor and apolipoprotein A1), which attach to PGRN and allow its proteolytic breakdown. The recognition of PGRN and PGRN-derived proteins as TNFR antagonists may bring an innovation in the treatment of several TNF-α mediated pathologies for instance, RA [29, 30].

Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22)

The PTPN22 is seen in hematopoietic cells and it guards T and B cell receptor (TCR and BCR) signaling. In the TCR signaling pathway, it acts downstream of receptor binding and halt the action of key signaling effectors, thus reduction in T cell provocation occurs. Contemporary investigations have revealed that through BCR signaling, B cell population and their tolerance checkpoints are associated with LYP, but not yet established its precise mechanisms. Balance of LYP protein isoforms have been seen in healthy patients and they are inclined with lower incidence of W620 allele (R620W variant) of PTPN22 and an increased rate of Q263 allele, which predispose a lesser chance with rheumatoid arthritis. Contrary to it, patients with rheumatoid arthritis have increase rate of W620 allele and a lower rate of Q263 allele. Such variances may precipitate foremost infections in patients with rheumatoid arthritis [31].

So far, most investigations have emphasized TCR and BCR signaling, while exploration of other immune cell types must also be done so as to attain complete understanding of PTPN22 function in health and sickness [32]. In order for therapeutic prospective of R620W, consensus regarding nature of mutation must be reached. Appreciating disruptions instigated by R620W in signaling forces that inclines individuals to pathogenic autoimmunity remains a hard challenge. PTPN22 remains a fair gene candidate for further study and its uninhibited presence in multiple autoimmune diseases may indicate an unrewarding mechanism underlying the development of autoimmune disease. These finding will definitely implicate our current understanding of autoimmunity and may end up as treatment beneficial for community [32]. It has also been postulated that ill effects of R620W variant on TCR and BCR signaling may regress the selective inhibitor of LYP, thus might constitute good target therapy for carriers of rheumatoid arthritis patients [31].

CONCLUSION

Rheumatoid arthritis entails complex pathophysiologic mechanisms. Recent therapeutic approaches in the management of arthritis accompany slight emphasis on selective and individualized therapy based on underlying pathogenesis. Hence, there is a pressing

need to develop innovative therapies devoid of shortcomings as associated with conventional treatment. Innovative therapies are directed against specific targets in several multifaceted pathophysiologic pathways that have not been established therapeutically so far. In this review, an attempt has been made to pinpoint numerous targets not being targeted until now. Hence, it is worthwhile to say that development of drugs either synthetic or herbal in origin might be highly useful for the management and cure of rheumatoid arthritis thus improving the quality of life among arthritic patients.

REFERENCES

1. Kim W, Park S, Choi C, Kim YR, Park I, Seo C, *et al*. Evaluation of anti-inflammatory potential of the new Ganghwaljetongyeum on adjuvant-induced inflammatory arthritis in rats. Evid Based Complement Alternat Med. 2016; 2016: 1230294.
2. Zheng C-J, Zhao X-X, Ai H-W, Lin B, Han T, Jiang Y-P, *et al*. Therapeutic effects of standardized Vitex negundo seeds extract on complete Freund's adjuvant induced arthritis in rats. Phytomed. 2014; 21(6): 838-46.
3. Sukketsiri W, Chonpathompikunlert P, Tanasawet S, Choosri N, Wongtawatchai T. Effects of Apium graveolens extract on the oxidative stress in the liver of adjuvant-induced arthritic rats. Prev Nutr Food Sci. 2016; 21(2): 79-84.
4. Wei ZF, Jiao XL, Wang T, Lu Q, Xia YF, Wang ZT, *et al*. Norisoboldine alleviates joint destruction in rats with adjuvant-induced arthritis by reducing RANKL, IL-6, PGE2, and MMP-13 expression. Acta Pharmacol Sin. 2013; 34(3): 403-13.
5. Adeneye AA, Oreagba AI, Ishola IO, Kalejaiye HA. Evaluation of the anti-arthritic activity of the hydroethanolic leaf extract of Alchornea cordifolia in rats. Afr J Tradit Complement Altern Med. 2014; 11(2): 402-10.
6. Rong-jun HE, Zhi-hong YU, Zhang R, Zhang Z. Protein tyrosine phosphatases as potential therapeutic targets. Acta Pharmacol Sin. 2014; 35(10): 1227-46.
7. Scheller J, Chalaris A, Garbers C, Rose-John S. ADAM17: a molecular switch to control inflammation and tissue regeneration. Trends in Immunol. 2011; 32(8): 380-7.
8. Rose-John S. ADAM17 shedding, TACE as therapeutic targets. Pharmacol Res. 2013; 71: 19-22.
9. Kim S, Chen Z, Chamberlain ND, Volin MV, Swedler W, Volkov S, *et al*. Angiogenesis in rheumatoid arthritis is directly fostered by TLR5 ligation and indirectly through IL-17 induction. Arthritis Rheum. 2013; 65(8): 2024-36.
10. Kim S, Chen Z, Chamberlain ND, Essani AB, Volin MV, Amin MA, *et al*. Ligation of TLR5 promotes myeloid cell infiltration and differentiation into mature osteoclasts in rheumatoid arthritis and experimental arthritis. J Immunol. 2014; 193(8): 3902-13.
11. Hamaguchi M, Kawahito Y, Ishino H, Takeuchi N, Tokunaga D, Hojo T, *et al*. Mucin from rheumatoid arthritis synovial fluid enhances interleukin-6 production by human peripheral blood mononuclear cells. Human Immunol. 2011; 72(3): 241-8.
12. Morand EF, Leech M, Bernhagen J. MIF: a new cytokine link between rheumatoid arthritis and atherosclerosis. Nat Rev Drug Discov. 2006; 5(5): 399-410.
13. Kasama T, Ohtsuka K, Sato M, Takahashi R, Wakabayashi K, Kobayashi K. Macrophage migration inhibitory factor: A multifunctional cytokine in rheumatic diseases. Arthritis. 2010; 2010: 106202.
14. Auger I, Charpin C, Balandraud N, Martin M, Roudier J. Autoantibodies to PAD4 and BRAF in rheumatoid arthritis. Autoimmun Rev. 2012; 11(11): 801-3.
15. Shoda H, Fujio K, Shibuya M, Okamura T, Sumitomo S, Okamoto A, *et al*. Detection of autoantibodies to citrullinated BiP in rheumatoid arthritis patients and pro-inflammatory role of citrullinated BiP in collagen-induced arthritis. Arthritis Res Ther. 2011; 13(6): R191.
16. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, Gizinski A, Yalavarthi S, Knight JS, *et al*. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med. 2013; 5(178): 178ra40.
17. Rabquer BJ, Koch AE. NK4 therapy: a new approach to target angiogenesis and inflammation in rheumatoid arthritis. Arthritis Res Ther. 2013; 15(5): 119.
18. Romero V, Fert-Bober J, Nigrovic PA, Darrah E, Haque UJ, Lee DM, *et al*. Immune-mediated pore-forming pathways induce cellular hypercitrullination and generate citrullinated autoantigens in rheumatoid arthritis. Sci Transl Med. 2013; 5(209): 209ra150.
19. Walle LV, Opdenbosch NV, Jacques P, Fossoul A, Verheugen E, Vogel P, *et al*. Negative regulation of the NLRP3 inflammasome by A20 protects against arthritis. Nature. 2014; 512(7512): 69-73.
20. Chen S, Sun B. Negative regulation of NLRP3 inflammasome signaling. Protein Cell. 2013; 4(4): 251-8.
21. So A, Busso N. The concept of the inflammasome and its rheumatologic implications. Joint Bone Spine. 2014; 81(5): 398-402.
22. Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, *et al*. Tenascin-C is an endogenous activator of Toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. Nat Med. 2009; 15(7): 774-81.
23. Ruhmann M, Piccinini AM, Kong PL, Midwood KS. Endogenous activation of adaptive immunity. Tenascin-C drives interleukin-17 synthesis in murine arthritic joint disease. Arthritis Rheum. 2012; 64(7): 2179-90.
24. Chen X, Oppenheim JJ, Howard OMZ. Chemokines and chemokine receptors as novel therapeutic targets in rheumatoid arthritis (RA): Inhibitory

effects of traditional Chinese medicinal components. Cell Mol Immunol. 2004; 1(5): 336-42.
25. Shadidi KR. New drug targets in rheumatoid arthritis focus on chemokines. Biodrugs. 2004; 18(3): 181-7.
26. Szekanecz Z, Pakozdi A, Szentpetery A, Besenyei T, Koch AE. Chemokines and angiogenesis in rheumatoid arthritis. Front Biosci (Elite Ed). 2010; 1: 44-51.
27. Issuree PDA, Maretzky T, McIlwain DR, Monette S, Qing X, Lang PA, *et al*. iRHOM2 is a critical pathogenic mediator of inflammatory arthritis. J Clin Invest. 2013; 123(2): 928-32.
28. Lichtenthaler SF. iRHOM2 takes control of rheumatoid arthritis. J Clin Invest. 2013; 123(2): 560-2.
29. Tang W, Lu Y, Tian QY, Zhang Y, Guo FJ, Liu GY, *et al*. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science. 2011; 332: 478-84.
30. Liu C. Progranulin: A promising therapeutic target for rheumatoid arthritis. FEBS Lett. 2011; 585(23): 3675-80.
31. Diaz-Gallo LM, Martin J. PTPN22 splice forms: a new role in rheumatoid arthritis. Genome Med. 2012; 4(2): 13.
32. Burn GL, Svensson L, Sanchez-Blanco C, Saini M, Cope AP. Why is PTPN22 a good candidate susceptibility gene for autoimmune disease? FEBS Lett. 2011; 585(23): 3689-98.