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Review Article

A REVIEW ON MACROPHAGES AND THE IMPACT OF PROTEASOME INHIBITORS ON RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid Arthritis (RA) is a common autoimmune disease that causes chronic inflammation of the tissues around the joints, which eventually results in systemic complications and bone destruction. Macrophages are critical cells in many tissues and organs essential to an innate and adaptive immune response. It is one of the most common cell types in the synovium of rheumatoid arthritis. Various conventional and experimental therapies for RA target proteins, cytokines or their synthetic pathways, T lymphocytes, and B lymphocytes. The Fibroblast-Like Synoviocytes (FLS) and macrophages are abundantly activated in RA, and the drugs targeting the monocytes and macrophages are explored significantly less. The drugs targeting monocytes and macrophages may provide a better therapeutic strategy for RA. Proteasome inhibitors act as a potential remedy for autoimmune and inflammatory diseases. Targeting the monocytes and macrophages with proteasome inhibitors may improve the therapeutic approaches to RA. This paper reviews the types and significance of macrophages in RA, various conventional and experimental therapy approaches targeting monocytes and macrophages, and the effect of proteasome inhibitors on macrophages in RA.

Keywords: Monocytes, Macrophages, Rheumatoid arthritis, Proteasome inhibitor, Cytokine

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory disease characterized by the infiltration of immune effector cells such as macrophages, fibroblasts, B cells, Dendritic cells, T cells, and Osteoclasts in the synovial tissues, leading to autoantibody production, inflammation, cartilage, and bone destruction. It affects 0.5-1% of the world's population. The incidence of RA is higher in women, especially in the elderly population, than in men [1, 2]. The etiology of RA is still unclear, but some risk factors include air pollution, smoking, and obesity. The type A synovial cells (macrophages) and type B synovial cells (fibroblasts) present in the synovial membrane play a central role in the pathophysiology of inflammation and are activated in rheumatoid arthritis. Macrophages are abundantly present in the rheumatoid synovium, the pannus junction, and the pannus of inflammatory vascular tissue in RA. The number of macrophages in the biopsy specimen correlates with the risk of radiographic joint destruction [3-5].

The therapeutic target in RA includes cytokines and Proteins themselves or their synthetic pathways. Disease-modifying anti-rheumatic drugs such as methotrexate, biologics such as Tumor Necrosis Factor (TNF)-alpha inhibitors, monoclonal antibodies including infliximab, adalimumab, etanercept, non-steroidal anti-inflammatory drugs have been used for the treatment of RA [6]. Lately, the drugs targeting protein catabolism and its regulations have been focused. The regulation of proteasome complexes by proteasome inhibitors has implications and potential benefits in treating RA. This review about macrophages, proteasome inhibitors, and rheumatoid arthritis was extensively prepared by a comprehensive assessment of available literature via major scientific databases such as Google Scholar, Pubmed, Science Direct, Scopus, and Wiley Online Library. Keywords used for collecting the data were Proteasome inhibitors in RA, Macrophages as therapeutic targets and conventional and therapeutic drugs in rheumatoid arthritis. A literature review was conducted over the past 20 y, and about 111 articles were analyzed. After the manuscripts' collection, results were analyzed and categorized according to the objective of this review and section. Many reviews in RA prioritize rheumatoid arthritis-related macrophages, and properties focus on the polarisation of macrophages, metabolism, apoptosis, and proteasome inhibitors in autoimmune disorders. However, none of the reviews focused specifically on the effect of proteasome inhibitors on macrophages. This review focused on different types of macrophages, the way to target macrophages in various diseases, inflammation, and RA, and the effects of cytokine and cell surface receptors on macrophages of RA. It also discussed conventional and experimental RA therapeutic approaches targeting monocytes and macrophages and the impact of proteasome inhibitors on macrophages of RA.

Macrophages

Macrophages are mononuclear phagocyte systems derived from the bone marrow progenitor cells, which differentiate to form monocytes, enter into circulation, and then reside in tissues. They play a crucial role in innate and adaptive immune responses to pathogens and mediate inflammatory processes. It exhibits proinflammatory and anti-inflammatory properties depending on the disease stages and the signals received. The multifunction of macrophages includes the development and repair of tissues, metabolic homeostasis, Immunity, clearance of cellular debris, and regulation of angiogenesis. The main functions of macrophages are wound healing, resolution of inflammation, matrix remodeling, tissue repair and remodeling, coordinating cell migrations, and angiogenesis [7].

Macrophages are critical in many chronic diseases, including cancer, multiple sclerosis, fibrosis, inflammatory bowel diseases, asthma, atherosclerosis, and rheumatoid arthritis. They are the source of inflammatory cytokines and are involved in the pathogenesis of many autoimmune diseases, including inflammatory bowel diseases, multiple sclerosis, and Rheumatoid arthritis. In some circumstances, macrophages are differentiated into osteoclast-like cells and involved in bone resorption [8].

Macrophage subsets

M1 and M2 macrophages

Macrophages are mainly differentiated into two types. Type I Macrophages (M1), or Conventionally Activated Macrophages (CAM), are known for their pro-inflammatory characteristics. Type II

Macrophages (M2), also known as Alternatively Activated Macrophages (AAM), are known for their anti-inflammatory effects [fig. 1].

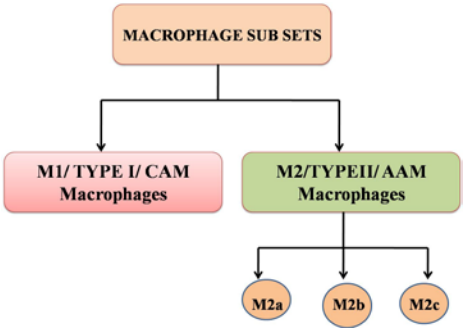

Fig. 1: Macrophage subsets. The image was sourced from BioRender.com

CAM is activated in response to Interferon-γ (IFN-γ), microbes, or microbial products such as LipoPolySaccharide (LPS). This type of activation leads to high levels of expression of Interleukine-12 (IL-12) and IL-23 and shallow levels of IL-10, implying that type I macrophages promote strong Th1-polarized immune responses. Concomitantly, it exhibits cytotoxic solid, microbicidal, and anti-proliferative activities, all stem from producing Reactive Oxygen Species (ROS), reactive nitrogen species, and pro-inflammatory cytokines. AAMs are activated in response to IL-4 or glucocorticoids. It is characterized by high expression of scavenging molecules, polyamines, ornithine, mannose, and galactose receptors. In neoplastic tissues, it is linked to tumor growth and metastasis. M2 macrophage has several subsets, such as M2a, M2b, and M2c, and exert different physiological roles. M2 macrophages are usually anti-inflammatory and characterized by the increased secretion of IL10 and decreased secretion of IL12 and IL23 [9, 10]. It exerts high phagocytic capacity. These types of macrophages were involved in the healing phases of acute inflammation, chronic inflammatory diseases such as RA, psoriasis, and wound healing.

It abundantly presents in the human placenta and protects the fetus. It may also be involved in the three phases of healing, such as the down-regulation of inflammation, angiogenesis, and the elimination of tissue debris and apoptotic bodies. Macrophages exert plasticity, which is a significant property that helps the body switch from a pro-inflammatory phenotype (M1macrophages) to an anti-inflammatory state (M2 macrophages) [11]. Tumors activate Tumor-Associated Macrophages (TAM) and have different phenotypes. These types of macrophages resemble M2 macrophages. In carcinogenesis, these macrophages interact with tumor cells, stimulating proliferation, growth, invasion, and angiogenesis but inhibiting T helper cell immune response [12].

Targeting macrophages in various diseases

The critical aspect of drug delivery is releasing the drug and genes to the targeted macrophages. These macrophages are involved in infections, including tuberculosis, leishmaniasis, and lung cancers. Macrophages with cellular backpacks, such as catalase-loaded backpacks, act as target drug delivery for treating many neurodegenerative diseases [13, 14].

Macrophages act as nanocarriers for drug delivery in the central nervous system diseases. It is a novel therapeutic strategy for treating major nervous system diseases. The chemokines secreted from the central nervous system induce the migration of macrophages to the brain and advance neuron degeneration, promoting inflammation and angiogenesis. Huiling Peng *et al.* reviewed and discussed the role of macrophage polarization in the pathological processes of vascular skin diseases. Engineered macrophages act as near-infrared light-activated drug vectors for chemo-photodynamic therapy of primary and bone metastatic breast cancer [15-17]. Some reviews on macrophages explained their role in inflammation, tissue repair, regeneration, resolution of inflammation, the drug delivery system to macrophages, and the origins, differentiation, and functions of tissue macrophages in inflammation and lung disease [18-21].

Cytokine and cell surface receptors on macrophages of rheumatoid arthritis

Macrophages in the lining layer differ from the sub-lining layer of rheumatoid synovium in the expression of adhesion molecules and secreted mediators. Macrophages in the lining layer are significant sources of numerous cytokines, including TNF-α and IL-1. These are the critical cytokines that play an essential role in the pathogenesis of RA [fig. 2].

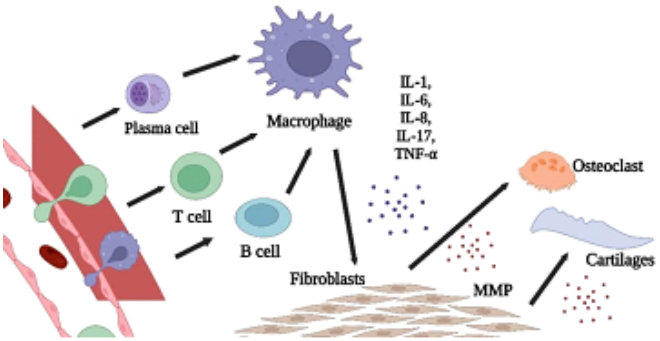

Fig. 2: Pathogenesis of rheumatoid arthritis

Pathogenesis of RA occurs due to the infiltration of macrophages, fibroblasts, T cells, B cells, and plasma cells from blood-activated macrophages and fibroblasts. Activated cells release proinflammatory cytokines IL-1, IL-6, IL-8, IL-17, TNF-α, and Matrix Metallo Proteins (MMP), eventually destroying cartilage and bone. The image was sourced from BioRender.com

The other cytokines exert either stimulatory (IL-6, IL-12, IL-15), Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF), or inhibitory effects IL-1 Receptor Antagonist (IL-1Ra), Transforming Growth Factor-Beta (TGF-β) on immune and inflammatory processes. TNF-α induces the production of Matrix Metallo Proteinase-1 (MMP-1), cytokines, and adhesion molecules in the synovium and ROS, Nitric Oxide (NO) from macrophages, which plays a primary role in RA pathogenesis.

The other proinflammatory cytokine, IL-1, causes articular destruction in RA by stimulating the release of MMP-1, MMP-3 inhibiting proteoglycan synthesis, and degrading proteoglycan. TGF-β produced from macrophages stimulates it to release reactive

oxygen species via the FcγRIII receptor. Macrophages promote the synthesis of MMP-13 production in chondrocytes, which causes cartilage destruction in RA. Overexpression of CD147 along with IL-1 and TNF-α activates the production of MMPs such as MMP-1, MMP-2, and MMP-3 and causes fibroblast activation. Macrophage Migration Inhibitory Factor (MIF) is a cytokine that also plays a vital role in cartilage degradation by stimulating Synovial fibroblasts to produce MMP-1 and MMP-3 [22].

Macrophages play an essential role in synthesizing lipid mediators of inflammation, destruction of cartilage and bone, and antigen presentation to T cells. Some cytokines cause either stimulation, suppressive effect, or both effects on macrophages. The cytokines that stimulate macrophages include TNF-α, TNF-R, IL-1, IL-15, IL-17, IL-18and IL-23. MIF, chemokines such as IL-8, MCP-1, and suppressive cytokines include IL-1Ra, IL-4, IL-10, IL-11 and IL-13. IL-6 and TGF-β exert a dual effect on monocytes/macrophages of RA [23].

The cell surface receptors expressed on synovial macrophages include the p55 and p75 TNF receptors; low-affinity IgG receptors FcγRII and FcγRIII; adhesion molecules CD31 and CD44 influence the activity of macrophages. The macrophages cause infiltration in inflammatory sites and are hence activated by many factors such as IL-1β, TNF-α, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-18, INF-γ, immune complexes, opsonized particles, pathological collagen deposition and T-lymphocytes [24, 25]. An increased expression of class II MHC (Major Histocompatibility Complex), Monocyte Chemoattractant Protein-1 (MCP-1), GM-CSF, TGF-β, Macrophage Inflammatory Protein (MIP), prostaglandin E2 (PGE2), MMP 2, MMP 7, MMP 9 and MMP 12 also exert macrophage activation [23].

Macrophages and angiogenesis

Macrophages promote angiogenesis and produce pro-angiogenic factors in RA. The antiangiogenic factor ThromboSpondin-2 (TSP-2) produced from macrophages in the synovial lining layer or the stroma of diffuse synovitis reduces the inflammation and neoangiogenic vessels in RA tissue. Macrophages in synovial tissue stimulate TNF-α, IL-1, and TGFα cytokine and produce Vascular Endothelial Growth Factor (VEGF). Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1) is critical in macrophage activation and angiogenesis in RA. Chung *et al.* studied the induction of new blood vessels by VEGFR-3 via macrophage activation [26, 27]. An increased number of macrophages in hypoxic tissues of synovial membrane induces VEGF production and expression of hypoxia-inducible factor 1α in RA. The angiogenic cytokine fractalkine released from synovial tissue macrophages enhances angiogenesis *in vitro* and *in vivo.* It also releases another angiogenic cytokine, IL-8, which increases the expression of Epithelial Neutrophil-Activating Protein-78 (ENA-78) and leucocyte adhesion molecule. A research study by Cuschieri *et al.* demonstrated the critical role of cellular proteasome in regulating LPS-induced signaling within macrophages and inhibition of proteasome eventually converted to an anti-inflammatory phenotype [28, 29].

Different therapeutic approaches for the treatment of rheumatoid arthritis

Although the monocytes or macrophages play a central role in inflammation, their plasticity makes them an ideal target for treating inflammatory diseases such as RA. Various therapies target T cell function (CTLA4-Ig), B cells (anti-CD-20), and cytokines such as TNF-α, IL-1, IL-6, and IL-17 [30, 31]. Chloroquine inhibits TNF-α, IL-1β and IL-6 in human monocyte/macrophages on LPS stimulation. Dehydroxy methyl epoxy quinomicin is a newly developed compound that inhibits macrophage cytokine production via Nuclear Factor Kappa B (NFkB) inhibition and suppresses murine collagen-induced arthritis [32]. Some therapeutic approaches, such as conventional and experimental anti-macrophage therapies, were used to treat RA [table 1].

Table 1: Summary of different therapeutic strategies in rheumatoid arthritis

RA models	Type of cells	Mechanism	Impact/Outcome of RA	References
RatAntigen -Induced Arthritis (AIA)	Synovial macrophages	Liposomal Clodronate eliminates synovial macrophages	Reduced inflammation and Joint Destruction	[33]
LPS stimulated	Murine macrophages	Resveratrol, a potent proteasome inhibitor, suppresses the expression of genes and inflammatory products.	Inhibition of nitric oxide and inflammatory cytokines	[34]
Streptococcal induced arthritis	Synovium of Rats	MG 132 proteasome inhibitor	Induces apoptosis	[35]
Raw264.7 macrophages model	Raw264.7 macrophages	Salinosporamide A	Potentiates apoptosis and suppresses osteoclastogenesis	[36]
Rheumatoid arthritis	Fibroblast like synoviocytes	Bortezomib (PS341)	Induced apoptosis	[37]
Rheumatoid arthritis patients	Activated T cells	Bortezomib (PS341)	Inhibits the release of NFkB inducible cytokines and induces apoptosis	[38]
Adjuvant induced arthritis	Splenocytes and Fibroblast like synoviocytes	Bortezomib (PS341)	Inhibits NFkB DNA binding, reduced inflammation, and bone disease	[39]
Transgenic mice model	Transgenic mouse lines	Monoclonal Antibodies to TNF	Suppressed chronic inflammatory polyarthritis	[40]
Collagen-induced Arthritis in mice	Arthritic paw and joints	Neutralization of TNF using antibodies	Decreased paw swelling	[41]
Human murine SCID arthritis	Synovial membrane	Blocking of TNF	Decreased RA inflammation	[42]
Rat Adjuvant-Induced Arthritis (AIA)	Synovial inflammation	Delivery of Adenoviral vector inhibits Ikk2 activity	Decreased NFkB DNA binding and Decreased RA	[43]
Human peripheral monocyte	Human peripheral monocyte	Abatacept inhibits osteoclastogenesis	Decreased RA	[44]
TypeII Collagen-InducedMice (CIA)	Synovial tissues	Neutralizing monoclonal Antibodies against CD 40	Reverse joint inflammation and block the immune cell infiltration into the synovial tissue.	[45]
CIA mice	Arthritic joints	Antisense oligonucleotide against CD 4 by liposome-mediated delivery system	Decreased paw swelling, reduced inflammation	[46]
RA models	Synovial macrophages	Novel syk inhibitor	Suppression of inflammation and bone erosion	[47]
CIA rats	synoviocytes	Delanzomib, a novel proteasome inhibitor in combination with adalimumab	Ameliorate RA	[48]
IL-1 beta-induced rheumatoid arthritis patients	macrophages	Proteasome inhibitor AM114	Induced apoptosis and ameliorates proinflammatory cytokines IL6, IL8	[49]

Disease-Modifying AntiRheumatic Drugs (DMARD), gold compounds, methotrexate, antimalarial drugs, corticosteroids, and non-steroidal anti-inflammatory drugs such as aspirin are the conventional anti-macrophage therapies for the treatment of RA. A recent study exerts the effect of methotrexate on rheumatoid arthritis. The correlation between pulmonary function tests and disease activity was evaluated [50]. Leukapheresis, apoptosis-inducing agents such as liposome-encapsulated bisphosphonates, DMARD, bucillamine, and control of gene transcription, vitamin D3, and gene therapy with IL-1 receptor antagonist are some of the experimental anti-macrophage therapy approaches for the treatment of RA. Tramadol Hydrochloride (TH) is an analgesic drug used to treat rheumatoid arthritis [51]. The potential experimental therapeutics against arthritis by targeting monocytes or macrophages are Cytosolic Phospho Lipase A2 Alpha (cPLA2α) and Osteoclast differentiation using lipoplexes and dendrimers [52].

Different therapeutic strategies such as clodronate liposomes, targeting folate receptors, and photosensitizer-linked nanoparticles have been attempted to reduce the inflammation in Rheumatic diseases [53, 54]. Differential activation of intracellular signal transduction pathways is the macrophages' primary effector. Specific inhibitors of the signal transduction pathways and critical metabolic enzymes act as a selective therapeutic target for anti-rheumatic therapy. The Novel therapeutic approaches for RA include TNF inhibitors, Autophagy suppression by autophagy inhibitors (Rapamycin, chloroquine and Hydroxychloroquine), Jannus-activated kinase inhibitors (Baricitinib and Tofacitinib), Co-stimulation blockers (Abatacept), CD20 (Rituximab, Ofatumumab) and CD22 (Epratuzumab) targeting on B-cell surfaces and plasma cell targeting therapies (Anti-Thymocyte Globulin), IL-1 and IL-6 targeting monoclonal antibodies (Anakinra and Tocilizumab) and intraarticular administration of mesenchymal stem cells [1, 55, 56].

Proteasome inhibitors and rheumatoid arthritis

Proteasome inhibitors are potential remedies for autoimmune and inflammatory diseases, acting chiefly by inhibiting NFkB. Proteasome inhibition may benefit patients with RA via modulation of three different mechanisms: apoptosis, Th1 response, and angiogenesis Few studies have focused on the effect of proteasome inhibitors such as bortezomib and MG132 on RA cell types such as FLS, adjuvant-induced arthritis, and streptococcal-induced synovium of rats have been reviewed [57, 58].

The MG 132 proteasome inhibitor induces apoptosis in streptococcal-induced arthritis in the synovium of rats. The epoxomicin proteasome inhibitor exerts anti-inflammation in the picryl chloride pre-immunised mice model. The proteasome inhibitor salinosporamide A showed the apoptosis and suppression of osteoclast genesis in RAW 264.7 macrophage cells [36]. In the same way, the Proteasome inhibitor bortezomib showed induction of apoptosis and inhibition of the release of NFkB inducible cytokines in T cells of RA. Moreover, it also showed the inhibition of NFkB DNA binding on adjuvant-induced arthritis, inflammation, and bone diseases. A recent review on the proteasome inhibitor Bortezomib explained its beneficial effect in treating autoimmune disease [37-39, 59].

Proteasome inhibition induced macrophage apoptosis via mitochondrial dysfunction. A study on macrophages demonstrated that proteasome inhibition by MG 132 proteasome inhibitor can induce macrophage apoptosis by promoting the production of mitochondrial reactive oxygen species and mitochondrial dysfunction [60]. Although monocytes/macrophages play a critical role in RA, none of the current therapies specifically focus on monocytes/macrophages of RA. The study's results on the efficacy of proteasome inhibitor AM114 on the signal transduction pathway in macrophages of RA showed the induction of apoptosis and augmentation of proinflammatory cytokine release in macrophages. The study's results may provide a better understanding of proteasome inhibitors' effect on RA macrophages [61]. Therefore, targeting monocytes or macrophages using a proteasome inhibitor may give more knowledge about the functions of the cells and act as a therapeutic target in the treatment of RA.

CONCLUSION

Macrophages play a crucial role in the pathogenesis of malignant diseases, atherosclerosis, and chronic inflammatory diseases, such as RA. Many conventional and experimental therapeutic approaches and biotherapies have changed the pathogenesis of RA, and alternatives are worth considering. An alternative proteasome inhibitor may be used since it induces apoptosis and changes the release of proinflammatory cytokines in RA. Thus, targeting monocytes and macrophages with proteasome inhibitors may change outcomes and complications in RA.

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AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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