WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 2, 1266-1270. Review Article ISSN 2277– 7105

ROLE OF METALLOPROTEINASES IN THE PATHOPHYSIOLOGY OF RHEUMATOID ATHRITIS

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Article Received on
19 Dec. 2019,

Revised on 09 Jan. 2020,
Accepted on 30 Jan. 2020,

DOI: 10.20959/wjpr20202-16772

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease of heterogeneous origin. RA occurs when the immune system is triggered by an unknown antigen resulting in cascade of inflammatory mediators. This disease is characterized by symptoms such as joint tenderness, muscle weakness, reduced range of motion and metatarsophalangeal joint pain. Since there is no complete cure for RA, the primary goal of treatment is to prevent further structural damage of connective tissues and the joints. This review discusses about pathophysiology of rheumatoid arthritis with emphasis on role of metalloproteinases and cathepsins in pathophysiology of RA.

KEYWORDS: Rheumatoid arthritis, autoimmune disorder, metalloproteinases.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease whose aetiology is completely heterogeneous. The annual incidence of RA has been reported to be around 40 per 100000. Women are 3 times more affected by RA when compared to men. It is mainly associated with early morning stiffness, pain, swelling, redness, warmth with constitutional symptoms such as fever, decreased muscle strength, weight loss, fatigue and loss of appetite. It can also cause pulmonary, cardiovascular, brain diseases, splenomegaly, anemia, leukopenia, thrombocytopenia and leg ulcers.[1] Early treatment of the disease reduces inflammation and joint destruction. Currently available treatment strategy of RA includes non steroidal anti-inflammatory drugs, disease modifying anti-rheumatoid drugs and biological agents. These drugs when given in combination attenuate inflammation at all

stages of RA but are associated with severe adverse effects. This review focuses on role of matrix metalloproteinases and cathepsins in the pathophysiology of RA.

PATHOPHYSIOLOGY OF RA

Modification of shared epitopes by DNA methylation and histone modification initiates RA**.** Citrullination is the cardinal process in genesis of RA and mainly takes place in the apoptotic cells. Citrullinations take place by the post translational modification of arginine residue in presence of peptidyl arginine deaminase (PAD) where arginine is converted to citrulline.[2] PAD normally remains inactive but during inflammation, influx of calcium from the extracellular space activates PAD leading to citrullination. Evidence shows that microorganisms such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* triggers anti citrullinated protein antibodies (ACPA). *Porphyromonas gingivalis* which causes periodonitis produces citrullination by increasing the expression of PAD enzyme on C-terminal end of amino acid arginine. *Aggregatibacter actinomycetemcomitans* produces leukotoxin A intercedes citrullination on binding with β2 integrin which is present on neutrophils and thus leading to influx of extracellular calcium ions.[3] The citrullinated neoantigens activates T cells in secondary lymphoid tissues or bone marrow which in turn induces B cells to produce ACPA. ACPA acts in 3 ways. It directly activates monocytes by binding on Grp 78 protein that leads to expression of nuclear factor kappa B (NFκB) and cytokine.[4] Secondly it increases the generation of neutrophil extracellular trap (NET) to stimulate the activation of chemokines and cytokines. Thus the synovium becomes infiltrated by leukocytes and the synovial fluid gets overloaded with proinflammatory mediators such as interleukin 1β, interleukin 6 and tumor necrosis factor alpha (TNF alpha) which produces pain, synovial inflammation and joint destruction. Thirdly ACPA binds to osteoclast precursors ($CD68^{+}$) in bone marrow and induces CXCL1/2 expression in the joints and CXCL1/2 release that culminates in osteoclastogenesis, bone resorption and bone loss.[5-8] Rheumatoid factor, C reactive protein and erythrocyte sedimentation rate are the main biological markers in RA. ACPA can be detected in the serum and synovial fluid.

ROLE OF MATRIX METALLOPROTEINASES IN RA.

Matrix metalloproteinases are zinc dependent metallopeptidases and contains 2 main domains such as pre-domain and prodomain. These peptidases are commonly called as metzincins implicated in rheumatoid arthritis, Alzheimer's disease, asthma, atherosclerosis, atopic dermatitis, bullous pemphigoid, chronic obstructive pulmonary disease, gout, inflammatory

bowel disease, ischaemia reperfusion injury, multiple sclerosis, osteoarthritis, psoriasis, sarcoidosis, systemic lupus erythematosus, type 1 diabetes mellitus, ulcerative colitis, Helicobacter pyroli gastritis, hepatitis C, Neisserial or pneumococcal meningitis and tuberculosis.[9] MMP's is divided in to 5 types.

Collagenases (MMP-1, 8 and 13)

Gelatinases (MMP-2 and 9)

Stromelysins (MMP-3, 10 and 11)

Matrilysins (MMP -7 and 26)

Membrane type metalloproteinases (MMP-14, 15, 17, 24 and 25).[10]

MMP 1 and 8 are found in the surface of cartilage and MMP 13 is present in deep layers. MMP 2 and 9 are mainly present in the synovial fluid.[11] MMP 3 and 10 are present in osteoblast[12] while MMP 11 is expessed in fibroblastic cells.[13] MMP 7 is more commonly localized in articular cartilage.[14] MMP 14 is expressed in both superficial and transitional zones of osteoarthritic cartilage.[15] MMP 25 mostly expressed in brain regions.[16]

MMP IN CARTILAGE DESTRUCTION

Structural rigidity of the joints is maintained by type 1 collagen in the tendons and type 2 collagen in the cartilage. Collagenase cleaves collagen between Glycine 775 and Leucine 776 resulting in unwinding of collagen.[17] Collagen molecules get denatured and are further degraded by MMP's. MMP's are activated by inflammatory pathways such as NFκB and mitogen activated protein kinase. Activator protein (AP-1) plays a crucial role in regulating the transcription of MMP's. NFκB is mainly found as inactive state in cytoplasm and remain bounded to IkB. TNF alpha or interleukin 1 beta on activation leads to phosphorylation of IkB and produces transcription of MMP's. Transforming growth factor alpha which is mainly found in arthritic joint also stimulates transcription of MMP's. Metalloproteinase along with disintegrin and thrombospondin plays a major in the degradation of connective tissue and components of extracellular matrix such as collagens, non-collagenous glycoproteins, hyaluronan and proteoglycan. This results in synovial proliferation on the surface of the cartilage and produces tumor like mass called "pannus" due to the expression of p-53. This pannus formation thus alters the structural rigidity of connective tissue and produces rheumatoid arthritis.

CATHEPSINS

These are the cysteine proteinases and is of following types as B, K, L, S, H, F, C, X and O.[8] Among these types cathepsins S and K are mainly involved in rheumatoid arthritis and predominantly contribute to the cartilage destruction by deregulation of chondrocytes. Cathepsin S is a protease enzyme and involved in the processing of antigens. It is present in dendritic cells. It is stable at neutral and mild alkaline pH. During inflammation synovial macrophages gets activated. This activated macrophages secrets cathepsin S and degrades extracellular elastin.[18] Cathepsin K is expressed in synovial fibroblasts and macrophages. It is involved in degradation of collagen. It also degrades aggrecan at acidic pH.

CONCLUSION

RA is a delicate autoimmune disease whose underlying mechanism is that immune system starts attacking the joints. Even though several factors are involved in the development of the disease, the formation of ACPA's metalloproteinases and cathepsins are the prompt factors for collagen degradation and joint destruction. Available drugs relieve only the symptoms at the early stage of disease while complete cure of the disease at the late stage is still obscure. Futuristic development for curing the disease is indeed to overcome not only the disease but also the other extra articular manifestations.

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