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Review

Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis

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ABSTRACT

This review is intended to provide a summary of the pathogenesis, diagnosis and therapies for rheumatoid arthritis. Rheumatoid arthritis (RA) is a common form of inflammatory autoimmune disease with unknown aetiology. Bone degradation, cartilage and synovial destruction are three major pathways of RA pathology. Sentinel cells includes dendritic cells, macrophages and mast cells bound with the auto antigens and initiate the inflammation of the joints. Those cells further activates the immune cells on synovial membrane by releasing inflammatory cytokines Interleukin 1, 6, 17, etc., Diagnosis of this disease is a combinational approach comprises radiological imaging, blood and serology markers assessment. The treatment of RA still remain inadequate due to the lack of knowledge in disease development. Non-steroidal anti-inflammatory drugs, disease modifying anti rheumatic drugs and corticosteroid are the commercial drugs to reduce pain, swelling and suppressing several disease factors. Arthroscopy will be an useful method while severe degradation of joint tissues. Gene therapy is a major advancement in RA. Suppressor gene locus of inflammatory mediators and matrix degrading enzymes were inserted into the affected area to reduce the disease progression. To overcome the issues aroused from those therapies like side effects and expenses, phytocompounds have been investigated and certain compounds are proved for their anti-arthritic potential. Furthermore certain complementary alternative therapies like yoga, acupuncture, massage therapy and tai chi have also been proved for their capability in RA treatment.

Contents

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1. Introduction

Rheumatoid arthritis (RA) is a prevalent form of inflammatory arthritis represented as an autoimmune disease, happens in bone joints due to malfunction of the immune system. Approximately 1–2% of the world population get injured with rheumatoid arthritis, most frequently found in developed countries [1]. Women are predominantly more often get affected than men [2]. Number of symptoms is usually expressed on the onset of RA like warm fingers and toes, stiffness of joints and swelling. Sometimes it might happen also as silent or asymptomatic. This is an age related musculoskeletal disease most likely affect people in 30–50 years of age. The abnormal immune responses against synovial tissues attributes the cause of RA eventually the loss of joint mobility, subluxation, swelling and synovial inflammation. The connective tissues, subchondral bone, synovial membrane and weight bearing cushion materials of extracellular matrixes collagen and proteoglycans are destructed by own immune system [3]. Synovial fluid present just beneath the synovial membrane provides lubrication to the joints gets oozes out and cause inflammation. RA destruction may happen to the joints all over the body in a symmetrical pattern where distal interphalangeal and cervical spine is usually spared in the early stage of the disease progression. This is a systemic disease could affect some internal organs over the body includes heart and lungs. Aggressive conditions of RA may lead to atherosclerosis and respiratory lung diseases [4]. RA will be developed during the lack of sufficient cytokine suppressor, protease inhibitors, antioxidants and anti-angiogenic factors. Those factors are used as nonspecific serological markers for the disease diagnosis. While Rheumatoid factors (RF), Anti-ccp autoantibodies from B cell activated plasma cells are specific markers. Radiography like X-ray, ultrasonography and MRI scanning provide us structural information of the bone and connective tissues of the joints. Miserably, there is no permanent cure for RA, but it might be kept controlled by NSAIDs, DMARDs, and corticosteroids [5,6]. Arthroplastic surgeries like partial or total replacement of the joint are followed during aggressive conditions of RA. To overcome the issues aroused from these therapies, active phytocompounds and some alternative therapies have been investigated for their feasibility along with commercial drugs.

2. Etiology

The precise aetiology of rheumatoid arthritis is still unclear [7]. However, some research findings provide evidences for involvement of various factors in the cause of RA. Free radicals like reactive oxygen and nitrogen species can damage the articular components of the joints may lead to inflammatory arthritis. Free radicals such as hydroxyl radicals can degrade proteoglycans in extracellular matrix, hydrogen peroxidase blocks the synthesis of proteoglycan, tissue inhibitor of metalloproteinases are inactivated by peroxinitrate radical through destroying the cartilage tissue. Hypochlorous acid (HOCL) is an oxidising, chlorinating compound; it activates neutrophil collagenase and gelatinase lead to fragmentation of collagen matrix [8]. Myeloperoxide enzyme presents in neutrophils and monocyte are responsible for the generation of HOCL [9]. ROS is also functions as a signal mediator to activate NF kB, AP-1, etc. [8]. Smoking is associated with the severe risk of seropositive Anti citrullinated peptide antibody (ACPA) and Rheumatoid factor (RF). It citrullinizes connective tissue proteins by up-regulating the enzyme peptidylarginine deaminase [4]. Infectious arthrotropic microbes are one of the environmental factor for the cause of RA. Toll like receptors (TLRs) recognize the structure of the pathogen and provide first line defence by means of activating antigen presenting cells (APC) and releasing inflammatory cytokines. Different genes are involved in the RA initiation notably, MHC class II genes with HLA-DR4 allele association, Polymorphism of Protein tyrosine phosphatase-22 (PTPN22) and peptidyl arginine deiminase-14 (PAD14). Genetic factors involvement in RA development either hereditary or due to epigenetic modification. Even certain hormones are influencing the cause of RA and autoimmune diseases. Inflammatory mediators like TNF-α, IL-6 drive the estrogen hormones level higher. Estrogen exhibits the proinflammatory actions and that was controlled by progesterone, glucocorticoids and androgens. Studies identified the low levels of those hormones on women with RA and some other autoimmune diseases. Diet and lifestyle also have crucial roles in the development of rheumatoid arthritis. Consequently certain diseases like osteoarthritis and autoimmune diseases are contributory factors associated with the cause of RA [10].

Table 1
List of cytokines, autoantibodies and other mediators implicated in RA.

Intracellular mediators	Description
COX-2	Cyclooxygenase 2 is an isoenzyme carries the process of prostaglandins generation (inflammation mediator) from arachidonic acid
TNF-alpha	Tumour necrosis factor alpha is an inducer of inflammatory cytokines and GM-CSF
IL-1	Initial regulator cytokine of inflammation
IL-2	Activates the T cell differentiation
IL-6	Stimulates B cells for the production of autoantibodies RF & ACPA through plasma cells
IL-15	Stimulates proliferation of T cells
IL-16	Anergize CD4 expressing cells
IL-17	Increases inflammatory cytokines release from macrophages
IL-18	Regulates IFN-γ
IFN-γ	Facilitate in pannus formation and promotes fibroblast like synoviocytes (FLS)
OPG	Osteoprotogerin is a naturally occurring decoy receptor of RANK inhibits osteoclastogenesis
GM-CSF	Granulocyte macrophage-Colony stimulating factor stimulates the proliferation of granulocytes and macrophages
VEGF	Vascular endothelial growth factor is a pro-angiogenic cytokine.=
CRP	C Reactive protein active inflammatory mediator induces RANKL expression and directs precursor osteoclasts differentiation
RF	Rheumatoid factor (IgM) is an autoantibody found in RA patients, which targets the Fc region of IgG
ACPA	Anti citrullinated peptide antibody is an another autoantibody present in 80% of RA patients