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RHEUMATOID ARTHRITIS : AN UNDERSTANDING IN THE LIGHT OF HERBAL MEDICINES

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ABSTRACT

Rheumatoid arthritis (RA) is characterised by chronic polyarticular synovial inflammation and progressive erosion of cartilage and bone. The disease occurs at any age, but is common among those aged between 40-70 years. RA has a worldwide distribution with prevalence of 1 to 2%. Pathogenesis of RA remains a mystery for past 40 years. Genetic studies established that people who carry specific MHC haplotypes show a higher risk for RA. Cytokines have also been implicated as important mediators of disease. Analysis of cytokine mRNA and protein in RA tissue revealed that TNF-, IL-1, IL-6, GM-CSF, and IL-8 are abundant. Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) influences the inflammatory molecules. Antioxidants (exogenous or endogenous) are the compounds which prevent the generation of toxic oxidants. Treatment choice of the physician for RA is Non steroidal anti-inflammatory drugs (NSAIDs) and Disease modifying anti-rheumatic drugs (DMARDs). Herbal medicine is one of the oldest and traditional medicine systems around the world. Herbal products may contain a single herb or combinations of different herbs believed to have complementary effects. These contain potent bioactive substances.

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INTRODUCTION

Rheumatoid Arthritis

Rheumatoid arthritis (RA) was first proposed as a syndrome in the early 19th century. The backdrop of later research came up with several hypotheses. One of the oldest of these is the stress hormone hypothesis proposed by Selye, (1). According to this hypothesis, hormones released by the body, especially those released by the adrenal glands, cause an adverse reaction in the joint tissues when they are released in too large amounts or the wrong ratios either under altered conditions of environmental stress or psychic stress.

The most recent hypothesis is the autoimmune hypothesis. This hypothesis proposes that the body's immune mechanism gets out of order, and starts killing connective tissue cells. Most of the researchers consider it as a proven theory. A much higher association of antigen HLA-B27, which is a known immunity factor, has tended to reinforce this thought that they are on the right track.

RA is characterised by chronic polyarticular synovial inflammation and progressive erosion of cartilage and bone. The disease occurs at any age, but is most common among those aged between 40-70 years. In rheumatoid lesions which are formed during the progression of the disease, profound hypertrophic changes of the synovium with infiltration of immune cells, increased vascularity, and hyperplasia result in the formation of a synovial pannus. The cellular composition at sites of cartilage erosion varies greatly, and is characterised by the presence of macrophages, fibroblasts, mast cells, polymorphonuclear lymphocytes, and chondrocytes (2). Studies of Gordon and workers revealed that activated mast cells synthesized prostaglandins and leukotrienes, and released both preformed and cytokines such as TNF- and interleukins. Thus, infiltrated mast cells and their mediators contribute to the initiation and progression of the distributive inflammatory process and matrix degradation of RA (3). Findings of Olsson and colleagues proved the accumulation of mast cells and their activation/degranulation in rheumatoid synovial tissues and fluids (4).

Rheumatoid arthritis has a worldwide distribution with an estimated prevalence of 1 to 2%, irrespective of race. Both, incidence and prevalence of rheumatoid arthritis is thrice in women than in men. Although, rheumatoid arthritis may present at any age, patients most commonly are first affected in the third to sixth decades. High mortality rates have been observed in rheumatoid arthritic patients.

Immunology Of Rheumatoid Arthritis

Autoimmune diseases are common, with a prevalence of 10-15% in the general population. Autoimmunity is

defined as a loss of tolerance to autoimmune antigens, which the immune system mistakes for foreign antigens. Autoantibodies impose pathogenic effects in several autoimmune diseases in humans. Autoimmune phenomenon is a central pathogenetic principle involves in the induction, progression and perpetuation of a disease.

In the last few years, evidence prove that B cells play a key role in the pathogenesis of autoimmune diseases. B cells are not only the precursors of antibody-secreting plasma cells, but also remarkably effective antigen-presenting cells. This suggested a potential role for B cells in autoimmunity via abnormal autoantigen presentation. The antigen presenting role is crucial to the development and persistence of autoimmunity. Studies also demonstrated the secretion of many cytokines, including TNF-, from B cells, exacerbated autoimmune and inflammatory responses (5).

Innate immunity is the first line of defense against pathogenic microorganisms (bacteria, viruses, fungi and parasites). After a long period, innate immunity has been considered as a key regulator not only in preventing invasion of the body by microorganisms, but also in contributing to the pathogenesis of autoimmune and inflammatory diseases by deviated immune response. Innate immune response is specific for molecules found in the components of microorganisms, specifically the cell wall. Macrophages, dendritic cells, neutrophils, natural killer cells, and T lymphocytes contribute to innate immune response. All the factors involved in innate immunity contribute to the pathophysiology of RA. Medzhitov and Janeway observed that an inadequate or poorly regulated natural anti-microbial response may lead to the development of RA remains plausible (6).

Rheumatoid factor (RF) was discovered about 50 years ago by Waaler and Rose, who demonstrated that patient with RA had antibodies reactive with antigenic determinants on autologous IgG. RFs are autoantibodies directed to the crystallizable fragment of IgG molecules. IgG RF has a self binding capacity that can result in the formation of very large immune complexes, capable to activate the immune system (7,8). Classical RF's have been shown to be pentameric 19S IgM antibodies with a molecular weight of 9,00,000 (9). RF antibody is present in approximately 75-80% of RA patients, but its specificity is limited. Since RF is also found in patients with other autoimmune diseases (like Sjogren's syndrome), infectious diseases (like Hepatitis, Tuberculosis) and to a certain extent in the healthy population (3-5%) and healthy elderly individuals(10-30%). Despite of its relatively low specificity, the presence of RF has been widely used as diagnostic marker for RA (10).

Adaptive immune system have been clearly described in mammalian systems and is characterised by the presence of antigen-specific receptors on lymphocytes, and class I and class II MHC proteins for presentation of antigen to T cells. Moreover, cytokines are required to initiate and regulate immune responses. The involvement of cytokines in the mammalian adaptive immune response was first described by Mosmann (11). The cytokine production influences the outcome and nature of the adaptive immune response. Cytokines released by T cells act primarily in an autocrine or paracrine fashion on other lymphocytes to control the adaptive immune response. On the other hand, pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF-, released as part of the innate immune response are universal. The Th1-Th2 paradigm initially described the polarisation of murine CD4+ T cells into type 1 and type 2 helper cells, driving cell-mediated and humoral responses respectively. Although cytokines secreted by both T cells and non-T cells are present, macrophage derived cytokines (such as IL-1, TNF-, and IL-6) have been found in greater abundance than those of T cell origin (IL-4, IL-2 and IFN-) (12). The presence of several cytokines in the cells of synovial lining and sublining, including type A synoviocytes and other macrophage-like populations have been demonstrated (13).

Pathogenesis Of Rheumatoid Arthritis

Bone is a complex tissue comprising cells, collagenous matrix, and inorganic elements. It performs many essential functions, including mechanical support, protection to vital organs, a microenvironment for hematopoiesis, and a storage of calcium and other minerals. The growth, development, and maintenance of bone is a highly regulated process. The level of bone mass reflects the balance of bone formation and resorption, which at the cellular level involves the coordinate regulation of bone forming cells (Osteoblasts) and bone resorbing cells (Osteoclasts). Osteoblasts arise from mesenchymal stem cells, while osteoclasts differentiate from hematopoietic precursors of the monocyte-macrophage lineage and resorb bone matrix. Both these cell types are influenced by hormones, inflammatory mediators and growth factors. An imbalance of osteoblast and osteoclast functions results in skeletal abnormalities characterised by increased or decreased bone mass (14).

In arthritic condition, the synovium is transformed into tumor like structure called pannus, which invades and erodes the joint. The synovial tissue of patients with RA is characterised by cellular activities such as mononuclear cell infiltration, neovascularisation and proliferation of synovial fibroblasts. PDGF is produced in the RA synovium and play an important role in the

pathogenesis of RA. Also, the activated synovial fibroblasts (SFB) play a major role in the pathogenesis of RA. It has been speculated that their ability to induce and perpetuate inflammation is associated with the production of pro-inflammatory cytokines (15).

The pathogenesis of RA remains a mystery, despite the efforts of many investigators for the past 40 years. RA at one time was labeled as a 'collagen vascular disease', but the discovery of 'Rheumatoid factor' an immunoglobulin G sparked the idea that the RF itself or other antibodies could represent the pathogenic effector mechanism. Pathogenesis of RA have been a complex mechanism involving the infiltration and activation of various cell populations and release of inflammatory and destructive mediators, including cytokines, prostaglandins, and metalloproteinases. The cause of RA remains unknown, but several hypotheses have been postulated, involving superantigen-driven disease, as an autoimmune mechanism, and infectious stimulus (16).

The pathology of RA extends throughout the synovial joint and consists of acute and chronic inflammation, cell proliferation, followed by tissue destruction. An inflamed synovium is central to the pathophysiology of RA which shows pronounced angiogenesis; cellular hyperplasia; an influx of cell-surface adhesion molecules, proteinases, proteinase inhibitors (17). RA synovial fluid is enriched predominantly with neutrophils, but macrophages, T lymphocytes, and dendritic cells are also present. The lining layer of the joint is increased, from 1-2 cells to 6-8 cells thick, and is comprised mostly of activated macrophages with underlying layer of fibroblasts-like cells. The major site of irreversible tissue damage starts at the junction of the synovium lining the joint capsule with the cartilage and bone, a region often termed as *pannus*, an area rich in macrophages. The cells of pannus migrate over the cartilage and into the subchondral bone, cause the erosion of tissues (18) via activity of matrix metalloproteinases (MMPs), enzymes produced by activated macrophages and fibroblasts in response to pro-inflammatory cytokines such as IL-1 and TNF-. The MMP enzymes, collagenase (MMP-1) and stromelysin 1 (MMP-3), whose production is increased, play an important role in the destruction of bone and cartilage. Although various factors, including genetic factors, environmental factors, and including infectious agents (19), have been suggested for the cause of the disease, so far the exact pathogenesis has not been understood completely.

GENETICS OF RHEUMATOID ARTHRITIS

Studies of Aho have demonstrated the higher prevalence of disease among monozygotic twins (12-15%) than dizygotic twins (4%), indicating the influence of genetic factors (20). Heritability analyses of patients suggest that about 60% of population's predisposition to rheumatoid arthritis can be accounted for by genetic factors. It is well established that people who carry specific MHC haplotypes such as HLA-DR4 and DR1 are at higher risk for development of RA than those who carry other molecules, thus suggesting the ability to present specific pathogenic antigens correlates to disease susceptibility (21). Further, Genetic marker analysis indicates an association between development of rheumatoid arthritis and the presence of a shared epitope on small regions of the DRB1*0401 and *0404 alleles (22). The genetic basis for RA is extremely complex. Human leukocyte antigen (HLA) is associated with RA and has been a support for susceptibility to RA. MHC contains many genes that could be directly involved in disease risk, or might interact with DRB1 alleles to modify risk (23). TNF- is particularly a compelling candidate because of the obvious therapeutic importance of this cytokine. Polymorphisms in the TNF region may interact with DR alleles to modify susceptibility to RA. Positive associations between RA and a number of candidate genes have also been reported. Among the cytokines (other than TNF), a recent report of an association with IL-4 is provocative (24).

Rheumatoid Arthritis Is An Inflammatory Response

Inflammation is one of the most prevalent conditions limiting productivity and diminishing quality of life. It is characterized by redness, warmth, swelling and pain. Pathologically, inflammation is characterized by an increased supply of blood to the affected area, increased capillary permeability caused by retraction of the endothelial cells and infiltration of phagocytic, monocytic and polymorphonuclear cells into the site of tissue insult. The response is essential for protecting tissue from injury and infection (25). The inflammatory response consists of a sequential release of mediators and the recruitment of circulating leukocytes, which become activated at the inflammatory site and release further mediators. The response is resolved by the release of endogenous anti-inflammatory mediators as well as the accumulation of intracellular negative regulatory factors. These active metabolites cause damage to the underlying tissue. Warmth and redness result from dilation of the small blood vessels as they become more permeable during inflammation.

Prostaglandins (PG), derived from the cyclooxygenase (COX) pathway, are among eicosanoids that play important role in the initiation of inflammation and pain. These and other eicosanoids such as thromboxanes are produced as a result of arachidonic acid metabolism involving prostaglandin synthase

(26). Systemic inhibition of COX leads to decreased production of PG at the site of inflammation. Two isoforms of COX, COX-1 and COX-2, have been identified. COX-1 is an inducible isoform of the enzyme, while COX-2 isoform is prominent at the sites of inflammation. COX-2 is constitutively expressed in the macula densa of kidney and in brain. Currently available nonsteroidal anti-inflammatory drugs (NSAID) act by inhibiting the activity of both forms of COX enzymes. Another pathway that is involved in arachidonic acid metabolism and that contributes to the production of eicosanoids is lipoxygenase pathway (27). Inhibitors of cyclooxygenase pathway such as acetylsalicylic acid (aspirin), and the inhibitors of lipoxygenase pathway such as antioxidants have been used as pain relieving and anti-inflammatory agents.

Cytokines are local protein mediators involved in several biological processes, including cell growth and activation, inflammation, immunity and differentiation. Cytokines have been implicated as important mediators of inflammation and joint destruction in RA (28). Analysis of cytokine mRNA and protein in RA tissue revealed that TNF-, IL-1, IL-6, GM-CSF, and IL-8 are abundant. A variety of cytokines produced in synovium have been shown to possess both pro and anti-inflammatory activities. In addition, cytokines regulate the progression and maintenance of autoimmunity: blocking their action with antibodies can either reduce or exacerbate established disease. Many cytokines possess anti-inflammatory features, such as transforming growth factor (TGF-), IL-4 and IL-10. Several autoimmune diseases have been studied and their corresponding animal models have been characterized as being mediated by the Th1 pathway, based on cytokine expression patterns. Thus, cytokines play as important mediators for the pathology of RA (19).

Tumor necrosis factor-α (TNF-α) is one of the earliest cytokines released by activated macrophages, and play a pivotal role in the pathogenesis of inflammation, endotoxic shock, and tissue injury (29). Tumor necrosis factor-α is characterised by the ability to induce tumor cell apoptosis and cachexia, has now been considered as central mediator of a broad range of biological activities. TNF- is a pro-inflammatory cytokine, produced by activated monocytes-macrophages, B cells, T cells, and fibroblasts. It is expressed on the surface of these cells initially and released following cleavage by a serine metalloproteinase (30). The cytokine belongs to the larger family of ligands with a trimeric structure. Further, Trentham and workers has reported TNF- as an inducer of pro-inflammatory cytokines for eg. IL-1β, IL-6, IL-8 and granulocyte-monocyte colony stimulatory factor, and promoting inflammation by the stimulation of fibroblasts to express adhesion molecules such as intercellular adhesion molecule-1 (31).

Among cytokines, IL-1 has been recognized as another important molecule responsible for the inflammation. IL-1 was discovered and recognized as 'endogeneous pyrogen' because of its ability to produce fever (32). Biochemically, two IL-1 molecules have been cloned: IL-1 and IL-1. These two IL-1s share only small streches of similar amino acids (26% in the case of human IL-1). IL-1 and IL-1 are products of separate genes, both genes are located on chromosome 2 (33). IL-1 is also an important mediator of inflammation and is produced by various types of cells, including macrophages, monocytes, and synovial lining. It potentiates the catabolic effects of TNF. IL-1 and TNF act synergistically in the production of PGE from fibroblasts, and the induction of the local Shwartzman reaction, and exert numerous effects on both immune and inflammatory cells, including augmentation of T and B lymphocyte function (34). Again, the cytokine has been considered as a potent inflammatory mediator due to its presence in the joint fluid of individuals with inflammatory and destructive arthritis. The studies of Arend and Dayer, with RA patients revealed the contribution of IL-1 for joint damage via stimulating PGE2 and collagenase production in synovial fibroblasts and chondrocytes (35). IL-1 is synthesized as an inactive 31 kDa precursor which is activated by protease cleavage to its 17 kDa bioactive form by IL-1 converting enzyme (36). Osteoclast activation is also one of the properties of IL-1. Fibrosis and deposition of abnormal proteins in tissue appear to be mediated by IL-1 and in RA this contributes to the thickening of scar tissue which restricts joint movement. IL-1 knock out mice and IL-1R type I deficient mice show an increased mycobacterial outgrowth and also defective granuloma formation after infection with *M. tuberculosis* (37).

Interleukin-6 (IL-6) is another pleiotropic, 26 kDa pro-inflammatory cytokine produced by monocytes, T lymphocytes, and fibroblasts, responsible for various essential biological activities. It is also known as 2-interferon, and reported as a T cell factor that induces B cells to differentiate to immunoglobulin-producing cells (B cell stimulatory factor-2[BSF-2]) (38). Afterward, this BSF-2 was found to be identical to the 26 kDa interferon 2 proteins, a hybridoma/plasmacytoma growth factor and hepatocyte-stimulating factor that had been independently cloned as a different functional molecule. Both IL-1β and TNF- are responsible for the induction of synthesis and secretion of IL-6. The biologic activities of IL-6 are similar to those of IL-1 and TNF. High levels of IL-6 are observed in inflammatory synovial fluid of RA patients (39). Immunohistological staining of rheumatoid synovium again revealed that the

presence of IL-6 protein in fibroblasts.

Interferon-gamma (IFN-), a cytokine strongly associated with a Th1 response, is an important regulator of the production of IgG2a antibody, a subclass frequently associated with a pathogenic autoantibody response. IFN-, therefore, has been considered a prime target for modulating autoimmunity, with the hypothesis being that if IFN- expression can be downregulated, then both the Th pathway and the production of pathogenic autoantibody can be altered. A regulatory role of IFN- in models of autoimmune arthritis is also supported by studies using strains genetically non-susceptible to CIA. IFN- may not only mediate Th1 responses in arthritis but also suppress the destruction of cartilage and bone by inhibiting the generation of osteoclasts (40).

Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF) is an anti-inflammatory cytokine, capable of inhibiting synthesis of pro-inflammatory cytokines like IFN-, TNF- and IL-2 by cells such as macrophage and Th1 cells. IL-10 is produced in the joint in RA by macrophages and infiltrating blood lymphocytes. Regulation of its expression is poorly understood, but previous findings have suggested that physical interactions with T cells may play a role. Histological studies of synovium in RA have established that macrophages are in close contact with T cells in the inflamed interstitium (41), suggesting that contact signals between macrophages and T cells may be of importance in vivo in modulating cytokine production. Synovial macrophages, rather than SFB, are known to produce considerable amounts of IL-10 detected in primary culture RA-SFB in the present study are probably the product of the few remaining macrophages (42).

During an inflammation reaction, leukocytes transgress the vascular endothelium and migrate into peripheral tissues in response to chemotactic factors, such as chemotactic cytokines or chemokines. Chemotactic cytokines are largely responsible for recruitment of inflammatory cells to the site of infection. About 40 chemokines and 16 chemokine receptors have now been identified. These have a prominent role in inflammation (43). The chemokine family is characterized by the conservation of four cysteines. Their members have been classified in two major subfamilies, namely CXC and CC chemokines, depending on whether or not an amino acid separates the first two NH2-terminal cysteines. The CXC chemokine subfamily is further divided in ELR+ and ELR-CXC chemokines based on the presence or absence of the Glu-Leu-Arg (ELR) motif just in front of the first cysteine. While ELR+CXC chemokines are angiogenic and mainly attract neutrophils, ELR-CXC chemokines have angiostatic properties and are chemotactic for mononuclear leukocytes. CC chemokines exert chemotactic activity on a variety of leukocyte subsets (44).

Matrix metalloproteinases (MMP's), also known as matrixins, are a family of zinc-containing endopeptidases that share structural domains and have the capacity to degrade extracellular matrix components, as well as alter biological functions of extracellular matrix macromolecules. Under normal physiological conditions, MMP transcripts are expressed at low levels, but these levels increase rapidly during inflammation, wound healing and cancer (45). The MMP's have been categorised into three major functionally groups, based on substrate specificity: (1) The interstitial collagenases (MMP-1, 8, and 13), (2) The stromelysins (MMP-3, 10 and 11) and (3) The gelatinases (MMP-2 and 9) (46). Matrix metalloprotienases are produced at high levels by type B synoviocytes in RA. Additionally, metalloproteinases are required for remodelling and destruction of extracellular matrix. Their activity is regulated by tissue inhibitors of metalloproteins (TIMPs), serine proteinase inhibitors (SERPINS), and 2-macroglobulin. MMP's contribute to joint destruction in two ways: First, they directly enhance proteolytic degradation of the extra cellular matrix of cartilage and bone. Second, MMPs are important during angiogenesis, which is a prominent feature of RA (47). TNF- and IL-1 have been reported to act synergistically to release MMPs (48). It has been reported that macrophage migration inhibitory factor (MIF) upregulates mRNAs of MMPs-1 and 3 in synovial fibroblasts obtained from RA patients. Itoh and colleagues found that MMP-2 knockout mice exhibited a more severe clinical and histological arthritis than wild-type suggesting an active role of MMP-2 in the development of inflammatory joint disease (49).

Nuclear factor-kB (NF-kB) is a collective name for dimeric transcription factors comprised of the Rel family of proteins that include RelA, c-RelB, NF-kB1 and NF-kB2. The most abundant form found in the stimulated cells is the RelA/ NF-kB1 heterodimer, often referred to as a 'classic' NF-kB. Activation of the NF-kB proteins have been reported to play a central role in inflammation through the regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, chemokines, and inducible enzymes such as cyclooxygenase 2 (COX-2). NF-kB can be activated by a variety of pathogenic stimuli, including bacterial products and viral proteins, cytokines, growth factors, radiation, ischemia/reperfusion, and oxidative stress. Activated NF-kB has been detected in human synovial tissue on the early stage of joint inflammation as well as in the later stages of the

disease (50). Activation of NF-kB has also been detected in different animal models of RA such as rats and mice (51). Secreted products of activated T cells induce activation of macrophages, the major producers of inflammatory cytokines in RA synovium. NF-kB controls the expression of cytokines IL-1 and TNF-, the essential mediators of inflammation in RA. Suppression of NF-kB inhibited expression of many inflammatory molecules, including IL-1, TNF-, IL-6. This suggests that NF-kB activation facilitates the impaired balance of pro-inflammatory and anti-inflammatory molecules in the arthritic joint. Further, mast cells have been considered as inflammatory cells with importance for both acute and chronic inflammatory processes. These cells store a number of mediator molecules in their granules, such as histamine, heparin, and proteases, and release these mediators into the extracellular space upon activation.

Mast cells are reported to accumulate in the synovial tissues and fluids of human suffering from RA (52), reflecting the presence of mast cell chemotactic or survival activities such as SCF and transforming growth factor- (TGF-) in the synovial fluid. Increased number of mast cells (MCs) has been reported at sites of cartilage damage, as well as in the synovial tissues and fluids of patients with rheumatoid arthritis (53). Findings of Malfait and workers revealed the accumulation of mast cells in the swollen paws of mice suffering from induced arthritis, and their degranulation during the disease process. The invading mast cells are responsible for the production of several inflammatory mediators such as TNF-, IL-1 and vascular endothelial growth factor (VEGF) (54). These findings suggest that mast cells and their mediators contribute to the initiation and progression of the destructive inflammatory process during RA. The cause of mast cell hyperplasia in RA is not known.

Similarly, dendritic cells (DCs) have been considered as specialised cells to initiate primary immune responses. Their maturation process involve cell migration, alteration in major histocompatibility complex (MHC) class II biosynthesis, upregulation of co-stimulatory molecules, down regulation of endocytosis and induction of cytokine release. DCs have a prominent role in the pathogenesis of autoimmunity, and have been reported to be present in the large quantities in the serum and synovial fluid of patients with rheumatoid or juvenile arthritis (55). The well defined maturation of DCs occur in response to inflammatory signals evoked by the interaction of pathogens with the innate immune system. These signals induce TNF- which is transduced via molecules of TNF receptor family. DCs matured in this way prime T helper 1 type (Th1) immune responses via the release of IL-12 by DCs; inturn IL-12 induces Th cells to secrete IFN- (56). According to Kalinski *et al.,* DCs generated in the presence of prostaglandin E_2 secretes IL-10 but not IL-12, and caused naïve T cells to secrete Th2 type cytokines (57).

Mechanisms Of Cartilage And Bone Damage In Rheumatoid Arthritis

Destruction of the extracellular matrix leads to significant disability in patients with RA. Current concepts of joint destruction suggest that distinct mechanism contribute to bone and cartilage damage. Cartilage destruction is mediated in large part through the elaboration of proteases by synoviocytes and cellular invasion not the matrix. Metalloproteinases and aggrecanases, induced by IL-I, TNF-α, and IL-17, play a key role in this process. In addition RA, FLS can be permanently altered in the inflammatory synovial environment.

Altered DNA repair potentially cause mutations in certain key genes, such as the p53 tumor suppressor, and can increase synoviocyte proliferation and cartilage invasion. Although synoviocytes and chondrocytes are involved in cartilage destruction, it is now known that bone erosion is mediated by the RANK/RANKL system. The RANKL, receptor, RANK is expressed on OsteoClasts, osteoclast precursors and chondrocytes. RANKL is expressed by various cells in rheumatoid synovium including T cells and synoviocytes, and induces osteoclast maturation and activation. The soluble decoy receptor to RANKL, osteoprotegerin (OPG), inhibits bone resorption and osteoclast function. Administration of OPG to rate with adjuvant arthiritis blocks bone destruction. In most animal models OPG has minimal effect on inflammation or cartilage damage (58).

Rheumatoid Arthritis And Therapies

NSAIDs exert their effects through inhibition of prostaglandin synthesis. In rheumatoid arthritis, tissue breakdown causes production of prostaglandin from cell membrane constituents. Prostaglandins have physiological role in protecting the gastric mucosa and maintaining renal blood flow. NSAIDs have been found to inhibit cyclo-oxygenase (COX), the enzyme which converts arachidonic acid to prostaglandin. COX exists in 2 structurally different forms. COX-1, the constitutive form produces the prostaglandins that mediate gastric cytoprotection, renal perfusions and platelet aggregation. COX-2, the inducible, activated by inflammatory stimuli and produces the prostaglandins that mediate inflammatory response. The reduction of prostaglandin levels provides the analgesic and anti-inflammatory properties to NSAIDs. NSAIDs are commonly termed as COX-2 inhibitors. Most prescribed Cox-2 inhibitors to the rheumatoid arthritis patients include Aspirin, Etodolac, Meloxicam,

Celecoxib, Rofecoxib, Ibuprofen, Indomethacin, Naproxen, Piroxicam, Azapropazone etc.

Aspirin has been synthesized as an ester of salicylic acid and also called as acetyl salicylic acid (ASA). It had been considered as an active NSAID. It is the standard drug to which all other NSAIDs are compared. The drug is mainly used for treatment of inflammatory musculoskeletal disorders. Principal anti-inflammatory of ASA is contributed to the formation of active metabolite. Both, aspirin and its major metabolite, salicylate, are active NSAIDs. The drug has pharmacological activity through reverse acetylation of cyclooxygenase and is reported to be hydrolysed to salicylic acid (59). Further metabolism of salicylate to gentisate, also contribute to pharmacologic effects. Interestingly, salicylates have been reported to be well absorbed and better tolerated by gastrointestinal tract due to minimized exposure to mucosa. Studies of White house and Cleland revealed ASA to possess high clearance rate of approximately 60% (60).

Second choice of the physician for the treatment of rheumatoid arthritis is the prescription of Disease modifying anti-rheumatic drugs (DMARDs), a group of drugs which effectively modify the course of the disease in the arthritic patients. These specifically modify the disease process. Exact mechanism is poorly understood but these reduce the activity of arthritis i.e., pain, stiffness and synovial swelling. DMARDs act by inhibiting pyrimidine synthesis which in turn prevents T lymphocyte proliferation, eventually blocking an important step in the pathogenesis of disease. Although these drugs are capable to retard and in some cases can halt the progress of disease, these drugs have been proven very effective if prescribed within the three months of the onset of the disease. Moreover, DMARDs work better in combination with NSAIDs and other drugs. Apart from the efficacy, these DMARDs impose their adverse side effects such as lung injury, neutropenia and congestive heart failure (61). Most commonly prescribed DMARDs are Leflunomide, Azathioprine, Methotrexate, Sulphasalazine, sulfasalazine etc.

Recent developments have led to the use of different biological molecules for the treatment of arthritis. There are different such molecules for eg. Infliximab, Etanercept, Adalimumab, Rituximab etc. Infliximab is a chimeric anti-TNF- monoclonal antibody. It has a murine anti-TNF- Fab2 grafted onto a human immunoglobin-1 Fc. Response to the treatment has been found rapid in swollen joint count falling from 18 to 5. Its efficacy was confirmed in a double-blind, randomised placebo-controlled trial (62).

Rheumatoid Arthritis And Herbal Therapies

Complimentary and alternative medicine (CAM) is defined as diagnosis, treatment and/or prevention which complement traditional medicine by contributing, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine. RA has been shown to respond to supplementation with several different oils containing omega-6 or omega-3 fatty acids and have been shown to have both immunosuppressive and anti-inflammatory effects. Evening primrose oil (EPO) has produced equivocal results in patients with RA (63). Fish oil is also a good source of the anti-inflammatory omega-3 fatty acids and has been investigated in several controlled trials following which significant reduction in the morning stiffness was observed. Black currant seed oil (BCSO) which contains both gamma-linolenic acid (GLA) and the omega-3 fatty acids alpha-linolenic and stearidonic acid, has also been tested as treatment for RA and proved to be statistically significant improvement in pain and joint tenderness (64). Ginger has been used for thousands of years in ayurvedic medicine as an anti-inflammatory agent. Oral administration of ginger oil suppressed the induction of adjuvant induced inflammation in rats (65). A study conducted by Flugge and colleagues (1999) daily dose of 100mg/kg body weight of *Gentiana macrophylla* root extract to arthritic rats has resulted to exhibit significant inhibitory effect and marked anti-inflammatory action. Regular use of CAM by arthritis patients demonstrates holistic benefits as compared to conventional treatments (66,67).

Herbal medicine is one of the oldest and traditional medicine systems around the world. Herbs are defined as any form of a plant or its product such as leaves, stems, flowers, roots, and seeds. Herbal products may contain a single herb or combinations of several herbs to exert complementary effects. Some herbal products may include animal products and minerals. They contain bioactive substances. Nearly one third of pharmaceutical drugs were originally derived from plants. Herbal products are considered as safe because they are natural. Herbal products are sold as either raw plants or extracts of portions of the plant. Extraction involves boiling or percolating the herb in water, alcohol, or other solvents to release biologically active constituents of the plant. These liquid extracts may then be heated or dried to create more concentrated liquids, pastes or powders. The extract prepared from a herb contains complicated mixtures of organic chemicals, the levels of which may vary depending upon many factors related to growth, production and processing of the herbal product. Both the raw herb and the extract contain mixtures of organic chemicals, which may include fatty acids, sterols, alkaloids, flavonoids,

glucosides, saponins, tannins, and terpenes (68). It is difficult to determine which individual component, if any, of the herb show biological activity in humans. Often, the processing of herbs, such as heating or boiling, may alter the pharmacological activity of the constituents present in them. Similarly, a host of environmental factors such as soil, altitude, seasonal variation in temperature, atmospheric humidity, length of daylight, rainfall pattern, shade, dew, and frost conditions, may affect the levels of components in any batch of an herb. Currently, some herbal markers are known to have pharmacological activity, but very few are known to have clinical effects. It is believed that the clinical effect of the herb cannot be attributed to a single active principle but to a host of ingredients present in the Medicinal plants provide various effective chemical source that directly provide about 25% of currently used crude drugs, with another 25% derived from chemically altered natural products (69).

Traditional medicine systems around the world, Chinese medicinal system, Indian medicinal system (composed of two major branches-Unani and Ayurveda), rely heavily on herbs for health preservation and healing. Many herbal medicines have been described in traditional texts, and used as antimicrobial, anti-inflammatory and antiviral medicine for the cure of allergies, arthritis, infections, wound healing and fever (70). There are various herbal plants and their preparations capable to fight against the inflammation and related disorders such as rheumatoid arthritis, systemic lupus erythmatosus, diabetes etc.

Fig 1: Ananas Comosus

Pineapple has also been used as a medicinal plant. Bromelain, an extract of pineapple stem, has been reported to possess anti-inflammatory property. Active components of bromelain include peroxidase, acid phosphatase, several protease inhibitors etc. When bromelain was administered to RA patients, 72% of total patients reported reduced swelling and pain (71) (Fig.1).

Fig 2: Curcuma Longa

Turmeric (*Curcuma longa*), commonly used in Indian (Ayurvedic) and Chinese medicine system, possess curcumin which is an active anti-inflammatory component. The rhizome, the root, of curcuma is used in medicinal and food preparations. Significant improvement in morning stiffness, walking time and joint swelling have been observed as anti-arthritic effects after regular curcuma consumption by RA patients (72) (Fig.2).

Fig 3: Zinziber Officinalis

Ginger (*Zinziber officinalis*, Zinziberacea) has been used for centuries in Indian ayurvedic medicine and traditional medicine system as an anti-inflammatory agent. Five constituents of ginger have been identified as inhibitors of prostaglandins. According to an Indian study, oral administration of ginger oil suppressed the induction of adjuvant induced inflammation (Fig.3) (65).

Fig 4: Crocus Sativus

Saffron (Crocus sativus, Iridaceae) is commonly used as folk medicine for various purposes such as aphrodisiac, antispasmodic and expectorant. Saffron stigma is reported to exhibit anti-inflammatory action due to presence of crocetin and carotenoids. Aqueous and ethanolic extracts of saffron petals have been shown to exhibit radical scavenging as well as anti-inflammatory effects in xylene and formalin induced inflammation (73,74) (Fig.4).

Fig 5: Swertia Chirayita

Chirayita (*Swertia Chirayita*), a herb found abundantly in the temperate regions of Himalaya, is commonly used for chronic fever, anemia and asthma. Chirayita comprises of swerchirin, swertanone and swertianin, as active components responsible for the anti-inflammatory activity. Chirayita has been reported to reduce the elevated levels of Pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) in experimental arthritis, as well as in asthmatic conditions (75) (Fig.5).

Fig 6: Tripterygium Wilfordii Hook F

Among the Chinese traditional medicine system, 'Thunder God Vine' (*Tripterygium wilfordii* Hook F, TwHF) occupy the foremost place for the treatment of autoimmune and inflammatory diseases such as RA, systemic lupus erythematosus, psoriasis etc. Its anti-inflammatory activity is reported to be due to presence of Triptolide, the main active component. Dose dependent studies of ethyl acetate extract of TwHF roots have in symptomatic improvement in 50% of RA cases during the first 4 weeks of treatment. Suppression of adhesion molecules like E-selectin, ICAM-1 and VCAM-1 contribute for the anti-inflammatory action of the TwHF extract (76) (Fig.6).

Fig 7: Nyctanthes Arbortristis

Nyctanthes arbortristis is one of the medicinal plant which is indigenous to India. It has its distribution mainly in East Asia. It is also known by other names

such as Bruscia, Nictanthes, Nyctanthos, Pariaticu, Parilium and Scabrita etc. Nyctanthes arbortristis Linn. (Hindi- Harsingar) is a large shrub which is widely cultivated throughout India as a garden plant. It is a small tree with rough leaves and sweet scented flowers. The flower petals are white; the stalks are orange-red tubes. In ancient times, the dye obtained from these tubes was used for dying the orange-red robes of monks (77). *Nyctanthes arbortristis* has been extensively used for the preparation of decoction of leaves by Ayurvedic physicians for the treatment of arthritis, obstinate sciatica, malaria, intestinal worms and as a tonic, cholagogue and laxative (78). Inspite of its wide clinical use, particularly in inflammatory conditions, the plant has not yet been systemically screened (79,80) (Fig.7).

Nyctanthes has also been prescribed as a helminthocide, and a liver and nerve tonic. The powdered seeds have been recommended for the treatment of scurvy (81). Phytochemical investigations of the seeds led to the isolation of several iridoid glycosides, some of which have shown antiviral activity against encephalomyocarditis and anti-tumor activity against methylcholanthrene induced fibrosarcoma. The inflorescence and young fruits powdered in water has been used for relief in cough by tribal people of central India (82). Few iridoid glycosides have also been reported from the leaves (83). Many workers have isolated nyctanthoside (84), arbortristosides A and B and polysaccharides from seed kernels (85), further crocin-1, 2 and 3 were isolated from corolla tubes (86), nyctanthic acid, oleanolic acid, friedlin, lupeol, stragalin and fructoflorin from leaves (87). Iridoids in general show a wide spectrum of biological activity, arbortristoside A showed 80% regression of methylcholanthrene induced fibrosarcoma.

Till date there is no permanent cure for rheumatoid arthritis inspite of a heavy presence of drugs for arthritis in the market. Therefore there is a need for several other alternative drugs for rheumatoid arthritis. Plant derived products appears to be a good choice because of its natural origin as against the synthetic drugs and these drugs are widely accepted and popular among the Asian as well as the peoples of the western countries.

CONCLUSION

Rheumatoid arthritis is a chronic polyarticular disease of cartilage and bone. Almost people of all age groups suffer from the disease at any or the other time point in life. The disease has a prevalence of 1 to 2%. Pathogenesis of RA is not clear till date. Several researchers have worked on different animal species by inducing the arthritis. Freund's complete adjuvant has been the choice of immunological adjuvant. Cytokines play an important role in perpetuating the disease. Reactive oxygen species and Reactive nitrogen species exaggerate the inflammatory molecules. Non steroidal anti-inflammatory drugs (NSAIDs) and Disease modifying anti-rheumatic drugs (DMARDs) are the first choice of treating the disease. Several herbal remedies are prevalent around the world for the cure of RA. These contain potent bioactive substances. We can conclude that the use of herbal preparations is safe and effective towards several debilitating disease.

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