CURCUMIN AND AUTOIMMUNE DISEASE

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Abstract: The immune system has evolved to protect the host from microbial infection; nevertheless, a breakdown in the immune system often results in infection, cancer, and autoimmune diseases. Multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, myocarditis, thyroiditis, uveitis, systemic lupus erythromatosis, and myasthenia gravis are organ-specific autoimmune diseases that afflict more than 5% of the population worldwide. Although the etiology is not known and a cure is still wanting, the use of herbal and dietary supplements is on the rise in patients with autoimmune diseases, mainly because they are effective, inexpensive, and relatively safe. Curcumin is a polyphenolic compound isolated from the rhizome of the plant *Curcuma longa* that has traditionally been used for pain and wound-healing. Recent studies have shown that curcumin ameliorates multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease in human or animal models. Curcumin inhibits these autoimmune diseases by regulating inflammatory cytokines such as IL-1β, IL-6, IL-12, TNF-α and IFN-γ and associated JAK-STAT, AP-1, and NF-κB signaling pathways in immune cells. Although the beneficial effects of nutraceuticals are traditionally achieved through dietary consumption at low levels for long periods of time, the use of purified active compounds such as curcumin at higher doses for therapeutic purposes needs extreme caution. A precise understanding of effective dose, safe regiment, and mechanism of action is required for the use of curcumin in the treatment of human autoimmune diseases.

1. INTRODUCTION

The immune system has evolved to discriminate self from non-self antigens, thereby protecting the host from microbial infection and cancer.[1] Nevertheless, a breakdown in the fundamental immune response often results in the development of chronic infectious diseases, malignant tumors, and organ-specific autoimmune diseases. Although the etiology of autoimmune disease is not known, it is generally believed to be mediated by autoimmune cells that are influenced by genetic, environmental, and behavioral factors. Although the induction of an immune response involves the orchestrated interaction of phagocytes and lymphocytes, autoimmune diseases are characterized by deregulated immune responses. Traditionally, these diseases are categorized as either cell mediated, with a particular role for Th1 cells,

or humoral, with autoantibodies playing a key role in disease manifestation,[2,3] It is now realized that cytokines, chemokines, adhesion molecules, and other components of inflammatory responses also mediate tissue damage in autoimmune diseases. Despite recent improvements in patient care, a cure for autoimmune disease is still wanting. Human diets of plant origin, containing many hundreds of biologically active compounds called nutraceuticals, appear to play a role in the regulation of immune diseases and maintenance of health. In view of their ability to alleviate pain and inflammation with fewer side effects, the use of herbal medicine and dietary supplements is on the rise in patients with autoimmune diseases. In some cases, the disease process is partially understood, where the elements of protection can be related to a single compound or group of compounds in the diet. These bioactive components are featured with antioxidant, anti-inflammatory, and anticancer properties. Curcumin is a polyphenolic compound isolated from the rhizome of the plant *Curcuma longa,* which has traditionally been used in the treatment of inflammation and cancer. Recent studies have demonstrated promise in the use of curcumin for the treatment of autoimmune diseases.[5]A precise understanding of the effect and mechanism of action of curcumin will help develop new strategies to use it in the treatment of autoimmune diseases.

2. AUTOIMMUNE DISEASES

An immune response is initiated when phagocytic cells, such as macrophage, microglia and dendritic cells, and endocytose foreign antigens, degrade to peptides and present to $CD4^+$ T-lymphocytes in conjunction with major histocompatibility complex (MHC) or human leukocyte antigen (HLA) antigens.[6] The activated antigen-presenting cells (APCs) migrate to the regional lymph node and spleen and encounter naive or memory lymphocytes, leading to differentiation of Th1/Th2 cells, maturation of antigen-reactive B-cells, and migration to inflammatory sites. Whereas immunological memory is the basis for beneficial effects of vaccines, the autoimmune memory B- and T-cells mediate autoimmune diseases. The immune system is highly evolved to react only to foreign antigens but to maintain tolerance to self antigens.[7–9] Despite the highly evolved immune system, the autoimmune cells escape immune tolerance and induce organ-specific autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, myocarditis, thyroiditis, uveitis, systemic lupus erythromatosis, and myasthenia gravis, all of which are major health problems throughout the world. The autoimmune disease usually begins in young adulthood and affects women three times more frequently than men.[11]Although the etiology is not known, it is generally believed that genetic, environmental, and behavioral factors influence the pathogenesis of autoimmune diseases. In humans, the most potent genetic contribution to autoimmunity is from alleles of the MHC class II (HLA-DR) locus.[10] Although microbial infection and autoantigens can trigger organ-specific autoimmune diseases, cytokines, chemokines, and signaling molecules in the target organs determine the final outcome of the disease. Thus, the identification of drugs

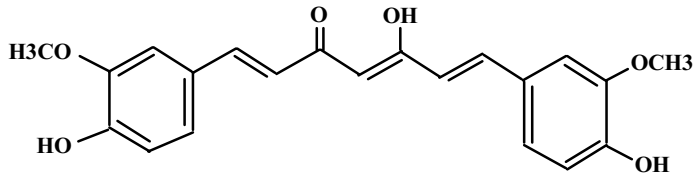

Figure 1. Chemical structure of curcumin: Curcumin [1,7-bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione] belongs to curcuminoids and its chemical structure is similar to diarylheptanoids.[30,31] The anti-inflammatory activity of curcumin is associated with the hydroxyl and phenol groups. It also has a b-dicarbonylic system with conjugated double bonds and the diene ketone system provides lipophylicity and better penetration.

that regulate autoimmune responses is critical in the treatment of organ-specific autoimmune diseases.

3. CURCUMIN IN THE TREATMENT OF AUTOIMMUNE DISEASES

Traditional medicines have used edible and medicinal plants to treat human diseases in different parts of the world.[12] There is a large variety of phytochemicals that can be extracted and purified from these edible and medicinal plants for the treatment of human diseases.[13]Curcumin (diferuloylmethane) (Figure 1) is a naturally occurring yellow pigment isolated from the rhizomes of the plant *Curcuma longa* (Linn) (turmeric) and is commonly used as a coloring and flavoring agent in food products. Traditional medicine in India and China uses curcumin to treat sprain and swelling caused by injury.[14] The medicinal value of curcumin has been well recognized, as it has profound anti-inflammatory and antitumor activities. *In vivo* treatment with curcumin induces complete protection in chronic and acute models of inflammation.[15−20]Curcumin inhibits reactive oxygen-generating enzymes such as lipoxygenase (LOX), cyclooxygenase (COX), xanthine dehydrogenase, and inducible nitric oxide synthase (iNOS) associated with inflammation.[21,22] Curcumin inhibits lipopolysaccharide (LPS) and interferon (IFN)-γ-induced nitric oxide production in macrophages.[23−25] and protein kinase C (PKC) activation and c-jun expression in fibroblasts.[26] It also inhibits skin inflammation and associated c-Fos and c-Jun expression and hydrogen peroxide formation.[27] Curcumin inhibits COX and LOX activities associated with inflammation *in vivo* and *in vitro*.[28,29] In view of its anti-inflammatory property, we and others have examined the use of curcumin in the treatment of autoimmune diseases (Table 1).

4. CURCUMIN AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that afflicts millions of people worldwide.[44] About 30% of

Table 1. Effect of curcumin in autoimmune diseases.

DISEASE	EFFECT OF CURCUMIN	REFERENCE
MS	No report on human MS	—
	Ameliorates EAE model of MS in mice	(32)
Type I diabetes	Inhibits glucose in human diabetic patients	(3, 34)
	Protects pancreatic β-cell death	(35)
	No report in animal models of type 1 diabetes	—
RA	Alleviates RA in humans	(36)
	Inhibits RA in animal models	(37)
Psoriasis	Inhibits psoriasis in humans	(38)
	Inhibits psoriasis in animal model	(39)
IBD	Inhibits IBD in humans	(40)
	Inhibits IBD in animal models	(41–43)
Myocarditis	No report in animal or human myocarditis	—
SLE	No report in animal or human SLE	—
Myasthenia gravis	No report	—

MS patients develop clinical paralysis and become wheelchair-bound for the rest of their lives.[45] Although the destruction of the oligodendrocyte myelin sheath in the CNS is the pathological hallmark of MS,[46] axonal degeneration contributes to irreversible long-term disability.[47] Activation of immune cells, secretion of inflammatory cytokines, and differentiation of encephalitogenic Th1 cells are key processes associated with the pathogenesis of MS.[48,49] Immunosuppressive agents have been commonly used to treat MS, but there is no medical treatment available that can cure MS. Experimental allergic encephalomyelitis (EAE) is an autoimmune disease of the CNS. EAE can be induced in susceptible rodents and primates by immunization with whole-brain homogenate or purified neural antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). The clinical and pathological features of EAE show close similarity to human MS; therefore, EAE has been commonly used as a model system to study the mechanism of MS pathogenesis and to test the efficacy of potential therapeutic agents for the treatment of MS.[4,5,50–53] To test the use of curcumin in the treatment of MS, we examined the protective effect of curcumin on EAE in SJL/J mice. We found that *in vivo* treatment (i.p.) with 50 or 100 μg curcumin every other day decreased the clinical and pathological severity of EAE in SJL/J mice.[5] Curcumin also induced a dose-dependent decrease in neural antigen-induced T-cell proliferation, Th1 differentiation, and IFN-γ production. These results suggest the use of curcumin in the treatment of MS.[5] However, there is no study so far examining the effect of curcumin in human MS. Although daily intake of low doses of curcumin as a dietary beverage might reduce the incidence and severity of autoimmune inflammation, controlled systematic studies in human patients are required before this can be used to treat MS and other human autoimmune diseases.

5. CURCUMIN AND TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease of the pancreas in which the pancreatic β-cell destruction leads to insulin deficiency in 5–10% of diabetes cases worldwide.[53,54] Patients with type 1 diabetes are also susceptible to other autoimmune conditions, including Hashimoto's thyroiditis, Graves' disease, Addison's disease, coeliac disease, myasthenia gravis, and vitiligo.[55,56] In susceptible individuals, the autoimmune B-cells produce antibodies to β-cell antigens such as insulin (IAA) and glutamic acid decarboxylase (GADA/GAA), and the protein tyrosine phosphatase IA2 (IA-2AA) and autoimmune T-cells mediate inflammation within the islets. Continuing destruction of β-cells leads to progressive loss of insulin reserve and insulin deficiency, resulting in the development of diabetes.[53] Although nutritional planning and insulin pumps help patients manage their disease,[57] a cure for diabetes is still wanting. Earlier studies have shown that dietary curcumin inhibits blood sugar levels in diabetic patients and its animal models.[33,34] Curcumin treatment also inhibits diabetes associated complications such as renal lesion, wound-healing, and cataracts in human patients and animal models.[58–61] The islet β-cells are susceptible to damage caused by oxygen free radicals, and curcumin protects pancreatic β-cells against reactive oxygen species (ROS)-mediated damage by enhancing antioxidants and reduces hyperglycemia in chemically induced diabetes.[35] Although there is no systematic study examining the effect of curcumin on human or animal models of type 1 diabetes, these results suggest the potential use of curcumin in the treatment of type 1 diabetes.

6. CURCUMIN AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory condition that affects approximately 0.8% of the population worldwide. RA is characterized by synovitis within diarthrodial joints, and angiogenesis is an important early event. Activated macrophages and dendritic cells are important sources of key proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, that promote the accumulation of inflammatory cells and the synthesis of cytokines, chemokines, matrix metalloproteinases (MMPs), COX-2, and other inflammatory mediators. $CD4^+$ T-cells with a Th1 phenotype appear to play a key role in orchestrating the immune response, and B-cells contribute to the ongoing inflammation by activating T-cells and producing potentially pathogenic autoantibodies in RA.[62,63] The primary goals of therapy for RA are relief of pain, reduction of inflammation, preservation of functional status, prevention of complications, and resolution of the pathogenic process. Historically, RA has been managed with nonsteroidal anti-inflammatory drugs (NSAIDs). Howeer, now there are earlier treatments with disease-modifying antirheumatic drugs, including methotrexate, hydroxychloroquine (HCQ), sulfasalazine, and leflunomide.[64] With a better understanding of the immunopathogenesis of the disease, researchers are now investigating other immunomodulatory approaches. Earlier studies have shown that curcumin has

antirheumatic activity in humans.[36] Many recent studies have shown that curcumin inhibits RA in association with inhibition of inflammatory cytokines and matrix metalloproteinase by blocking signaling pathways, including mitogen-activated protein kinases (MAPKs), activator protein (AP)-1 and nuclear factor (NF)-κB transcription factors in articular chondrocytes.[65–67] Curcumin also protects human chondrocytes from IL-lβ-induced inhibition of collagen type II and β1-integrin expression and activation of caspase-3. Curcumin synergistically potentiates the growth-inhibitory and proapoptotic effects of celecoxib in osteoarthritis synovial adherent cells.[68] Recent studies have also shown that curcumin inhibits disease in an animal model of RA.[37] These reports suggest that curcumin is useful in the treatment of human RA.[69]

7. CURCUMIN AND PSORIASIS

Psoriasis is an autoimmune inflammatory disease of the skin and joints in which intralesional T-lymphocytes trigger primed basal stem keratinocytes to proliferate and perpetuate the disease process.[70–72] Although the self-antigens have not been identified, drugs that regulate complex interactions among susceptibility genes, immunologic effector mechanisms, and environmental triggers that elicit the disease process in skin will prove to be useful in the treatment of psoriasis. Interestingly, recent studies have shown the antipsoriatic actions of curcumin. *In vitro* treatment with curcumin results in a significant decrease in the proliferation of keratinocytes in culture. Topical administration of curcumin inhibits the symptoms of psoriasis in a mouse model, suggesting its use in the treatment of psoriasis.[39] Curcumin-induced suppression of phosphorylase kinase activity correlates with the resolution of human psoriasis as assessed by clinical, histological, and immunohistochemical parameters.[38] Curcumin also inhibited keratinocyte transferrin receptor expression, severity of parakeratosis, and density of epidermal $CD8^+$ T-cells in psoriasis.[38,67,73] These studies suggest that curcumin is useful in the treatment of psoriasis.

8. CURCUMIN AND INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) characterized by Crohn's disease and ulcerative colitis is a common health problem worldwide.[74] Several cytokines, including TNF-α and IL-1β, have been shown to be upregulated in IBD and amplify and perpetuate tissue damage. Furthermore, chemokines are upregulated, thus providing a continuous signal for the influx of leukocytes.[75] Animals with knockouts of inflammatory factors such as IL-2, IL-10, and T-cell receptor serve as models of bowel inflammation.[76]Management of IBD involves the use of immunosuppressives, such as corticosteroids and monoclonal antibodies against TNF-α, which demonstrate clinical efficacy.[77,78] However, these agents are expensive and not without side effects, thus warranting the need for alternative drugs that might

be equally or more effective and inexpensive. Interestingly, recent studies have shown the beneficial effects of curcumin in the murine models of IBD.[41–43] The anti-inflammatory effects of curcumin involve a reduction in myeloperoxidase activity, a reduction in the number of infiltrating neutrophils, as well as a reduced expression of IL-1β.[40] A recent study has also shown the effect of curcumin in reducing the clinical symptoms of IBD in human patients, but precisely how curcumin ameliorates IBD is not clear. However, these encouraging studies suggest that curcumin might prove to be an inexpensive, well-tolerated, and effective therapy for the treatment of IBD in human.

9. CURCUMIN AND MYOCARDITIS

Myocarditis is an inflammatory disease of the myocardium.[79] This disease might be idiopathic, infectious, or autoimmune and might heal or lead to dilated cardiomyopathy (DCM), the most common cause of heart failure.[80,81] Thus, in a patient subset, myocarditis and DCM are thought to represent the acute and chronic stages of an organ-specific autoimmune disease of the myocardium. The cardiac autoantibodies are predictive markers of progression to DCM.[82,83] Cellular as well as humoral autoimmune responses are critically associated with the pathogenesis and progression of myocarditis and cardiomyopathy. Animal models greatly advanced our knowledge of the pathogenesis of myocarditis and inflammatory cardiomyopathy. In susceptible mice, for example, infection with enteroviruses results in a biphasic myocarditis, with an early acute stage 5–8 days after inoculation, followed by a chronic stage of low-grade inflammation.[84] Interestingly, T-cells from mice with enteroviral myocarditis transfer the disease into syngeneic severe combined immunodeficiency (SCID) recipients lacking B- and T-cells, which suggests a crucial role for autoreactive T-cells in disease pathogenesis.[85,86] Furthermore, immunization of susceptible mice with α-myosin-derived peptides (MyHCα) results in $CD4^+$ T-cell-mediated experimental autoimmune myocarditis.[87] Cytokines play critical roles in accentuating or regulating autoimmunity; hence, cytokines represent new therapeutic targets in the treatment and prevention of autoimmunity-mediated myocarditis and cardiomyopathy. Curcumin is a potent inhibitor of inflammation and autoimmune diseases[88] and recent studies have shown that curcumin inhibits myocardial inflammation associated with ischemia.[89,90] However, there is no study thus far examining the effect of curcumin in human or animal models of autoimmune myocarditis.

10. CURCUMIN AND SYSTEMIC LUPUS ERYTHROMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of multiple autoantibodies that react with various components of the cell nucleus.[91] Specific autoantibodies might correlate with particular organ involvement and prognosis in SLE and related autoimmune conditions. Many

autoantibodies, such as SS-A and SS-B and anti-Smith, double-stranded DNA (dsDNA) have been shown to be pathogenic in SLE. A higher titer of dsDNA and its deposition along the glomeruli is associated with active glomerulonephritis, and antiphospholipid antibodies are associated with a hypercoagulable state in SLE.[92,93] Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neuropsychiatric disorder, hematologic disorder, immunologic disorder, and antinuclear antibody are the symptoms of SLE. Therapy for SLE depends on the particular organ system involved. Patients with minor manifestations can often be controlled with low-dose steroids, but moderate and severe disease might require higher doses of steroids or other immunosuppressive agents. A great deal of research is currently ongoing to assess the efficacy of targeting B-cells with specific inhibitors.[94,95] Although curcumin has been known to inhibit B-cell activation in inflammation, there is no study examining the effect of curcumin in human or animal models of SLE.

11. CURCUMIN AND MYASTHENIA GRAVIS

Myesthenia gravis (MG) is an autoantibody-mediated neuromuscular disease.[96] Weakness and fatigability of voluntary muscles characterize both MG and experimental autoimmune MG (EAMG).[96–98] Although the autoantibodies produced by B-cells cause the symptoms of MG, there is ample evidence that T-cells have a key role in the etiopathology of the disease in humans and animals.[99,100] Peptides representing different sequences of the human acetylcholine receptor (AchR) α-subunit or its peptides p195-212 and p259-271 are able to stimulate the peripheral blood lymphocytes (PBL) of patients with MG.[96,97] EAMG can be induced in mice and rats by immunization with AChR in complete Freund's adjuvant.[99,100] The cytokines IFN-γ and IL-12 upregulate and IFN-α downregulates the pathogenesis of EAMG.[101,102] However, the Th2 cytokine IL-4 fails to play a significant role in the development of antibody-mediated EAMG. Antigen-specific tolerance and downregulation of pathogenic cytokines could achieve effective therapy of EAMG and probably MG. Although curcumin has been shown to inhibit inflammatory cytokines, there is no study examining the use of curcumin in the treatment of myasthenia gravis.

12. CURCUMIN REGULATION OF AUTOIMMUNE CELLS

Antigen-presenting cells such as macrophage, microglia, and dendritic cells play a critical role in mediating innate immunity and pathogenesis of autoimmune diseases.[103] Toll-like receptors (TLRs) are a family of cell-surface receptors expressed on APCs that are key components of the innate immune response.[104] When microbial ligands or autoantigens engage a TLR, a cascade of signaling through the NF-κB pathway will be initiated, leading to secretion of inflammatory cytokines, including IL-12, NO, IL-1β, and TNF-α, and surface receptors. CD40

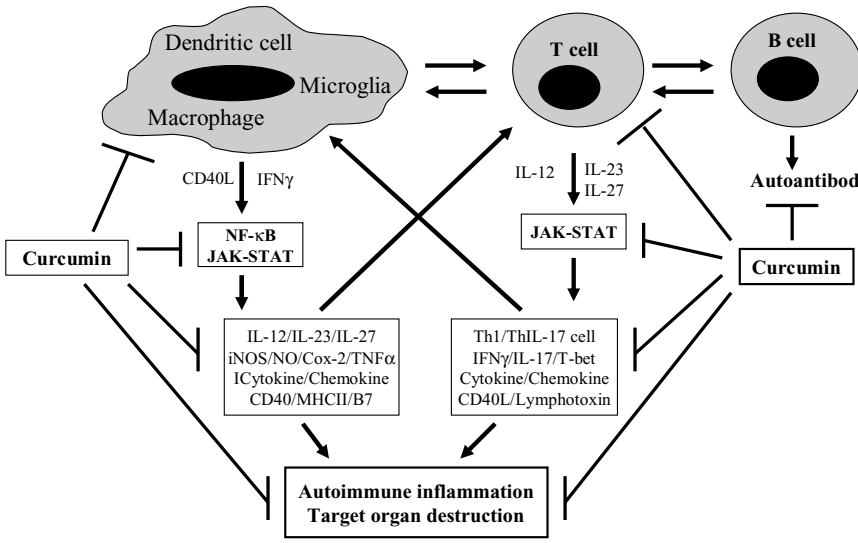

Figure 2. Curcumin regulates autoimmune cells. Upon interaction with autoimmune T-cells, the professional APCs secrete proinflammatory cytokines, which, in turn, induce the differentiation of autoimmune T- and B-cells and secretion of autoantibodies and inflammatory cytokines, resulting in target-organ destruction. Curcumin targets activation and differentiation of APC, T- and B-cells, secretion of inflam-matory cytokines, and target-organ destruction in autoimmune diseases.

is another receptor that activates APCs upon interaction with CD40L expression on Th1 cells, resulting in the secretion of inflammatory cytokines.[105] There is emerging evidence that TLRs and CD40 are involved in the pathophysiology of autoimmune diseases.[104,105] Recent studies have shown that curcumin inhibits lipopolysaccharide (LPS)-induced expression of TLR2 in mouse macrophages[106] and TLR4-dependent chemokine MIP-2 expression in kidney cells.[107]Further investigations are required to define the molecular mechanisms in the regulation of innate immune responses by curcumin in autoimmune diseases.

Among the many lymphocytes, the $CD4^+$ Th1 cells play critical roles in mediating autoimmune diseases, including MS, RA, type 1 diabetes, SLE, myocarditis, thyroiditis, and uveitis.[108] Systematic studies in human and animal models demonstrate that inflammatory cytokines such as IFN-γ and lymphotoxin produced by Th1 cells determine the final outcome of these autoimmune diseases. Alternatively, $CD4^+$ type 2 helper T-cells (Th2) represent an anti-inflammatory population of lymphocytes that produce large amounts of immunoregulatory cytokines (e.g., IL-4 and IL-5).[2] Earlier studies have shown that curcumin inhibits neural antigen-induced Th1 differentiation in an EAE model of multiple sclerosis.[5] Curcumin also inhibits IL-12-induced Th1 differentiation in culture,[5,109] suggesting that the regulation of Th1 differentiation is a mechanism by which curcumin inhibits Th1-cell-mediated autoimmune diseases (Figure 2).

B-Lymphocytes also play a key role in mediating autoimmune responses by producing antibodies, acting as APCs, providing support to other mononuclear cells, and contributing directly to inflammatory pathways. It has long been recognized that auto-antibodies produced by B-cells play a critical role in the pathogenesis of autoimmune diseases such as myasthenia gravis and SLE.[3,110] The autoantibodies present in the cerebrospinal fluid of patients with MS recognize myelin antigens, suggesting the importance of B-cells in the pathogenesis of Th1-cell-mediated autoimmune diseases.[111] These studies provide a rationale for targeting B-cells as a potential therapeutic strategy in autoimmune disorders.[112] Further investigations are required to examine the effect of curcumin on B-cell activation and antibody production in autoimmune diseases.

There are several lymphocyte subsets that can regulate autoimmune diseases. The CD4+ Th2 cells that secrete IL-4 are known to inhibit Th1 responses and Th1-cell-mediated autoimmune diseases. $CD4^+CD25^+$ regulatory T-cells secrete IL-10 and transforming growth factor (TGF)-β and suppress $CD4^+$ and $CD8^+$ T-cell responses in autoimmune diseases.[113,114] NKT cells that express TCR and NKR recognize glycolipids presented in the context of CD1d, resulting in the secretion of IFN-γ and IL-4, and they regulate Th1/Th2 differentiation in autoimmune diseases. Although there is no study examining the effect of curcumin on Treg or NKT cells in autoimmune diseases,[115,116] understanding the effect of curcumin on these regulatory cells is important for determining its mechanism of action in autoimmune diseases.

13. CURCUMIN REGULATES INFLAMMATORY CYTOKINES IN AUTOIMMUNE DISEASES

The organ-specific autoimmune diseases are characterized by the presence of many inflammatory cytokines in the target organs. (See Table 2.) Among the many proinflammatory cytokines, TNF-α, IL-1β, and IL-12 play critical roles in the pathogenesis of autoimmune diseases, whereas anti-inflammatory cytokines such as TGF-β, IFN-α, IL-10, and IL-4 confer recovery. Thus, the amelioration of autoimmune diseases by curcumin might be associated with the inhibition of

Table 2. Curcumin regulates inflammatory cytokines.

AUTOIMMUNE DISEASE	INFLAMMATORY CYTOKINES	REFERENCE
MS	No report	—
EAE	Inhibits IL-12 and IFNγ	(5)
Type I diabetes	No report	—
RA	Inhibits TNFα, IL-1, IL-6, NO, IL-12, IFNγ	(117, 118, 120)
Psoriasis	No report	—
IBD	Inhibits IL-1β, TNFα, enhances IL-10	(24, 121–124)
Myocarditis	No report	—
SLE	No report	—
Myasthenia gravis	No report	—

proinflammatory cytokines or upregulation of anti-inflammatory cytokines. TNF-α is a proinflammatory cytokine produced by macrophages, polymorphonuclear cells, mast cells, NK cells, activated T-cells, and endothelial cells.[117] When stimulated with TNF-α, the target cells produce cytokines, chemokines, iNOS, COX-2, and adhesion molecules.[118] Overproduction of TNF-α is associated with septic shock, MS, psoriasis, RA, and IBD. The importance of TNF-α in inflammation has been demonstrated by the efficacy of TNF-αα-targeting agents in the treatment of autoimmune diseases.[119,120]

Earlier studies have shown that curcumin inhibits TNF-α production and TNF-α-induced responses in immune cells.[24,121–124] IL-β is another proinflammatory cytokine that also plays a key role in mediating cartilage degradation in osteoarthritis (OA) and RA. At the cellular level, IL-β activates matrix-degrading enzymes, downregulates the expression of matrix components, and induces chondrocyte apoptosis.[125] Curcumin inhibits IL-1β secretion from macrophage cells and IL-1β-induced responses in immune cells.[126] Curcumin also inhibits IL-β-induced degenerative changes and caspase-3 activation in human chondrocytes. These studies suggest that curcumin targets proinflammatory cytokines in autoimmune diseases (Table 2).

14. CURCUMIN REGULATION OF IL-12 FAMILY CYTOKINES IN AUTOIMMUNE DISEASES

Interleukin-12, IL-23 and IL-27 are three IL-12 family cytokines produced by macrophage, microglia, and dendritic cells that play critical roles in the pathogenesis of autoimmune diseases. (See Figure 3.) The biologically active IL-12 is a 70-kDa heterodimeric protein composed of covalently linked p35 and p40 subunits.[127] IL-12 induces T-cell proliferation, Th1 differentiation, and pathogenesis of autoimmune diseases. The increased expression of IL-12 in the target and lymphoid organs has been shown in many autoimmune diseases. Interestingly, treatment with neutralizing anti-IL-12 antibodies or agents that inhibit IL-12 production was sufficient to inhibit the pathogenesis of autoimmune diseases.[128–130]

Interleukin-23 is another IL-12 family heterodimeric cytokine composed of a common IL-12 p40 subunit and an IL-23 p19 subunit specific to IL-23.[131] Like IL-12, IL-23 is also secreted by macrophage, microglia, and dendritic cells that induce the differentiation of ThIL-17 from memory T-cells and pathogenesis of autoimmune disease.[132,133] Targeted disruption of IL-23 p19 was effective in preventing the pathogenesis of EAE and suggested that IL-23 plays a critical role in the pathogenesis of EAE.[134] Recent studies have also shown the importance of T-bet transcription factor in the differentiation of Th1 cells.[135] IFN-γ and IL-27 are potent inducers of T-bet in naive T-cells,[136] and targeted disruption or siRNA inhibition of T-bet is sufficient to prevent the pathogenesis of EAE[137,138] IL-27 is a heterodimeric cytokine composed of EBI3 and IL-27 p28 that induces the proliferation of naive $CD4^+$ T-cells.[139] Recent studies have also shown the inhibition of EAE by neutralizing antibodies to IL-27 in mice.[140] Thus, a thorough

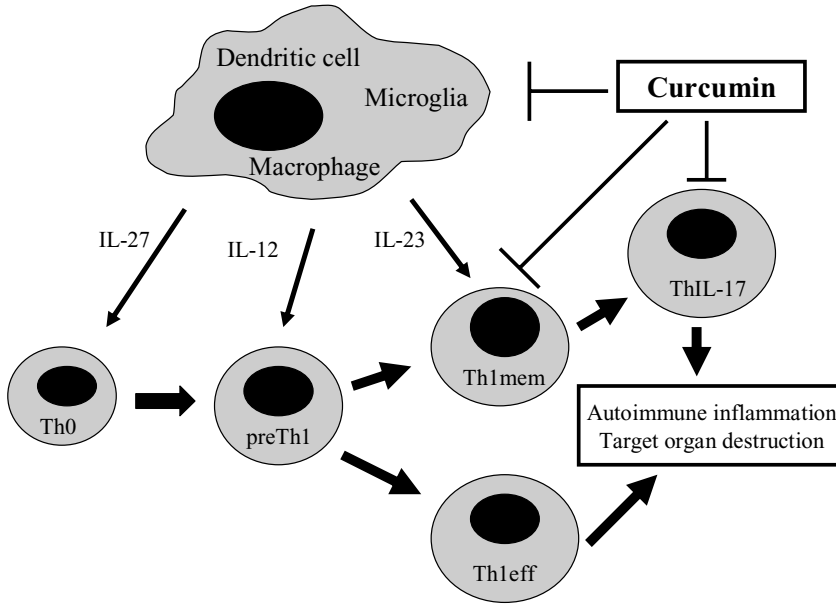

Figure 3. Curcumin inhibits IL-12 in autoimmune diseases. Activation of macrophage, microglia, and dendritic cells through TLR/CD40 leads to secretion of IL-12, IL-23, and IL-27 and differentiation of Th1 and ThIL-17 cells, which mediate autoimmune inflammation and organ destruction. Curcumin inhibits IL-12 family cytokines and prevents organ-specific autoimmune diseases.

understanding of the effect of curcumin on the activation of IL-12/IFN-γ, IL-23/IL-17, and IL-27/T-bet axes is essential to understand its mechanism of action in autoimmune diseases (Figure 3). Because Th2 cytokines such as IL-4, IFN-β, and IL-10 inhibit the activation of macrophage and microglial cells, expression of inflammatory cytokines, and differentiation of Th1 cells, it is important to test the effect of curcumin on these cytokines in autoimmune diseases as well.[108,141]

15. CURCUMIN REGULATION OF NF-κB PATHWAY IN AUTOIMMUNE DISEASES

The IL-12 family cytokines are produced by macrophage, microglia and dendritic cells in response to autoantigens, TLR ligands and CD40 ligands.[127] In earlier studies, we and others have shown that autoimmune cells secrete IL-12 in response to antigens and that this response was inhibited by treatment with curcumin in culture.[5,110] Curcumin also inhibits LPS and CD40L-induced secretion of IL-12 from macrophage, microglia and dendritic cells.[5,110]The induction of IL-12/IL-23 gene expression involves activation of the NF-κB signaling pathway in APCs.[142] NF-κB is a heterodimeric transcription factor composed of p50 and p65 subunits

from the Rel family of proteins. It is sequestered in the cytoplasm as an inactive complex when associated with its inhibitor, IκB.

Upon stimulation with specific inducers, IκB becomes phosphorylated and degraded through proteosome-mediated pathways. The activated NF-κB then translocates into the nucleus and binds to specific 10-bp response elements of the IL-12/-23/-27 gene.[142,145] Activation of NF-κB is a complex process involving the successive action of proximal NF-κB-inducing kinase (NIK) and the IκB kinases, IKKα, IKKβ, and IKKγ.[146] The expression of the IL-12 p40 subunit is controlled by proximal cis-acting elements (NF-κB half-site) interacting with NF-κB family members.[147] Inhibitors of IL-12 gene expression, including retinoids, acetyl salicylic acid, and 1,25 dihydroxyvitamin D3, block NF-κB activation and binding within the IL-12p40 promoter.[148,149] Earlier studies have also shown that curcumin inhibits the NF-κB pathway leading to IL-12 gene expression in phagocytic cells,[43,143,] suggesting that the blockade of the NF-κB pathway is a mechanism by which curcumin regulates IL-12 production in autoimmune diseases (Figure 4, Table 3).

16. CURCUMIN REGULATION OF JAK–STAT SIGNALING PATHWAY IN AUTOIMMUNE DISEASES

The antigen-induced proliferation of autoimmune T-cells is a two-step process in which signaling through the T-cell receptor (signal 1) drives T-cells from the resting G0 phase to the activated G1 phase of the cell cycle, whereas signaling through the IL-2 or IL-12 receptor (second signal) is required for T-cells to transit from the G1 phase to the S/G2/M phase of the cell cycle (proliferation). IL-12 is a potent inducer of G1 to S/G2/M phase transition and differentiation of Th1 cells that are critical in the pathogenesis of EAE. IL-12 signals through IL-12 receptor β1 and β2, members of the gp130 cytokine receptor super-family, expressed primarily on activated NK cells and T-cells. Coexpression of IL-12Rβ1 and Il-12Rβ2 leads to the formation of high-affinity IL-12 receptors.[127] Signaling through its receptor, IL-12 induces tyrosine phosphorylation and activation of JAK2, TYK2, STAT3, and STAT4 in T-cells and NK cells.[150,151] Activation of the JAK–STAT pathway leads to the transcription of IL-12 response genes associated with proliferation, Th1 differentiation, and IFN-γ production. IL-23 receptor is composed of a common IL-12Rβ1 and a specific IL-23 receptor subunit.[152] Signaling through its receptor, IL-23 induces the activation of JAK2, TYK2, STAT1, STAT3, STAT4, and STAT5 in T-cells.[152] Activation of the JAK–STAT pathway leads to transcription of IL-23 response genes, including IL-17, which are associated with the proliferation of memory T-cells,[153] whereas IL-27 and IFN-γ activate a specific JAK–STAT pathway in T-cells, resulting in the induction of T-bet in naive T-cells.[154] Modulation of cytokine signaling by targeting protein tyrosine kinases or transcription factors has been considered a novel strategy for the treatment of autoimmune diseases.[155,156] We have shown earlier that the blockade

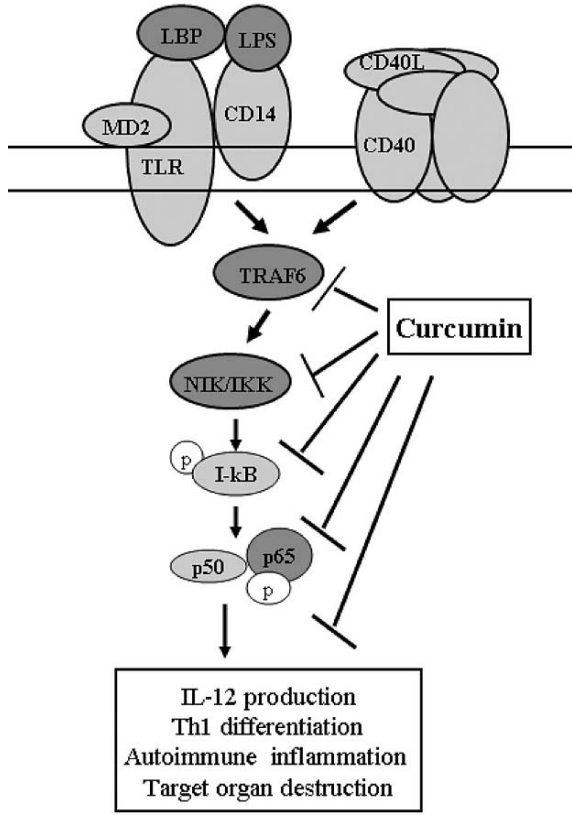

Figure 4. Curcumin targets the NF-κB pathway in autoimmune disease. The activation of the NF-κB pathway through TLR/CD40 involving NIK/IKK-mediated phosphorylation of IκB leads to expression of IL-12 and other inflammatory cytokines and pathogenesis of autoimmune diseases. Curcumin ameliorates autoimmune diseases by targeting the NF-κB signaling pathway, leading to the secretion of IL-12 and other inflammatory cytokines.

Table 3. Curcumin targets inflammatory signaling molecules in autoimmune diseases.

AUTOIMMUNE DISEASE	INFLAMMATORY CYTOKINES	REFERENCE
MS	No report	—
EAE	Inhibits IL-12-induced JAK- STAT pathway	(5)
Type I diabetes	No report	—
RA	Inhibits AP-1, ERK, p38, JNK, MAPK, NF-κB	(43,143, 144)
IBD	Inhibits NF-κB, p38 MAPK	(43)
Psoriasis	Inhibits AP-1, Lipoxigenase, Phosphorylase kinase	(38, 39)
Myocarditis	No report	—
SLE	No report	—
Myasthenia gravis	No report	—

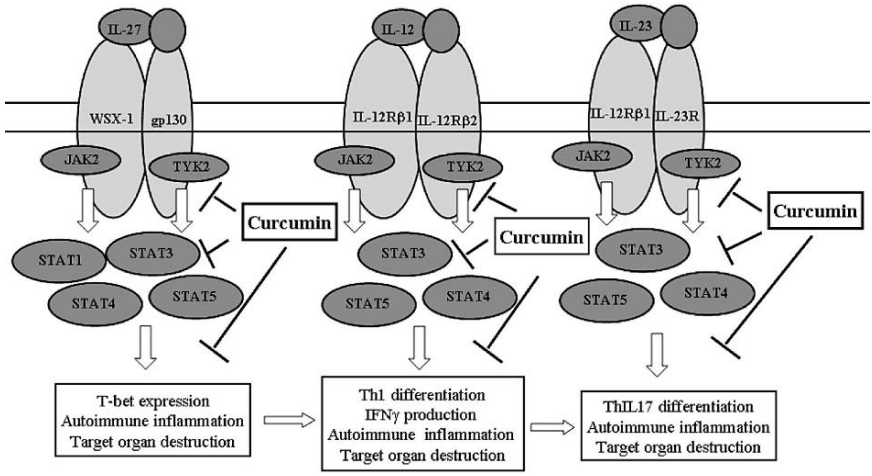

Figure 5. Curcumin regulates IL-12 signaling in T-cells. The IL-12 family cytokines, IL-12, IL-23, and IL-27, signals through the JAK–STAT pathway, leading to induction of IFN-γ/T-bet/IL-17 genes associated with Th1 and ThIL-17 differentiation, autoimmune inflammation, and target-organ destruction. Curcumin targets IL-12 signaling through the JAK–STAT pathway, leading to Th1 differentiation in autoimmune diseases.

of IL-12 signaling through the JAK–STAT pathway by treatment with a JAK-2 inhibitor, tyrphostin AG490, peroxisome proliferator-activated receptor-γ (PPARγ) ligands, Quercetin, and vitamin D inhibit Th1 differentiation and pathogenesis of EAE.[5,51,157–159] We have also shown recently that curcumin inhibits IL-12-induced tyrosine phosphorylation of JAK2, TYK2, STAT3, and STAT4 in T-cells, differentiation of Th1 cells, and pathogenesis of EAE.[5,157] These findings suggest that IL-12 signaling through the JAK–STAT pathway is a molecular target in the regulation of autoimmune diseases by curcumin (Figure 5, Table 3).

17. CURCUMIN REGULATION OF MAPK AND AKT PATHWAYS IN AUTOIMMUNE DISEASES

MAPK and AKT and other immune signaling pathways also play critical roles in the pathogenesis of autoimmune diseases. It was interesting to note that curcumin attenuates inflammatory activity in association with the inhibition of MAPKs in an experimental model of IBD. More recent work has demonstrated that the use of p38 MAPK inhibitors can be effective for human autoimmune diseases. Thus, it was anticipated that the inflammatory response might entail activation of p38 MAPK in the infiltrating immune cells.[160] The exact role played by activated p38 MAPKs at these sites remains unclear, but it might involve secretion of chemokines, neuropeptides and other trophic factors. Similarly, activation of the PI3K–AKT

signaling pathway has been linked to macrophage activation and inflammation.[161] Thus, the inhibition of MAPK and AKT might be other molecular targets in the amelioration of autoimmune diseases by curcumin (Table 3).[162]

18. CURCUMIN REGULATES CHEMOKINES IN AUTOIMMUNE DISEASES

Chemokines are small heparin-binding proteins that promote the movement of circulating leukocytes to sites of inflammation and injury throughout the body and play crucial roles in mediating adaptive immune responses and pathogenesis of a variety of autoimmune diseases. There are approximately 50 human chemokines grouped into 4 families on the basis of differences in structure and function.[163] The largest family consists of CC chemokines, which attract mononuclear cells to sites of chronic inflammation. The most studied CC chemokine, monocyte chemoattractant protein 1 (MCP-1), is a potent agonist for monocytes, dendritic cells, memory T-cells, and basophils. Other CC chemokines include macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5). IL-8 (CXCL8) is the prototypic CXC chemokine that attracts polymorphonuclear leukocytes to sites of acute inflammation. CXCL8 also activates monocytes and might direct the recruitment of these cells to vascular lesions. Chemokines affect cells by activating surface receptors that are seven-transmembrane-domain G-protein-coupled receptors. The binding of the chemokine to the receptor activates signaling cascades that culminate in the rearrangement, change of shape, and cell movement of actin. Chemokine receptors are important drug targets that regulate inflammation and antoimmunity.[164,163]There are reports showing the inhibition of chemokine and chemokine receptors by curcumin in immune cells,[166] suggesting this is a molecular target in the regulation of autoimmune diseases by curcumin.

19. THERAPEUTIC POTENTIAL AND FUTURE PROSPECTS OF CURCUMIN IN AUTOIMMUNE DISEASES

The ability of herbal medicines and dietary supplements to alleviate pain and clinical symptoms has led to an increased use of complementary and alternative medicine in patients with autoimmune diseases. Although many more new compounds are being isolated and tested for their anti-inflammatory and anticancer properties, these nutraceuticals are of considerable interest because they are effective, inexpensive, and relatively safe. The protective effect of curcumin in the treatment of autoimmune disease has been proven, but its use in the treatment of many human autoimmune diseases is yet to be determined. With the available information, it is difficult to predict the type of dietary modifications containing curcumin that can better reduce the risk, incidence, or severity of autoimmune diseases. Although it is generally believed that the nutraceuticals induce minor side

effects during dietary consumption at low levels, one needs to be extremely cautious about the use of purified active compounds such as curcumin at higher doses for therapeutic purposes. Much work needs to be done to determine the effective dose, safe regimens, and molecular mechanisms of action before these nutraceuticals can be used for the treatment of human autoimmune diseases. We believe that curcumin ameliorates autoimmune diseases by inhibiting proinflammatory responses or by enhancing anti-inflammatory responses in the target organs. Interestingly, the research on nutraceuticals has now taken a new dimension that will unravel many unanswered questions on the use of curcumin in the treatment of organ-specific autoimmune diseases.

20. CONCLUSION

Autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, myocarditis, thyroiditis, uveitis, systemic lupus erythromatosis, and myasthenia gravis are common health problems affecting more than 5% of the population worldwide. Although the etiologies are not known, these autoimmune diseases manifest following deregulated activation of self-reactive immune cells influenced by genetic, environmental, and behavioral factors. Curcumin is a polyphenolic compound isolated from the rhizome of the plant *Curcuma longa* that has traditionally been used in the treatment of inflammation and cancer. Recent studies have shown promise in the use of curcumin to treat autoimmune diseases.

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