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Curcumin has bright prospects for the treatment of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS). It is associated with a variety of pathophysiological features, including breakdown of the blood–brain barrier (BBB), autoimmune attack, injury of axons and myelin sheaths. Th17 cells are considered as a key immunological player for the pathophysiological process of MS. Neuroprotective approaches work best prior to the initiation of damage, suggesting that some safe and effective prophylaxis would be highly desirable. Curcumin, a dietary spice from turmeric, has outstanding anti-inflammation and neuroprotective effects. Herein, we review key features of curcumin involved biology, pharmacology, and medicinal chemistry and discuss its potential relevance to pathophysiological progress of MS.

1. Introduction

Multiple sclerosis (MS) is a neurodegenerative disease, and has many pathological, biochemical and immunological features in common with Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) [1–3]. The management of MS remains a challenge, even as our knowledge and understanding of MS continue to grow at an unprecedented rate [4–8]. Research that bridges the gap between basic science and clinical application is extremely important for the development of new therapeutics. With the discovery of Th17 cells in MS, rheumatoid arthritis (RA) and many autoimmune diseases [2,9–12], some questions about the physiopathology of these diseases can now be better understood, since the mechanism of such immune responses did not fit under the Th1 or Th2 paradigm. So there is a great deal of scope for novel therapeutic approaches.

Curcumin, the phytochemical component in turmeric, has been used as a dietary spice and a topical ointment for the treatment of inflammation in Asia for centuries. Modern scientific community discovers that curcumin has a great variety of pharmacological activities including anti-inflammatory, anti-bacterial, anti-protozoal, anti-oxidant and anti-tumor activity [13–15]. Based on early research conducted with cell cultures and animal models, pilot and clinical trials indicate curcumin may have potential as a therapeutic agent in several Th17 cell mediated inflammatory diseases such as MS, AD, PD, inflammatory bowel disease (IBD), as well as RA [16–19]. Numerous clinical trials are currently in progress that, over the next few years, will provide an even deeper understanding of the therapeutic potential of curcumin.

MS is associated with a variety of pathophysiological features, including breakdown of the blood–brain barrier (BBB), autoimmune attack, injury of axons and myelin sheaths [20–22]. Th17 cells, which are characterized by the production of interleukin-17(IL-17), are considered as a key immunological player for the pathophysiological process of MS [23,24]. Herein, we review how curcumin could be involved in this process of MS, together with the brief summary of its biology, pharmacology, and medicinal chemistry.

2. Overview of curcumin

2.1. Chemical properties of curcumin

Curcumin ($C_{21}H_{20}O_6$), the most active component of turmeric, makes up 2–5% of this spice. The yellow color of the turmeric is due to the curcumin compound. Curcumin was first described in 1910 by Lampe and Milobedeska and shown to be a diferuloylmethane, 1,7-bis

Abbreviations: AD, Alzheimer's disease; BBB, blood–brain barrier; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; IL-17, interleukin-17; MLC, myosin light chain; MS, multiple sclerosis.

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(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene -3,5-dione, and is practically insoluble in water. It is a *bis*-α-β-unsaturated β-diketone; under acidic and neutral conditions, the *bis*-keto form of the compound predominates, and at pH above 8, the enolate form is generally found [25]. Hence at pH 3–7, it acts as an extraordinarily potent H-atom donor and above pH 8, it acts mainly as an electron donor [26]. Curcumin is quite unstable at basic pH and degrades within 30 min. Human blood or antioxidants such as ascorbic acid or the presence of 10% fetal bovine serum in the culture media prevents this degradation [27]. Curcumin has a molecular weight of 368.7 and the commercial grade curcumin contains curcuminoids, 10–20% desmethoxycurcumin and less than 5% bisdesmethoxycurcumin. The commercial grade curcumin is just as effective as pure curcumin in preclinical models of carcinogenesis [28].

2.2. Pharmacokinetic and pharmacodynamic properties of curcumin

Absorption, metabolism and tissue distribution are important parameters to render a compound to be used as a therapeutic agent. In this regard, animal studies have shown curcumin is rapidly metabolized, conjugated in the liver, and excreted in the feces, therefore having limited systemic bioavailability.

A 40-mg/kg intravenous dose of curcumin given to rats resulted in complete plasma clearance at 1 h post dose. An oral dose of 500 mg/kg given to rats resulted in a peak plasma concentration of only 1.8 ng/ml, with the major metabolites identified being curcumin sulfate and curcumin glucuronide [29]. Data on the pharmacokinetics, metabolites, and systemic bioavailability of curcumin in humans, mainly conducted on cancer patients, are inconclusive.

A phase I clinical trial conducted on 25 patients with various precancerous lesions demonstrated oral doses of 4, 6, and 8 g curcumin daily for 3 months yielded serum curcumin concentrations of only 0.51 ± 0.11,0.63 ± 0.06, and 1.77 ± 1.87 μM respectively, indicating curcumin is poorly absorbed and may have limited systemic bioavailability. Serum levels peaked between one and two hours post dose and declined rapidly. This study did not identify curcumin metabolites, and urinary excretion of curcumin was undetectable [30].

Another phase I trial, involving 15 patients with advanced colorectal cancer, used curcumin at doses between 0.45 and 3.6 g daily for 4 months. In three of six patients given the 3.6-g dose, mean plasma curcumin measured after 1 h on day 1 was 11.1 ± 0.6 nmol/L. This measurement remained relatively consistent at all time points measured during the first month of curcumin therapy. Curcumin was not detected in the plasma of patients taking lower doses. Glucuronide and sulfate metabolites of curcumin were detected in plasma of all six patients in the high-dose group at all measurement points in the study [31].

While systemic distribution of curcumin tends to be low, Garcea et al. [32] demonstrated that 3.6 g curcumin given to 12 patients with varying stages of colorectal cancer for 7 days resulted in pharmacologically efficacious levels of curcumin in both malignant colorectal tissue (7.7 ± 1.8 nmol/g) and normal colorectal tissue (12.7 ± 5.7 nmol/g), perhaps accounting for the anti-inflammatory benefits of curcumin observed in diseases of the gastrointestinal tract [33].

Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. The roles of adjuvants, which can block the metabolism of curcumin, are of great interest. Combining curcumin with piperine has been shown to increase the bioavailability in rats and in human subjects. Piperine is an inhibitor of glucuronidation of curcumin. The study conducted by Shoba et al. [34] demonstrated that concomitant administration of curcumin with piperine produced 150% increase in bioavailability in rats and 2000% increase in human. Other ways to improve the bioavailability of curcumin is by making curcumin nanoparticles [35], liposomes [36], micelles and phoshoplipid complexes [37,38]. The possible advantages attributed to such formulations are as follows: (a) provide longer circulation, (b) increase the cellular permeability and (c) induce resistance to metabolic processes.

2.3. Biological activities of curcumin

Curcumin has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation. The process of inflammation has been shown to play a major role in most autoimmune illnesses.

In experimental autoimmune encephalomyelitis (EAE), an MBP induced animal model of MS, the treatment with 200 mg/kg curcumin significantly reduced the clinical severity of EAE and had a dramatic reduction in the number of inflammatory cells infiltration in the spinal cord. The proliferation of the MBP-reaction lymphocyte also was reduced in a curcumin dose-dependent manner, indicating curcumin amelioration EAE was due to inhibit differentiation and development of Th17 cells [19].

Baum et al. [39] led to a 6-month randomized, placebo-controlled, double-blind, clinical pilot study of curcumin in patients with AD. Thirty-four subjects started the 6-month trial and 27 completed (8 subjects on 0 g, 9 subjects on 1 g, and 11 subjects on 4 g curcumin per day). Curcumin groups when compared with placebo control showed increased plasma levels of vitamin E and increased serum Aβ40. The latter reflects an ability of curcumin to disaggregate Aβ-deposits in the brain. The authors recommended longer and larger trials to determine the efficacy of curcumin in AD patients [39]. Although there is no epidemiology that age-adjusted AD prevalence and incidence in an area with high curcumin intake (rural India) was surprisingly low compared to the United States and other Western countries [40]. In animal models of AD, curcumin decreased the amyloid pathology of AD by targeting several possible anti-amyloid mechanisms relevant to AD pathogenesis [17].

Dermatological diseases, in particular psoriasis, which is now regarded as a Th17 mediated autoimmune disease, are treated with curcumin [41,42]. Furthermore, curcumin is effective in the treatment of RA [43], IBD [44], osteoarthritis [45], pancreatitis and some autoimmune models [46], as well as prevention of atherosclerosis and diabetes [47,48].

Curcumin appears to normalize many pathological states. Because of its pluripotency, oral safety, long history of use, and inexpensive cost, curcumin has great potential for the treatment of MS and other Th17 cells mediated autoimmune inflammatory diseases for which current therapeutics are less than optimal.

In every published clinical trial, curcumin appears to be extremely safe. A phase 1 human trial with 25 subjects using up to 8 g of curcumin per day for 3 months found no toxicity from curcumin [49]. Of less importance are *in vitro* and animal trials that in select settings have demonstrated potentially adverse effects. *In vitro*, in the presence of copper and cytochrome p450 isoenzymes, curcumin induced DNA fragmentation and base damage [50]. There is also some evidence that curcumin inhibits the activity of certain chemotherapy drugs. Research reveals curcumin decreased camptothecin inducing death of cultured breast cancer cells and prevented cyclophosphamide-induced breast tumor regression in mice. Curcumin might also interfere with the absorption and efficacy of the chemotherapy drug irinotecan, which is used to treat colon cancer [51].

On the other hand, curcumin may enhance the effects of some chemotherapy drugs. In a mouse xenograft model of human breast cancer, curcumin in conjunction with paclitaxel (Taxol) significantly inhibited breast cancer metastasis to the lung to a greater degree than either curcumin or paclitaxel alone. Prevention of breast cancer metastasis in this study appeared to be via curcumin's inhibition of NF-κB [52].

3. Pathophysiological changes of the MS

MS is generally considered as be an autoimmune disease directed against CNS myelin and the myelin-producing cells, the oligodendrocytes [53,54]; however, as many other human chronic autoimmune diseases, the primary cause of autoimmunity is unknown. Most studies in people with MS and from the animal model of MS, EAE, which shares some of the clinical and neuropathological features of MS, suggest that Th17 cells are important in the initiation of episodes of demyelination in the relapsing-remitting phase of MS [4].

It is firmly established that disruption of the BBB and the trafficking of autoreactive T-cells from the systemic compartment into the central nervous system play an important role in early events of the development of MS lesions [55]. The BBB plays an important role in the homeostatic regulation of the brain microenvironment and maintains the immune-privileged status of the brain by restricting the entry of lymphocytes [56,57]. Th17 cells have emerged as critical autoimmune effectors in multi-focal perivascular infiltration of mononuclear cells with a relative breakdown in BBB integrity [58–61]. When a comparison was made between human Th1 cells versus Th17 cells, human Th17 cells migrated faster across the BBB than Th1 cells. Indeed a significant number of IL-17$^-$ and IL-22$^-$ expressing CD4$^+$CD45RO$^+$ memory lymphocytes upon their migration across BBB expressed IL-17$^+$ and IL-22$^+$ markers, which confirmed the ability of Th17 cells to cross the BBB *in vitro* and *in vivo*. The BBB endothelial cells (ECS) in MS lesions express IL-17R and IL-22R while they are undetectable in normal subjects, which are used by Th17 cells to infiltrate the BBB-ECS. The diffusion of cells or antigens, such as bovine serum albumin (BSA), across the BBB was enhanced significantly when IL-17 and IL-22 were added to monolayers of human BBB-ECS [55]. This enhanced permeability of BBB-ECS correlated with a decrease in the expression of occludin and zonulin (ZO-1) and alteration in junctional localization of ZO-1, the two important tight junction proteins. IL-17 activates the endothelial IL-17R which is followed by increased reactive oxygen species (ROS) production mediated by NAD(P)H oxidase and xanthine oxidases. The resulting oxidative stress activates the endothelial contractile machinery by increasing the amount of phosphorylated myosin light chain (MLC) and accompanied with a down-regulation of the tight junction molecule occluding and ZO-1. Phosphorylated MLC interacts with the actin cytoskeleton, leading to a cell contraction that *per se* increases the intercellular space of the endothelial cell monolayer (Fig. 1) [55,62].

4. Curcumin inhibit neuroinflammation of MS

4.1. Curcumin inhibit proinflammatory cytokines, chemokines and others

Curcumin, an NF-κB inhibitor, is effective in preventing disruption of the BBB induced by Th17 cells through affecting the expression and subcellular localization of ZO-1, inhibiting MLC phosphorylation, and abolishing ROS generation (Fig. 1) [63]. Pre-treating with the curcumin (10 μM) for 1 h before human corneal epithelial (HCE) cells exposure to TNF-α (0–30 ng/ml), curcumin prevented a decrease of TNF-α inducing concentration- and time-dependent manner in the transepithelial electrical resistance (TER) of HCE cells transwell cultures. ZO-1 and occluding were localized at the interfaces of adjacent HCE cells in the absence of TNF-α. However, exposure of the cells to TNF-α for 24 h resulted in loss of ZO-1 immuno-reactivity from the cellular borders, and this effect was blocked by curcumin. In contrast, the distribution of occludin at the cell surface was not affected by TNF-α in the absence or presence of curcumin. Incubation of HCE cells with TNF-α also resulted in the appearance of the phosphorylated form of MLC; however, this MLC phosphorylation was inhibited by curcumin [63]. Effect of curcumin is confirmed by using an *in vitro* intestinal epithelial system consisting of filter grown Caco-2 monolayers. Curcumin blocked the increase of TNF-α inducing a concentration- and time-dependent in Caco-2 tight junctions permeability. The treatment of curcumin was accompanied by up-regulation of ZO-1 proteins and alteration in

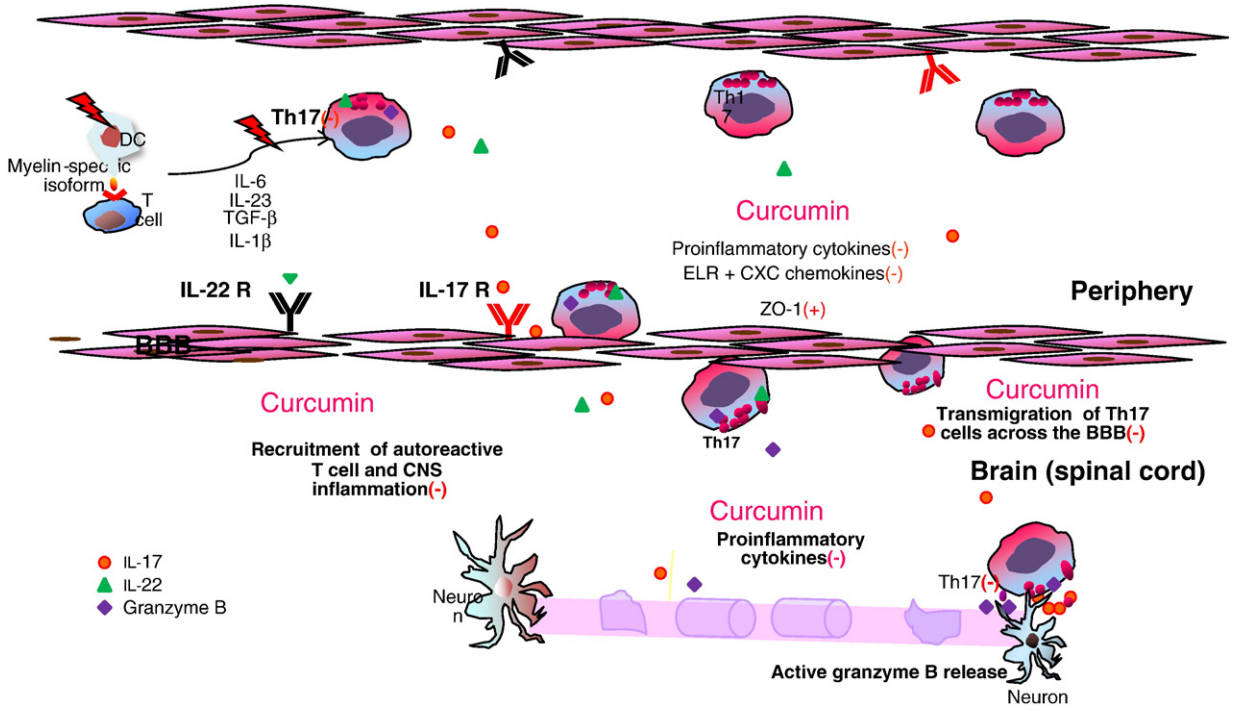

Fig. 1. *Curcumin inhibits neuroinflammation through multiple mechanisms in MS.* DC captures CNS antigens and presents antigen to T lymphocytes, induction inflammatory response, production of cytokines and increasing the Th17 cells number in circulation. Expression of IL-17 receptors (IL-17R) and IL-22 receptors (IL-22R) on BBB-ECS results in the binding of Th17 cells to BBB tight junctions. This disrupts the tight junctions, and the Th17 cells then transmigrate across the BBB, setting the stage for the killing of neurons by the release of granzyme B. Curcumin inhibits the differentiation and expansion of Th17 cells in circulation induced by inflammatory cascade, enhances the expression of ZO-1, an important tight junction protein, and down-regulates expression of CXC chemokines and receptor. Curcumin resulting in the repair of the BBB decrease Th17 cells to transmigrate across the BBB and the inhibition of autoreactive T cells transmigration can reduce neuroinflammation.

junctional localization of ZO-1 proteins [64], indicating that curcumin blocked the increase in permeability and the decrease of ZO-1 expression was associated with inhibiting NF-κB activation. Curcumin has been claimed to represent a potential antioxidant agent with phytonutrient and bioprotective properties. Curcumin abolished both PMA and thapsigargin-induced ROS generation. The pattern of these ROS inhibitory effects as a function of dose-dependency suggests that curcumin mechanistically interferes with protein kinase C (PKC) activity and Ca^{2+} entry [65,66].

Th17 cells transmigrate efficiently across BBB-ECS to promote CNS inflammation through lymphocyte recruitment [55]. An important function of IL-17 is to induce production of CXC chemokines, such as CXCL1, CXCL2 and CXCL8/IL-8 and receptors CXCR1, CXCR2 in the recruitment of circulating lymphocytes and monocytes to the CNS during EAE and MS [67]. Transfers of encephalitogenic CD4 positive Th17 cells are sufficient to induce CXCL1 and CXCL2 transcription in the spinal cords of naive, syngeneic recipients. Blockade or genetic silencing of CXCR2, abrogates BBB breakdown, CNS infiltration by leukocytes, and the development of clinical deficits during the presentation as well as relapses of EAE [67,68]. In EAE mice or rats, curcumin decreased obviously inflammatory cells, especially Th17 cells, infiltration and differentiation in CSN [19,69]. Curcumin reduce the mRNA and protein expression of CXCL1 and CXCL2 by down-regulated NF-κB activation correlated with CXC production [70]. CXCL8 belongs to the CXC chemokine subgroup. It is a chemotactic cytokine that activates and elicits the migration of leukocyte. CXCL8 affects the functions of human neutrophils, including enhanced chemotaxis, enzyme release, and expression of surface adhesion molecules. CXCL8 stimulates neutrophils via specific chemokine receptors, namely CXCR1 and CXCR2. Curcumin, a specific inhibitor of JNK, also concentration-dependently reduced IL-17-induced CXCL8 production and intercepted of CXCL8 promoting signal transduction in neutrophils. Curcumin treatment resulted in a decrease in the amount of both CXCR1 and CXCR2 present on the cell surface. In particular, after CXCL8 promoted receptor internalization, the amount of CXCR1 and CXCR2 on the neutrophil cell surface is significantly decreased. The decrease in the amount of CXCR1 and CXCR2 present on the cell membrane was not only due to degradation but also curcumin may affect the ligand-promoted trafficking pathway of the CXCR1 and CXCR2. Curcumin delayed the trafficking pathway in the cytosol, and this resulted in the blockage of the recycling pathway to the cell surface [71–73].

IL-17 itself is a crucial effector's cytokine with potent proinflammatory effects. It activates IL-6 synergistically with other cytokines, including IL-1β, IFN-γ, TNF-α and IL-23 along with nitric oxide (NO) and expression of cyclooxygenase-2 (COX-2) [74], prostaglandin E2 (PGE2), and activate microglia, astrocyte, macrophage and DC in CSN by triggering NF-κB isoform consists of the canonical pathway components, p65 and p50, which coordinate the induction of many genes that encode inflammatory mediators (Fig. 2) [75]. The activated microglia, astrocyte, macrophage and DC promote recruitment and antigen-specific activation of infiltrating leukocytes and facilitates the production of key proinflammatory cytokines such as TNF-α, IL-6 and IL-17, IL-1β or IL-23, PGE-2 [76–78]. Then these cytokines act in an autocrine manner to express IL-17 on microglia, astrocyte, macrophage and benefit the differentiation of expansion of Th17 from naïve CD4+ T cells. Such as, PGE2, which affect DC proinflammatory phenotype and altered IL-12/IL-23 balance, which strongly favors IL-23, promote Th17 and inhibit Th1/Th2 differentiation *in vitro* and *in vivo* [79,80].

Curcumin blocks cytokines mediated NF-κB activation through inhibition of IκBα kinase and AKT by different inflammatory stimuli, down-regulates the expression of the NF-κB regulated gene products such as, IL-17, IL-1β, TNF-α, IL-6, IL-8, MIP-1, PGE2, C-reactive protein (CRP), CXCR-4, and others induced by inflammatory stimuli (Fig. 2) [81–83]. Curcumin modulates the cytokine milieu, which differentiation and proliferation/survival of Th17 cells such as, the production and activity of IL-1β, IL-6, TGF-β, and IL-23, STAT3 by inhibiting NF-κB activity in inflammation circulation. In SJL/J mice, curcumin reduced the duration and clinical severity of active immunization and adoptive transfer EAE. Recognized curcumin also inhibited EAE in association with a decrease in IL-12 production from macrophage/microglial cells and differentiation of neural Ag-specific Th1 cells [69]. Curcumin also has been reported to bind to COX-2 and 5-LOX and to inhibit their activity [84,85].

4.2. Curcumin inhibit Th17 differentiation and its related pathways

Th17 cells are at the center of attention in chronic inflammatory diseases' research. The importance of Th17 cells in CNS inflammation in MS patients and experimental autoimmune myasthenia gravis has been shown [23,86–88]. Recent evidences from EAE studies suggest Th17 expansion in circulation is a crucial step in disease initiation. It is well known that Th17 cells differentiation is induced by coexistence of IL-6 and TGF-β, enhanced by TNF-α and IL-1β, maintained and expanded by IL-23. The cytokine profile of CD4 positive T lymphocytes is dictated by the ability of antigen-presenting cells to secrete IL-12p70, favoring Th1 lymphocytes, or conversely the combination of TGF-β and IL-6, favoring a Th17 lymphocyte phenotype. Dendritic cell (DC) is considered the most potent antigen presenting cells. A line of evidence indicates that the development toward Th17 cells is regulated by DC-derived cytokines. IL-23 is now recognized as a DC-secreted molecule, which favors the expansion, rather than the differentiation of Th17 lymphocytes. The activated DC secretes high levels of TGF-β1, IL-1β and IL-6, favoring the differentiation of CD4 positive T lymphocytes into IL-17 secreting cells (Fig. 1) [89]. In addition, immature DC captures CNS antigens and migrates to secondary lymphoid tissues, then begins to mature, up-regulates MHC class II, CD80, CD86 and CD40, and acquires the ability to present antigen to naive myelin specific $CD4^+$ T lymphocytes at the inflammatory site in the CNS. Gi-Young Kim et al. [90] indicated curcumin influences the maturation and function of DC. BM cells were cultured for 7 days with 20 ng/ml GM-CSF and 20 ng/ml IL-4 in the presence or absence of different concentrations of curcumin for 24 h. Twenty-five micromolars of curcumin was sufficient to reduce the expression of CD80, CD86, and MHC class II molecules on CD11c positive cells on day 7. The inhibitory DC mature effect of curcumin was dose dependent and targeted primarily the expression of CD86 and MHC class II molecules [90]. Another major attribute of mature DC is the synthesis and release of cytokines with important modulatory functions in inflammation. Curcumin inhibited proinflammatory cytokine IL-23, IL-1β, IL-6, and TGF-β release in LPS-stimulated mature DC by inhibiting NF-κB activation with MAPK signal pathway suppression. DC treated with curcumin skewed naive T cells away IL-17 producing T cells. Furthermore, although DC treated with curcumin migrates to T cell areas of secondary lymphoid tissue, they fail to induce normal cell-mediated contact hypersensitivity [90]. It was demonstrated that curcumin significantly impaired the capacity of DC and modulated cytokine milieu to initiate and proliferate Th17 responses [91,92].

The Th17 differentiation of naïve T cells is initiated by TGF-β and IL-6. TGF-β1, TGF-β2, and TGF-β3 are the three isoforms that have been identified in mammals. Among these three isoforms, TGF-β1 is predominantly expressed in the immune system and is believed to be an important pleiotropic cytokine with potent immunoregulatory properties. TGF-β1 induces Foxp3-positive regulatory T cells (iTregs) in the presence of IL-2, while in the presence of IL-6, induces pathogenic IL-17 producing Th17 cells. In the presence of IL-6, TGF-β first binds to the TGF-βR, which then primarily activates Smad transcription factors, Smad2 and Smad3, Smad2 or Smad3 is directly phosphorylated and activated by TGF-βR and heterodimerizes with Smad4 or TIF1γ. The activated Smad-complex translocates into the

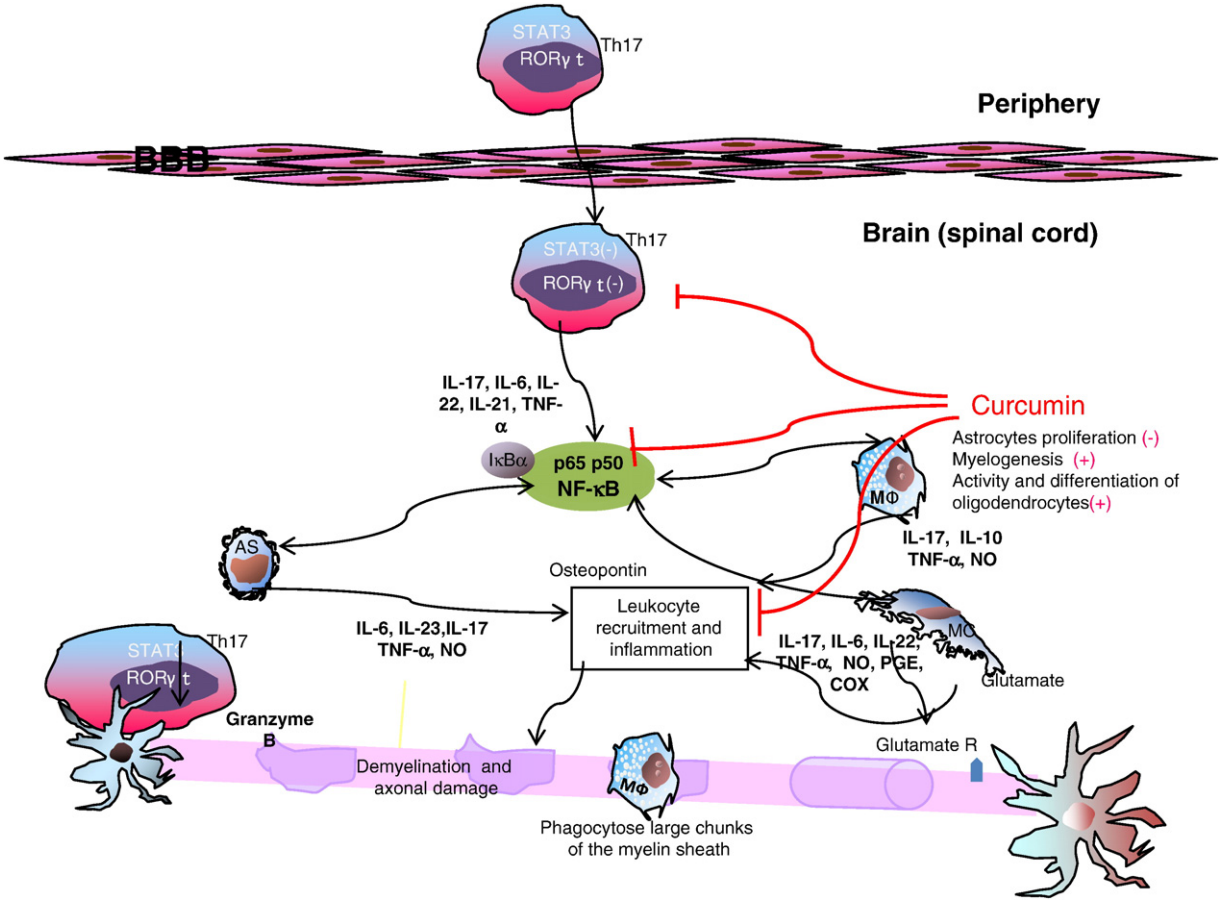

Fig. 2. *Curcumin blocks IL17 and others, which lead to CSN tissue destruction in MS.* Infiltrating Th17 cells produce IL-17, which synergizes with other pro-inflammatory cytokines present in the CNS, leading to the activation of microglia (MC), astrocyte (AS), macrophage (MΦ) in CSN by triggering NF-κB isoform, that producing a local milieu conducive to Th17 development, and they secret cytokines and chemokines, e.g. IL-17, TNF-α, NO, osteopontin, further up-regulating inflammation, inducing demyelination and the macrophage to phagocytose large chunks of the myelin sheath. Curcumin inhibits differentiation and development of Th17 cells depends on down-regulating expression of IL-6, IL-21, RORγt signaling and inhibition STAT3-phosphorylation. Curcumin down-regulates of NF-κB activation in microglia, astrocytes and macrophages, reduces of leukocyte recruitment and CSN inflammation, decreases demyelination and axonal damage. Additionally, curcumin reduces astrocytes proliferation, improves myelogenesis and increases activity and differentiation of oligodendrocytes.

nucleus, and, in a cooperative manner with other nuclear cofactors, regulates the transcription of target genes [93]. Curcumin blocks multiple sites of the TGF-β signaling cascade. The inhibitory effect of curcumin was quite profound because TGF-β effects were almost completely blocked for an extended time even when curcumin was given after TGF-β stimulation was initiated. Curcumin decreased TGF-βR protein levels, This was associated with reduced Smad2 and Smad3 phosphorylation after curcumin treatment [94]. Smad2 and Smad3 were dispensable for the induction of RORγt, which directs Th17 cell differentiation. Curcumin inhibits the activity of the transcription factor c-jun and also has NF-κB inhibitory activity, and it is possible that curcumin limits essential transcription factor availability, which subsequently leads to reduced TGF-βR mRNA expression. Curcumin has been shown to be an inhibitor of the transcription factor c-jun/activator protein-1 (AP-1) through its ability to directly bind to c-jun and block its interaction with its DNA binding site [95].

STAT3 plays a critical role in the induction of the orphan nuclear receptor, RORγt, which directs Th17 cell differentiation by inducing the IL-23 receptor. The critical role of STAT3 in Th17 differentiation was also confirmed in human patients lacking functional STAT3. The role of IL-6/STAT3 is important in the generation of Th17 differentiation in the presence of TGF-β. IL-6 is necessary for the suppression of Foxp3 and for maintaining high levels of RORγt. STAT3 may suppress Foxp3 expression via a direct binding. In addition, IRF4 and c-Maf, which are up-regulated by STAT3, have been shown to be necessary for RORγt expression [96].

Curcumin inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. RPMI 8226 cells, which do not express constitutively phosphorylated STAT3, were treated with IL-6 to induce phosphorylation of STAT3, and the cells were then incubated with curcumin for different times and examined for IL-6-inducible STAT3 phosphorylation. IL-6-induced STAT3 phosphorylation was blocked by curcumin in a time-dependent manner. Exposure of cells to curcumin for 4 h was sufficient to completely suppress IL-6-induced STAT3 phosphorylvation. Human MM cell lines U266 which constitutively secretes IL-6 and activate STAT3 were incubated either with different concentrations of curcumin for 1 h or with 50μM curcumin for different times. Curcumin inhibited the constitutively active STAT3 in a dose- and time-dependent manner. Curcumin at 50μM for 1 h completely inhibited STAT3 phosphorylation and prevented translocation of the STAT3 to the nucleus in U266 cells. Compared with AG490, a well-characterized Janus kinase 2 inhibitor, curcumin was a more rapid and more potent inhibitor of STAT3 phosphorylation [97,98].

Recent work from our laboratory had shown curcumin modulated the differentiation and development of Th17 cells through multiple pathways in EAE. Treatment with 200 mg/kg curcumin decreased the clinical severity of acute EAE rat and inflammatory cells infiltration in spinal cord. Curcumin inhibits differentiation and development of Th17 cells depends on down-regulating expression of IL-6, IL-21, RORγt signaling and inhibition STAT3-phosphorylation in EAE rat. *In vitro* treatment of MBP immunized lymphocytes with curcumin

resulted in a significant decrease in the neural Ag-specific lymphocytes proliferation and IL-17 production. Meantime, *in vivo* the mRNA expression of IL-17 was reduced in spinal cord in curcumin-treated rats. We discovered curcumin inhibits obviously TGF-β, IL-6, IL-21 production and activity of STAT3, and its consequent transducer-production of RORγt *in vivo* and *in vitro*, suggesting that the inhibition of TGF-β, IL-6 and IL-21, and phosphorylation of STAT3 were a mechanism of regulation of EAE by curcumin (Fig. 2) [19].

5. Curcumin effect on MS induced neurodegeneration

The pathological hallmarks of MS are demyelination and axonal damage. Demyelinated lesions can occur anywhere within the brain and spinal cord, leading to disease complexity and heterogeneity of clinical signs and symptoms [54].

Th17 cells which highly express granzyme B transmigrate across BBB-ECS induce neurons apoptosis [55]. IL-17 activates many other inflammatory mediators. NO is an important inflammatory second messenger and is involved in the killing of oligodendroglial cells, and pathological NO is generated by inducible NO synthase (iNOS) during inflammation. IL-17 triggers a dose- and time-dependent expression of iNOS and concomitant increase in NO in various cell types [99–102]. Depending on the inflammatory environment in CNS, extensive microglial, astrocyte, macrophage and DC are activated. They amplify the destructive inflammatory environment by damaging myelin further, secreting IL-17, TNF-α, NO, osteopontin, and presenting antigen to T cells [79,102–105]. These secreted inflammatory cytokines induce the macrophage to phagocytose large chunks of the myelin sheath. The concerted attack by T cells and inflammatory mediators such as cytokines, osteopontin and NO produces areas of demyelination, which impairs electrical conduction along the axon and produces the pathophysiological defect (Fig. 2) [22].

Curcumin has a lipophilic property and can pass through all cell membranes and thus exerts its intracellular effects. Through its various anti-inflammatory effects, it may have a role in the cure of MS [106]. Curcumin transmigrates cross BBB to regulate homeostatic of the CNS microenvironment by inhibiting the key proinflammatory cytokine secretion pathway. Curcumin also inhibited TNF-α and NO release in a dose-dependent manner by inhibiting differentiation and proliferation of Th17 cells and down-regulating NF-κB activation [107]. Curcumin markedly inhibited the phosphorylation of STAT1 and STAT 3 as well as JAK1 and JAK 2 in microglia activated with LPS, or IFN-γ. Treatment of microglial cells with curcumin led to an increase in phosphorylation and association with JAK1/2 of SHP-2, which inhibit the initiation of JAK-STAT inflammatory signaling in activated microglia, suggesting curcumin suppresses JAK-STAT signaling via activation of SHP-2, thus attenuating inflammatory response of brain microglial cells [108]. In addition, curcumin has anti-proliferative and anti-differentiation actions on microglia. Researchers using doses of 4, 5, 10, 15, 20 μM concentration of curcumin in C-6 rat glioma 2B-clone cells, showed that curcumin dose dependently stops proliferative and differentiation of neuroglial by differentiate into a mature cell or undergo apoptosis. It has shown to decrease the glutamine synthetase (GS) assay, a marker enzyme for astrocytes. In the same study, curcumin was shown to increase CNP (2′3′-cyclic nucleotide 3′-phosphohydrolase), a marker enzyme for oligodendrocytes. The overall effect of curcumin on neuroglial cells involves decreased astrocytes proliferation, improved myelogenesis and increased activity and differentiation of oligodendrocytes [109].

6. Concluding remarks

Based on the main findings detailed above, curcumin will lead to a promising treatment for MS. The clinically studied chemical properties of curcumin and its various effects on MS shows the possibility to do further research and develop better drugs based on curcumin for treating MS. However, several unanswered questions remain: What is the one main chemical property of curcumin that can be exploited in treating MS? What is the role of curcumin in other neurological disorders such as Parkinson's, Huntington's and other dementias? Would it be effective when used alone or with other anti-inflammatory drugs? Furthermore, large-scale human studies are required to identify the prophylactic and therapeutic effect of curcumin carefully.

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