Biomedical & Pharmacology Journal, March 2022. Vol. **15**(1), p. 137-146

The Role of the Proinflammatory and Anti-inflammatory Cytokines in Multiple Sclerosis

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https://dx.doi.org/10.13005/bpj/2349

(Received: 26 March 2021; accepted: 10 January 2022)

Multiple sclerosis (MS) is an autoimmune disease affecting 2.5 million individuals globally. MS majorly affects younger adults, especially women, than males having an incidence ratio of 3:1. MS conditions are characterized by demyelination, axonal deterioration, gliosis, heterogeneous lesions, and lymphocytes entrance infiltrates into the CNS by breaching the blood brain barrier and leading to concurrent relapse remitting episodes. Environmental Factors have an essential role in the etiopathogenesis of the disease. The leukocytes infiltrate secrete the immune mediator's cytokines responsible for the inflammation milieu in the CNS and the disease progression through immune-mediated neurodegeneration. The Cytokines are the small protein molecules secreted for facilitating communication among other cells conducting a complex multicellular behavior. This review aims to discuss the role of the proinflammatory cytokines such as GM-CSF, IL-17, Il-6, IL-1ß, IL-22, INF-? accountable for the initiating and the MS progression. Even though the objective behind these inflammatory mediators' production is to protect the CNS tissue from further impairment, on the contrary sometimes they may severely damage the neurons, myelin sheath, and the other glial cells oligodendrocytes, microglia, and astrocytes in MS due to their pleiotropic nature whereas, the anti inflammatory cytokines such as IL-4 and IL-10 may possess protective role against MS which could potentially be a novel drug target and could lead us towards a new promising treatment for MS in the future.

Keywords: Anti Inflammatory Cytokines; Cytokines; Demyelination; Leukocyte Infiltrates; Multiple Sclerosis; Proinflammatory Cytokines.

Multiple sclerosis is a neurodegenerative disease[1] with visual myelin sheath loss,[2] axonal impairment[3] through oligodendrocytic damage[3,] and Plague formation[4] due to subsequent immune attack[2] by leukocytes [1] (macrophages, T cells, B cells)[5] infiltration[1] into the CNS[2].

MS is categorized as relapsing-remitting MS (RRMS), a clinical manifestation of neurological disability and simultaneous improvement from the disease progression followed by secondary progressive (SP), which has reduced inflammatory lesions contrary to the progressive neurological deterioration and brain atrophy.[6] MS is characterized as Primary progressive MS when the exacerbation is enhanced gradually since the beginning of the disease with clinical manifestation of consistent neurological function deterioration.[7]

80% of MS patients somewhere along the line are incapacitated with spasticity related to impaired ambulation, pain, and contractures development.[8] Other physical disability observed

in MS patient are vision impairment, reduced cognitive proficiency[5], loss of muscle coordination, weakness, and fatigue, numbness, depression[2], occurs in the MS patients during the disease progression in response to the CNS affected area[4] which may either be the white matter or the grey matter.[5] MS is more predominant among the females than in the male population, with an occurrence ratio of approximately 3:1.[4]

The Cytokines are small secreted proteins that aids in communication between the cells[3] further categorized as chemokines, lymphokines, interferons (IFNs), and growth factors[9], which, when dysregulated[9], are responsible for systemic inflammation via autocrine, paracrine, or endocrine mechanisms[3], thus contributing towards the etiopathogenesis of MS[9].

The secretion of proinflammatory cytokines and chemokines[8] directs the blood brain barrier's disintegration. It is responsible for triggering the astrocytes and microglia, thus causing neuroinflammation in MS patients' CSF. Furthermore, it facilitates the production of reactive oxygen species and glutamate, thus exacerbating disease conditions.[7] The proinflammatory cytokines have a crucial role in the MS pathogenesis as it regulates lymphocyte infiltration across the blood brain barrier.[1] Cytokine mediated signaling is regulated by signal transducer and activator of transcription (STAT) family, malfunction of the STAT family may contribute towards the MS pathology.[10]

This review aims to provide an insight into proinflammatory cytokines responsible for MS exacerbation. Furthermore, the critical role of anti-inflammatory cytokines such as IL-4 and IL-10, which possess a protective role against the disease progression, has been briefly mentioned. In summary, this review will provide us with an understanding of the cytokines responsible for MS immunopathogenesis.

MS causing Proinflammatory cytokines

GM-CSF

T cells and macrophages[11] produce a 114 amino acid polypeptide[12] monomeric glycoprotein referred to as GM- CSF. The GM-CSF being heterodimeric, the GM-CSF receptor has two subunits, alpha (á) subunit, and a typical beta chain (âc) subunit.[13] The detailed expression of GM-CSF may be accessed in various immune cells, namely the monocytes, macrophages, and DCs.[11]

In a study, 7–9 weeks old female C57BL/6 mice were immunized with myelin oligodendrocyte glycoprotein (MOG) 35–55. Dimethyl Fumarate was induced twice a day via an oral route from the outset of EAE induction throughout the end of the study (Day 23 post immunization). Both Spleenocytes and CNS-infiltrating mononuclear cells were isolated.CD4+ T cells were purified by proliferation assay in 96-well plates, stimulated by anti-CD3/28 were undertaken for 48 hours. A reduced expression of Th1 and cytokine GM-CSF was observed in the PBMCs, with a decreased level of IFN-ã was noted in CD4+ T cells when DF was administrated in EAE induced mice and MS patients than in control.[13]

In another study, convincing data from 20 weeks randomized, a double-blinded clinical trial had suggested that MOR103 (humanized monoclonal antibody) had efficacy against GM-CSF. Overall, the study concluded that MOR103 in the clinical trial had a good safety profile and was well tolerated in the relapsing-remitting MS and secondary progressive participants when given intravenously.[14]

A case study conducted on a Caucasian woman aged 51 years who had earlier suffered from Melanoma (III) was administered subcutaneous Sargramostim (rhGM-CSF) injections for three consecutive years in a phase II clinical trial to treat the Melanoma. Towards the end of the trial, Melanoma had significantly declined. Later the existence of a bright area in the T2 spinal cord and a deep white matter of the brain, multiple ovoid T2-bright regions were observed in January 2006 corresponding to MS. In June 2006, the MRI indicated several new lesions with16 white blood cells/mm3 in the spinal fluid. Thus, RRMS was confirmed through laboratory examination. A retrospective study of the MRI was observed before and during rhGM-CSF administration. The case study revealed that the two silent non-enhancing ovoid T2-bright areas were demyelinated when witnessed in August 2001 occurred the same till August 2004; therefore, no significant changes took place in the brain MRI scans. The study concluded that discontinued rhGM-CSF probably promoted an inflammatory response due to which activation

of quiescent demyelination occurred, causing the disease progression. In this study, the findings indicated a preference towards multiple blood tests obtained from the outpatient and proposed that GM-CSF increased the WBC beyond 10,000 and eosinophil count preceding 10%, signifying the active role of GM-CSF in the demyelination process of MS.[15]

Interferon- 6 (IL-6) is a 25-kDa secreting glycopeptide composed of 184 amino acids. A proinflammatory IL-6 cytokine facilitates a range of proteins liable for the inflammatory cascade. Following IL-6 dysregulation, raised IL-6 levels have been associated with causing multiple infections, cancer, or autoimmunity diseases such as Multiple sclerosis. Furthermore, stimulation through Toll-like receptors, IL-1, TNF-á contributes to increased IL-6 production.

IL-6 implies that to target IL-6 for medicinal gain, there are three approaches. First and foremost, utilizing the classic transmembrane IL-6 receptor (mIL-6R), forming soluble IL-6R via trans-signaling (sIL-6R) and finally, the Trans presentation, other words, signal-transducing subunit molecule gp130. It is worth noting that IL-6 comprises four helices, an IL-6R binding site, and two binding sites in gp130. The ubiquitous expression of gp130 is held responsible for the pleiotropic nature of the IL-6.[16]

Furthermore, increased IL-6 cytokine may also be secreted by the B cells, contributing to MS exacerbation.[17]

Sixty-seven subjects previously diagnosed with MS, priorly treated with glatiramer acetate and interferon-beta for a minimum of 6 months, were selected for a pilot study. The interventional group received 400mg of Epigallocatechin (EGCG) and 30ml of extra virgin coconut oil twice a day.

The study concluded an improvement in the MS conditions and lowered anti-inflammatory cytokine IL-6 subsequently, after the intake of 60 ml of extra virgin coconut oil when taken together with 800 mg EGCG capsules over four months. Furthermore, it was found that there was a significant improvement in both the anxiety state and BMI due to coconut oil and EPCG capsules' antioxidant property and the Mediterranean diet.[18]

Tnf á

Tumour necrosis factor-alpha is a pleiotropic cytokine that regulates the inflammatory response causing demyelination in MS.[19]

An *in vitro* study outcome revealed the possibility of TNFR2 activation eliciting the oxidative stress reaction in MS. The study further revealed that the oligodendrocyte's progenitor cells (OPCs) protected the axons from oxidative stress and accomplished the remyelination process.[19]

In a transcriptomic study, the effect of cytokines interleukin-1â (IL-1â), TNF-á, and IL-6 was observed. It was revealed that TNF-alpha overexpressed 5,001 genes whereas lowered expression of about 5,488 genes, thus having a significant role in astrocytes neuroinflammation, which may contribute to MS etiopathogenesis[20]

Meisam Sanoobar et al., in a randomized clinical trial, reported that coenzyme 10 supplementation, when administered in a capsule form to 24 patients for 12 weeks, significantly lowered TNF-á and IL-6 MS patients. However, no profound alteration was found in IL-4 and TGF-â cytokine levels after 12 weeks of the study.[21]

Heba R. Ghaiad and her colleagues revealed that when resveratrol administered orally, the male C57Bl/6 mice showed a significant reduction in brain inflammatory biomarkers such as Rel-A expression, pIêB-á level, and TNF-á gene expression; furthermore, inducing remyelination in the cuprizone induced multiple sclerosis model.[22]

A randomized pilot study revealed a lower significant change in the pro-inflammatory and antiinflammatory, TNF-á, and IL-10 levels in peripheral blood mononuclear cells (PBMC) and CD8+ T cells after being administered high doses of vitamin D supplementation in MS individuals than in the placebo group, respectively.[23]

IL-17

IL-17 is a proinflammatory mediator produced by Th 17 cells, which is overregulated in Multiple sclerosis.[24]

A significant relation was observed between proinflammatory CD4 T-cells and MS patients. Th1 CD4 T cells secreted IFN-ã and tumor necrosis factor á (TNFá) Th17 CD4 T cells produce interleukin (IL)-17, IL-21, IL-22 where IL-17 majorly maintains the Th17 integrity.

Also, the IL-17 RORC2 transcription factor's expression may be related to an amplified risk of plaques present in the brain tissue of MS patients.[24]

The IL-17 promotes the pathological

Table 1. Proinflammatory Cytokines responsible for MS exacerbation

Cytokines involved in MS pathology	Primarily Cytokines producers	Levels of the cytokines in MS	The activity of the cytokines in the EAE model	Clinical studies in MS patients
GM-CSF [37]	Astrocytes, T cells(Th1 and Th17 cells) [37]	Raised[37]	In the bone marrow, chimera inadequately expressed GM-CSF resulted in counteracting EAE. [37]	In CSF of RRMS patients, IL17A and GM-CSF levels were enhanced when these cytokines produced were expressed synergistically. [7]
IL-6 [16]	Monocytes and macrophages [16]	Raised [16]	IL-6 exacerbation encourages lymphoid organs to produce Th17 cells initializing neuroinflammation and demyelination in the EAE model. [39]	IL-6 attributes to the MS pathology by aiding T effector cells and opposing the regulatory T cells in RRMS individuals. [39]
IL-22 [40]	Th17 and Th22 lymphocytes [40]	Raised [40]	Kreymborg et al., in their study, found that for EAE development, cytokine IL-22 is unessential. IL-22 knockout mice eventually progress into the MS, the same as the wild-type mice. [40]	In MS, the new lesions produced in the CNS had raised levels of IL-22 and IL-17 cytokines. A study determined that the presence of IL-22 stimulated the oligodendrocytes, causing enhanced Fas expression, thereby elevating the chances of apoptotic cell death in MS patients. [40] Overexpression of the cytokine IL-22 was observed in the serum of RRMS patients. [1]
TNF-alpha [41]	Th1 lymphocytes and macrophages [41]	Raised [4]	-	Raised TNF-alpha was identified in the serum and CSF of MS individuals. [41]
Interleukin-1β [42]	monocytes and macrophages [42]	Enhanced		In MS patients, considerable levels of cytokine production, explicitly IL-1â, IL-6, and

				TNFá were produced by the monocytes (MO). [42]In MS patients, upregulated IL-1â was observed in the CSF and sera. Also, increased IL-1â levels were notable in the brain lesions. [42]
INF-γ [6]	Th1 cells [6]	Raised [6]	In a study, it was observed that IFNã administration enhanced MS disease progression. [6]	Notably, IFNã enhanced MS exacerbation through Treg cells. Furthermore, MS patients had improved levels of IFNã-secreting Foxp3+ T reg cells when compared with HCs. Also, it was found that Treg cells associated with IFNã showed ablated immune suppression than in Treg cells not related to IFNã. [6]Upregulated IFN-ã, when combined with CXCR3 downregulated IL-10, was observed in the Th17 cells of clinically active MS individuals. [7]
IL-17 [41]	Th17 cells [41]	Upregulated [7]	IL-17 overexpression by astrocytes enhances EAE. [7]	IL-17 suppresses the development and survivability of oligodendrocytes (OLs). Microglial activation, resulting from T cells and their consistently released proinflammatory cytokines, elicits demyelination and neurodegeneration due to impaired and apoptotic OLs in MS. In RRMS patients, when IL-17A acts synergistically with IL-6 facilitating BBB malfunction. [7]
Il-23 [34]	Activated microglia and infiltrating APCs [31]	Upregulated [31]	Enhanced IL-23 and IL-23R are responsible for inducing EAE in the mouse model. [31]	MS patient's peripheral blood showed elevated levels of cytokine IL-23. [31]T cells and dendritic cells are responsible for elevated levels of IL-12 and IL-23 in the MS lesions. [43]

immune response by overexpression of cytokines such as IL6, GM-CSF, TNF, and chemokines such as CXCL8, CXCL2 CCL20). CD161 (a large subset of CD8 cells produced by CD8 T cells, associated with the active lesions in the perivascular spaces in MS.[25]

A study indicated that cytokines IL-17A and IL-22 in T cells when stimulated, along with IL-23, were considered to exacerbate the diseased condition in EAE. However, despite the lack of genes for IL-17A in mice, they were still vulnerable to EAE. Another study revealed that the Astrocytes also facilitate IL-17 inside the brain, which liberates neutrophil-attracting chemokines, and neutrophils, responsible for brain inflammation in the EAE model.[26]

A strong relation between Mucosal-Associated Invariant T (MAIT) Cells and demyelination was mentioned in a recently published review. The secretion of both proinflammatory Th1 cytokines (IFN-gamma and TNF-alpha) and Th17 cells (IL-17 and IL-22 cytokines) were activated by the MAIT cells. The vital role of Th17 cells is initiating an inflammatory cascade response, causing autoimmune diseases such as MS. Furthermore, heightened levels of CCR6 have been related to the ligand CCL20 present in the vascular endothelial cells permitting their entry via the BBB and secreting proinflammatory cytokines such as IL-17A, which may hamper the remyelination process in MS.[27]

The proinflammatory cytokine IL-17 is also produced by the mucosal-associated invariant T (MAIT) cells apart from CD4+ T cells, particularly Th17 cells, thus directing towards MS etiopathogenesis.[5]

Increased IL-17 and IL-22 levels, responsible for secreting CD4+ T cells, are associated with active brain lesions in MS patients.[28] Thirty-five young adult MS patients in the remission phase were selected, out of which 21 patients (60%) had active brain lesions during the conduction of the study. It was concluded that MS patients had significantly raised IL-22, IL-6, and IL-17, which was lowered by serotonin administration as it enhanced IL-10 by activating CD4+ T cells in the MS patient[29]

A study revealed that during the initial EAE progressive stage, CD4 T cells (originated from Th17 cells) secreted a wide array of pro inflammatory cytokines IL17A, IL-17F, IFN-g, GM-CSF, IL-2, and IL-22. However, on the contrary, Lovett-Racke, in his study, mentioned that enhanced EAE induction was observed when Th17 differentiates with IL-6. While lack of EAE induction was noted in the naïve cells, the T cells differentiate with TGF-b1 and IL-6 or TGF-b3. Furthermore, blocking GM-CSF secretion followed by lowered IL-23R expression occurred on the Th17 cells surface when TGF-â and IL-6 enabled the T cell activation.[30]

Various endothelial and epithelial cells express elevated protein levels such as P-selectin, E-selectin, and raised chemokine levels, particularly CXCL1, CXCL2, CXCL5, GMCSF, and G-CSF, when IL-17 was collaborated with TNF-a causing oxidative stress-mediated oligodendrocytes apoptotic cell death.[31]

Interleukin 22 is a member of the interleukin 10. Studies have shown that Th17 and Th22 are the primary sources of IL-22 production, which exhibit both pro-and anti-inflammatory functions. The heterodimeric structure is present is IL-22. Binding of IL-22 with receptor co stimulated by IL-1â and IL-23 activates STAT3 further, causing the IL-22 accumulation. Transcription factors c-Maf and AHR (aryl hydrocarbon receptor (AhR)) regulate the IL-22. The former inhibits the IL-22 expression in Th17 cells, whereas AHR and RORãT have an agonistic action by promoting IL-22. Furthermore, it was observed that when C-Maf, combined with Sox5, enhanced the RORãT in Th17 cells, thus obliquely increasing the IL-22 production.[32]

A previous study revealed two key findings: (i) increased the level of serum IL-22 and (ii) activation of TH22 cells during relapse in MS patients. [33]

Evidence from a study suggested that the single nucleotide polymorphism IL22R A2 gene is connected with MS. Further, an increased prevalence of subunit IL-22 receptor in astrocytes was confirmed by an immunohistochemistry study.[34]

ATX-MS-1467 is a combination of four synthetic peptides when administered subcutaneously inhibited EAE in a humanized mouse model. Furthermore, the study indicated the enhanced level of IL-10, when administered

ATX-MS-1467, preventing the disease progression of SPMS patients. [35]

A cohort study conducted by Guillaume Perriard et al. among 141 MS and health controls concluded that serum had elevated IL-22 levels in the MS individuals. Furthermore, the study revealed upregulation of the cytokine IL-22 around the blood vessels and heterogeneous lesions in the astrocytes.[36]

Role of Antiinflammatory Cytokines in MS

IL-10 and IL-4

Antiinflammatory cytokine IL-10 and IL-4 have an essential role in improving the immune response of humans.

Activation of the Toll-like receptors such as LPS and bacterial lipoproteins is the underlying mechanism that IL-10 uses to inhibit the cytokines and chemokines production released by both the macrophages and dendritic cells. IL-10, IL-19, IL-20, IL-22, IL-24, etc., are associated primarily with the IL-10 family. A profound achievement was observed in an experiment against TNF-induced relapse in Lewis rats after IL-10 was administrated via nasal route.[34] IL- 10/TGF-â production from Tregs might curb the immune and the inflammatory factors, where TGF-â due to lack of significant immune and the inflammatory factors stimulate Treg cells. Contrastingly, MS lacks self-tolerance, leading to a progressive auto reaction between the lymphocytes, which might be related to the naïve CD4+cells stimulation caused by the TGF-â induced FoxP3 expression in the T cell receptor (TCR).[44]

In a study, MS individuals showed that the B-cells stimulated excessive proinflammatory response, which might help abnormal T-cell activation and autoimmunity through "bystander activation." It was also found that these patients lack interleukin 10 produced by regulatory B-cells (Bregs) responsible for maintaining homeostasis and defending against autoimmune diseases. Thus, the cytokines and chemokines generated in the brain due to lymphomagenesis favoured by the B-cell facilitate the progressive local immune damage.[45]

Inflammatory factors are regulated by the cytokines (proteins) against antigens that enter the body. Amplified cytokines (protein) IFN-ã may cause autoimmune diseases such as MS, whereas proinflammatory cytokines such as IL-4 opposes inflammation.[46]

A case-control study consisting of MS and Neuromyelitis Optica (NMO) individuals results revealed a considerable increase in the serum level of IL-4 the contrary to the placebo group.[47] In 28 days, randomized, double-blinded study, amplified levels of IL-4 and IL-10 cytokines were observed after administrating, Lipia citriadora extract (dietary supplement) to the interventional group consisting of MS individuals.[48]

CONCLUSION

Multiple sclerosis is an autoimmune disease that, to date, does not have entirely understood disease pathology. In MS, loss of myelin sheath (demyelination) may be caused due to immunological response gone wrong by the inflammatory mediators such as anti-inflammatory cytokines. This review describes cytokines' role: the protein molecules responsible for intercellular signaling dysregulated by pro-inflammatory cytokines such as GM-CSF, IL-17, IL-6, and IL-â, which triggers the inflammatory cascade in the CNS incapacitating the disease. Furthermore, the role of the anti-inflammatory cytokines IL-10 and IL-4 were discussed briefly, which, when increased, can lower the neuronal impairment associated with the disease progression. Even though the complete information regarding the mentioned cytokines was beyond the scope of our paper, we have been summarized a few *in vitro* studies and clinical trials associated with the cytokines as mentioned earlier in the hope that this review might scientifically interest readers and researchers towards these inflammatory mediators, which are responsible to either exacerbate or prevent the MS disease condition.

ACKNOWLEDGMENT

None.

Conflict of Interest

All authors have no conflict to report.

Funding Source

No funding to declare.

REFERENCES

1. Khaibullin T, Ivanova V, Martynova E, Cherepnev G, Khabirov F, Granatov E, et al.

Elevated proinflammatory levels cytokines in cerebrospinal fluid of multiple sclerosis patients. *Front Immunol.*; **8**(MAY):1–10 (2017).

2. Sacramento PM, Monteiro C, Dias ASO, Kasahara TM, Ferreira TB, Hygino J, et al. Serotonin decreases the production of Th1/ Th17 cytokines and elevates the frequency of regulatory CD4 + T-cell subsets in multiple sclerosis patients. *Eur J Immunol*.; **48**(8):1376–88 (2018).
3. Wang K, Song F, Fernandez-Escobar A, Luo G, Wang JH, Sun Y. The Properties of Cytokines in Multiple Sclerosis: Pros and Cons. *Am J Med Sci* [Internet].; **356**(6):552–60 (2018). Available from: sciencedirect.com/science/article/abs/pii/S000296291830346X
4. Palle P, Monaghan KL, Milne SM, Wan ECK. Cytokine Signaling in Multiple Sclerosis and Its Therapeutic Applications. *Med Sci.*; **5**(4):23 (2017).
5. Dargahi N, Katsara M, Tselios T, Androutsou ME, De Courten M, Matsoukas J, et al. Multiple sclerosis: Immunopathology and treatment update. *Brain Sci.*; **7**(7):1–27 (2017).
6. Wagner CA, Roqué PJ, Goverman JM. Pathogenic T cell cytokines in multiple sclerosis. *J Exp Med.;* **217**(1) (2020).
7. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L. T Helper Cells: The Modulators of Inflammation in Multiple Sclerosis. *Cells.*; **9**(2):482 (2020).
8. Patejdl R, Zettl UK. Spasticity in multiple sclerosis: Contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. *Autoimmun Rev*.; **16**(9):925–36 (2017). Available from: http://dx.doi.org/10.1016/j.autrev.2017.07.004
9. Becher B, Spath S, Goverman J. Cytokine networks in neuroinflammation. *Nat Rev Immunol.*; **17**(1):49–59 (2017). Available from: http://dx.doi.org/10.1038/nri.2016.123
10. Manoochehrabadi S, Arsang-Jang S, Mazdeh M, Inoko H, Sayad A, Taheri M. Analysis of STAT1, STAT2 and STAT3 mRNA expression levels in the blood of patients with multiple sclerosis. *Hum Antibodies.;* **27**(2):91–8 (2019).
11. Göbel K, Ruck T, Meuth SG. Cytokine signalling in multiple sclerosis: Lost in translation. *Mult Scler J*.; **24**(4):432–9 (2018).
12. Kostic M, Zivkovic N, Cvetanovic A, Stojanovic I. Granulocyte-macrophage colony-stimulating factor as a mediator of autoimmunity in multiple sclerosis. *J Neuroimmunol.;* **323**(March):1–9 (2018). Available from: https://doi.org/10.1016/j.jneuroim.2018.07.002
13. Safavi F, Thome R, Li Z, Zhang GX, Rostami A. Dimethyl fumarate suppresses granulocyte macrophage colony-stimulating factor-producing Th1 cells in CNS neuroinflammation. *Neurol Neuroimmunol neuroinflammation.*; **7**(4):1–10 (2020).
14. Monaghan KL, Wan ECK. The Role of Granulocyte-Macrophage Colony-Stimulating Factor in Murine Models of Multiple Sclerosis. *Cells.*; **9**(3): 611 (2020).
15. Chong J, Cohen M, Waubant E. Multiple sclerosis onset after granulocyte macrophage colony-stimulating factor withdrawal. *Mult Scler Relat Disord.;* **20**(August 2001):178–80 (2018). Available from: https://doi.org/10.1016/j.msard.2018.01.025
16. Uciechowski P, Dempke WCM. Interleukin-6: A Masterplayer in the Cytokine Network. *Oncol.*; **98**(3):131–7 (2020).
17. Waisman A, Ebering A. Unraveling the T–B tangle in anti-CD20 multiple sclerosis therapy. *Proc Natl Acad Sci U S A.*; **116**(51):25376–7 (2019).
18. Platero JL, Cuerda-Ballester M, Ibáñez V, Sancho D, Lopez-Rodríguez MM, Drehmer E, et al. The impact of coconut oil and epigallocatechin gallate on the levels of il-6, anxiety and disability in multiple sclerosis patients. *Nutrients.* **12**(2):1–10 (2020).
19. Pegoretti V, Baron W, Laman JD, Eisel ULM. Selective modulation of TNF-TNFRs signaling: Insights for multiple sclerosis treatment. *Front Immunol.*; **9**(APR):1–8 (2018).
20. Perriot S, Mathias A, Perriard G, Canales M, Jonkmans N, Kassar L El, et al. Human Induced Pluripotent Stem Cell-Derived Astrocytes Are Differentially Activated by Multiple Sclerosis-Associated Cytokines. *Stem Cell Reports.*; **11**:1199–210 (2018).
21. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: A double blind, placebo, controlled randomized clinical trial. *Nutr Neurosci.*; **18**(4):169–76 (2015).
22. Ghaiad HR, Nooh MM, El-Sawalhi MM, Shaheen AA. Resveratrol Promotes Remyelination in Cuprizone Model of Multiple Sclerosis: Biochemical and Histological Study. *Mol Neurobiol* [Internet].; **54**(5):3219–29 (2017). Available from: http://dx.doi.org/10.1007/s12035-016-9891-5
23. Rolf L, Muris AH, Bol Y, Damoiseaux J, Smolders J, Hupperts R. Vitamin D3 supplementation in multiple sclerosis: Symptoms and biomarkers of depression. *J Neurol Sci;* **378**:30–5 (2017).

Available from: http://dx.doi.org/10.1016/j.jns.2017.04.017

24. Zepp J, Wu L, Li X. IL-17 receptor signaling and T helper 17-mediated autoimmune demyelinating disease. *Trends Immunol*.; **32**(5):232–9 (2011). Available from: http://dx.doi.org/10.1016/j.it.2011.02.007
25. Kaskow BJ, Baecher-Allan C. Effector t cells in multiple sclerosis. *Cold Spring Harb Perspect Med.*; **8**(4): (2018).
26. Becher B, Spath S, Goverman J. Cytokine networks in neuroinflammation. *Nat Rev Immunol.;* **17**(1):49–59 (2017). Available from: http://dx.doi.org/10.1038/nri.2016.123
27. Dargahi N, Katsara M, Tselios T, Androutsou ME, De Courten M, Matsoukas J, et al. Multiple sclerosis: Immunopathology and treatment update. *Brain Sci.*; **7**(7):1–27 (2017).
28. Göbel K, Ruck T, Meuth SG. Cytokine signaling in multiple sclerosis: Lost in translation. *Mult Scler J.;* **24**(4):432–9 (2018).
29. Sacramento PM, Monteiro C, Dias ASO, Kasahara TM, Ferreira TB, Hygino J, et al. Serotonin decreases the production of Th1/Th17 cytokines and elevates the frequency of regulatory CD4 + T-cell subsets in multiple sclerosis patients. *Eur J Immunol.;* **48**(8):1376–88 (2018).
30. McGinley AM, Edwards SC, Raverdeau M, Mills KHG. Th17/ cells, ãä T cells and their interplay in EAE and multiple sclerosis. *J Autoimmun*.; **87**: 97–108 (2018).
31. Luchtman DW, Ellwardt E, Larochelle C, Zipp F. Cytokine & Growth Factor Reviews IL-17 and related cytokines involved in the pathology and immunotherapy of multiple sclerosis/ : Current and future developments. *Cytokine Growth Factor Rev* [Internet].; **25**(4):403–13 (2014). Available from: http://dx.doi.org/10.1016/j.cytogfr.2014.07.013
32. Göbel K, Ruck T, Meuth SG. Cytokine signaling in multiple sclerosis: Lost in translation. *Mult Scler J.;* **24**(4):432–9 (2018).
33. Zarobkiewicz MK, Kowalska W, Slawinski M, Rolinski J, Bojarska-Junak A. The role of interleukin 22 in multiple sclerosis and its association with c-Maf and AHR. *Biomed Pap.;* **163**(3):200–6 (2019). Available from: https://doi.org/10.5507/bp.2019.024
34. Wang K, Song F, Fernandez-Escobar A, Luo G, Wang JH, Sun Y. The Properties of Cytokines in Multiple Sclerosis: Pros and Cons. Vol. 356, American Journal of the Medical Sciences. Elsevier BV; p. 552–60 (2018).
35. Streeter HB, Rigden R, Martin KF, Scolding NJ. Preclinical development and first-in-human study of ATX-MS-1467 for immunotherapy of MS. 2015;1–9.
36. Perriard G, Mathias A, Enz L, Canales M, Schluep M, Gentner M, et al. Interleukin-22 is increased in multiple sclerosis patients and targets astrocytes. *J Neuroinflammation*.; **12**(1):1–18 (2015). Available from: http://dx.doi.org/10.1186/s12974-015-0335-3
37. Aram J, Francis A, Tanasescu R, Constantinescu CS. Granulocyte-Macrophage Colony-Stimulating Factor as a Therapeutic Target in Multiple Sclerosis. *Neurol Ther*.; **8**(1):45–57 (2019). Available from: https://doi.org/10.1007/s40120-018-0120-1
38. Imitola J, Rasouli J, Watanabe F, Mahajan K, Sharan AD, Ciric B, et al. Elevated expression of granulocyte-macrophage colony-stimulating factor receptor in multiple sclerosis lesions. *J Neuroimmunol.*; **317**(July):45–54 (2018).
39. Petkoviæ F, Castellano B. The role of interleukin-6 in central nervous system demyelination. *Neural Regen Res*.; **11**(12):1922–3 (2016).
40. Zarobkiewicz MK, Kowalska W, Slawinski M, Rolinski J, Bojarska-Junak A. The role of interleukin 22 in multiple sclerosis and its association with c-Maf and AHR. *Biomed Pap;* **163**(3):200–6 (2019). Available from: https://doi.org/10.5507/bp.2019.024
41. Trenova AG, Slavov GS, Georgieva M, Draganaova-filipova MN, Mateva NG. Alterations in serum levels of IL-17 in contrast to TNF-alpha correspond to disease-modifying treatment in relapsing-remitting multiple sclerosis. *Scand J Clin Lab Invest* [Internet]. (2017). Available from: http://dx.doi.org/10.1080/00365513.2017.1303843
42. Zhao R, Zhou H, Su SB. International Immunopharmacology A critical role for interleukin-1 â in the progression of autoimmune diseases. *Int Immunopharmacol.*; **17**(3):658–69 (2013). Available from: http://dx.doi.org/10.1016/j.intimp.2013.08.012
43. Ryan C, Thrash B, Warren RB, Menter A. The use of ustekinumab in autoimmune disease. 2010;587–604.
44. Dolati S, Babaloo Z, Ayromlou H, Ahmadi M, Rikhtegar R, Rostamzadeh D, et al. Nanocurcumin improves regulatory T-cell frequency and function in patients with multiple sclerosis. *J Neuroimmunol.*; **327**(December 2018):15–21 (2019).
45. Milo R. Therapeutic strategies targeting B-cells in multiple sclerosis. *Autoimmun Rev.*; (2016) Available from: http://dx.doi.org/10.1016/j.autrev.2016.03.006
46. Farhadi N, Oryan S, Nabiuni M. Serum Levels of

Melatonin and Cytokines in Multiple Sclerosis. 2014;2013–5.

47. Tahani S, Dehghani L, Jahanbani-Ardakani H, Shaygannejad V, Fazli A, Hamidavi A, et al. Elevated serum level of IL-4 in neuromyelitis optica and multiple sclerosis patients. *J Immunoass Immunochem* [Internet].; **40**(5):555–63 (2019). Available from: https://doi.org/10.1080/15321819.2019.1655649

48. Mauriz E, Vallejo D, Tuñón MJ, Rodriguez-López JM, Rodríguez-Pérez R, Sanz-Gómez J, et al. Effects of dietary supplementation with lemon verbena extracts on serum inflammatory markers of multiple sclerosis patients. *Nutr Hosp*.; **31**(2):764–71 (2015).