Multiple Sclerosis and the Relationship between Inflammation and Oxidative damage

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Abstract

Introduction

Inflammation and oxidative stress are discussed in relation to Multiple Sclerosis (MS), which is seen as an inflammatory and autoimmune illness, as damaging mechanisms.

Development

An imbalance between oxidants and antioxidants in favour of the oxidants has been used to describe the idea of oxidative stress. Although physiological processes like respiration are vital, in some circumstances the creation of reactive species overcomes the antioxidant mechanisms, which could lead to tissue damage. On the other hand, it is well known that inflammation is a complex response to various stimuli in the vascularized connective tissue. However, an uncontrolled, protracted inflammatory response can potentially result in tissue damage.

Conclusion

Since one may encourage the other, creating a harmful feedback system that leads to the inflammatory and demyelination processes in MS, inflammation and oxidative stress are related to one another.

Keywords: Oxidative stress • Inflammation • Multiple sclerosis

Introduction

A chronic inflammatory demyelinating disease of the CNS known as Multiple Sclerosis (MS) causes diffuse neurodegeneration throughout the whole brain in addition to isolated lesions in the grey and white matter [1]. Demyelination and varying degrees of axonal loss are hallmarks of MS, which has an unclear origin. Infiltrates of inflammatory lymphocytes, macrophages, and activated microglia in the early stages of the illness, followed by an overproduction of inflammatory mediators, cause demyelination and axonal conduction obstruction, which result in neurological impairment. MS shows up as CNS plaques and spots of localised demyelination in the brain, spinal cord, and optic nerve's white matter. The periventricular regions of MS plaques have an inflammatory infiltration that includes activated macrophages, microglia, T cells, B cells, and plasmatic cells [2].

The disease's characteristic progressive disability is caused by a variety of mechanisms, including (a) B-cell dysregulation; (b) CD8+ T cells that damage mitochondria and cause oxidative stress; (c) microglial cell activation linked to neuritic transection found in cortical demyelinating lesions; and (d) demyelination or axonal/neuronal damage. These several mechanisms can work together and are not mutually exclusive. In this review, we concentrate on the mechanisms underlying the pathophysiology of MS's stress, oxidative, and inflammatory processes.

Oxidative stress in MS

When oxidants and antioxidants are in an unbalanced ratio in favour of oxidants, redox signalling is disrupted, which can result in controllable molecular damage. This notion of oxidative stress was developed for research in redox biology and medicine in 1985. Increased oxidative stress is one of the most prevalent indicators of toxicity since it can cause harm to cellular structure and can lead to tissue destruction. Oxidative stress can be caused by any chemical, physical, or microbiological factor in tissues and cells [3]. But many essential aspects of life, including cell respiration, lipid synthesis, metal metabolism, lysosomes, phagocytosis, and the biotransformation of organic compounds by xenobiotics, entail oxidative reactions.

Any chemical entity that has one or more unpaired electrons in its outer orbit is said to be a free radical. Free radicals have many unpaired electrons, which makes them very reactive. With lipids, proteins, complex carbohydrates, and nucleic acids, they easily take part in chemical reactions. There are three classes of reactive species that are relevant to biology: The most important class of radical species produced in living systems are (1) Reactive Oxygen Species (ROS), which are derived from oxygen; they include superoxide, oxygen anion, hydroxyl radicals, and peroxyl radicals; (2) Reactive Nitrogen Species (RNS), which primarily include peroxynitrite anion and nitric oxide; and (3) Reactive Chlorine Species (RCS) [4]. The biological organelles mitochondria, xanthine oxidase, peroxisomes, and phagosomes are the internal sources of free radicals; smoking, environmental toxins, and various radiation types are some of the exterior sources. Significantly, in response to a stimulus such as a cytokine, growth factor, or hormone, the intracellular concentration of ROS is briefly raised. When conditions are physiological, the antioxidant regulatory mechanisms quickly control the release of ROS. However, when conditions are disease-or infection-related, the increased oxidative stress is sustained or not countered, overwhelming the antioxidant's protective abilities and causing ROS-induced tissue damage. Strong enzymatic and non-enzymatic antioxidant systems are present in biological systems to protect the integrity of cells and tissues and to fend off potential damage. These systems include reduced thiols, vitamins C and E, catecholamines, peroxidases, catalases, glutathione reductases, glutathione peroxidases, and thioredoxin reductases. For instance, it has been shown that a drop in glutathione peroxidase levels results in lasting harm in Experimental Autoimmune Encephalitis (EAE).

A shift in the prooxidant/antioxidant balance in favour of the first one is referred to as oxidative stress. The delicate balance between antioxidants and the generation of ROS may be harmed by being exposed to hazardous chemicals. For instance, during the phagocytosis of foreign particles or bacteria, the release of inflammatory precursors such as hydroxyl anion and superoxide anion may surpass the capacity of the body's antioxidant systems, causing oxidative and inflammatory damage to DNA, proteins, or lipids. Oxidative stress may have an impact on MS development because it's a crucial component linked to demyelination. Furthermore, because of its high oxygen requirement and restricted access to antioxidants, brain tissue is vulnerable to the effects of free radicals. Additionally, MS patients' Cerebrospinal Fluid (CSF) revealed higher advanced product oxidation. The specialised population of myeloid cells in the brain and spinal cord is known as microglia. It is regarded as a sentinel cell in the Central Nervous System (CNS), constantly monitoring its surroundings and extending and retracting its projections to react swiftly to symptoms of pathogen invasion or tissue damage. Oxidative processes are influenced by mitochondrial failure and activated microglia. Microglia normally monitor the brain environment, such as brain damage or immunological stimuli, in the mature brain and exist in a resting state with a ramified shape. However, microglia are easily triggered. Proteolytic enzymes, cytokines, oxidative by-products, and free radicals are released by microglia when T cells activate them. The primary method by which microglia generate neurotoxicity is through Pattern-Recognition Receptors (PRR), which the activated microglia employ to recognise neurotoxic inputs and drive NADPH oxidase activity.

Depending on the type and severity of the disease, MS microglia can develop a variety of phenotypes. Under demyelination and re-myelination circumstances, microglia display various morphologies. The differences in how lesions proceed over time, the possibility of re-myelination or neurodegeneration, and interactions with other cell types are all factors that contribute to the phenotypic heterogeneity of the microglia in MS.

Due to interactions between the Toll-like Receptor (TLR) receptor and ligands like INF-or by stimulation of the same microglia with immunoglobulins or serum complement proteins, macrophages and microglia in the M1 phenotype are pro-inflammatory, activated, and proliferating. Microglia can transition from an M1 phenotype to an M2 phenotype (anti-inflammatory) or they can enter a mixed transitional state known as M-Tran when they co-express M1 and M2 markers [5].

Along with producing external ROS, NADPH oxidase also produces superoxide and intracellular ROS, which are both frequently used by phagocytes as signalling molecules and control the development of a number of pro-inflammatory functions in microglia. In general, the inflammatory response is exacerbated as intracellular ROS levels rise until either apoptosis or necrosis takes place.

Inflammation in MS

Inflammation is frequently thought of as a complicated response to both foreign and endogenous stimuli in the vascularized connective tissue. The main objectives of this defensive response are to eliminate pathogens, the original source of cell injury, and the damage brought on by the production of inflammatory mediators [6]. There is plenty of evidence, meanwhile, to suggest that an excessive or uncontrolled extended inflammatory process can cause tissue damage and contribute to a number of chronic illnesses, including neurodegenerative diseases. Immune cells release ROS during an inflammatory situation, which causes oxidative stress. Through early nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B) activation, the ROS release can start an intracellular signalling cascade that increases the production of pro-inflammatory genes. As a result, oxidative stress and inflammation are two closely associated pathophysiological processes. TLRs and the inflammasome are the two main mechanisms by which the oxidative damage caused by free radicals drives inflammatory responses.

TLRs are a family of type I transmembrane receptors that make up PRR. They have an extracellular leucine-rich repeat domain that allows them to recognise different pathogen-associated molecular patterns, as well as an intracellular Toll/IL-1 receptor domain that is involved in the signalling process of TLRs. The ten members of the TLR family, TLR1–TLR10, are primarily divided into the intracellular and cell surface subfamilies based on where they are found. In contrast to intracellular TLRs, which are found in the endosome and comprise TLR3, TLR7, TLR8, and TLR9, cell surface TLRs include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10. TLRs are also capable of identifying chemical patterns linked to damage (DAMPs). They are brought on by a variety of sterile stimuli, such as pathogen-free inflammation produced by mechanical trauma, ischemia, poisons, minerals, crystals, chemicals, antigens, stress, and environmental pollution [7]. Myeloid differentiation primary response 88 (MyD88) and toll/IL-1 receptor (TIR)-domain-containing adapter-inducing interferon (TRIF)-dependent pathways make up the two main TLR signalling pathways. When a TLR is activated by its ligands, a group of Toll/IL-1 receptor domain-containing adaptors, including MyD88, TRIF, Toll-Interleukin 1 Receptor (TIR) domain containing adaptor protein (TIRAP), Trif-Related Adaptor Molecule (TRAM), Sterile-Alpha and Armadillo Motif-containing protein (SARM), and B-cell adapter for PI3K, are recruited (BCAP). All TLRs use MyD88 to activate NF-kB and Mitogen-Activated Protein Kinase (MAPK) signalling, which in turn causes the induction of inflammatory cytokine genes. MyD88 is attracted to the cell surface by TIRAP, a sorting adaptor, and TLR2, TLR4, and TLR9. A different route that enhances the activation of interferon regulatory factor 3 (IRF3), NF-kB, and MAPKs to trigger type I IFN and inflammatory cytokine genes is promoted by TRIF when it is bound to TLR3 and TLR4. To link TRIF and TLR4, TRAM is selectively recruited to TLR4 but not TLR3. SARM has the ability to specifically block TRIF-mediated TLR3 and TLR4 signalling. TLR signalling is regulated by BCAP [8]. In research using animals as a model for the investigation of MS, EAE has indicated potential involvement of these receptors in the physiopathology.

Additionally, MS patients have shown aberrant values for TLR2 and TLR4, particularly in B cells and sera. TLR2 may promote Th1/Th17 cell-related responses, downregulate regulatory T cells, prevent oligodendrocyte maturation, induce the poly ADP-ribose polymerase 1 pathway in microglia, macrophages, and astrocytes, and inhibit the expression of type I interferons. In addition, TLR2 may induce IL-17+ T cells, which are activated T cells that resemble IL-17+ T cells produced by the addition of IL-1 and IL-23. Direct cell-to-cell contact between neurons and T cells is necessary for the harmful effects of IL-17+ T cells on neurons to take place. Additionally, TLR2 and TLR3 activated the microglia, promoting oxidative stress and the inflammatory process. TLR-MyD88 signalling has also been linked to inflammation in MS, where it may play a role in the aetiology of the disease and EAE by controlling how dendritic cells present antigens, the health of the blood-brain barrier, and the activation of T and B cells. The development and maintenance of the disease may therefore be greatly influenced by these receptors, in addition to the maintenance of inflammation and the creation of oxidative stress [9]. While astrocytes produce anti-inflammatory cytokines in response to inflammatory stimuli, their activation by pro-inflammatory cytokines results in the production of IL-27. Thus, the participation of astrocytes in inflammatory processes can be both harmful and beneficial.

The inflammatory response in MS is facilitated by the inflammasome. The development and release of the pro-inflammatory cytokines IL-1 and IL-18, as well as the activation of the pore-forming protein Gasdermin D, are mediated by inflammasome-associated caspases, which play a role in neuroinflammation and demyelination. Additionally, inflammasome NLRP3 is active in EAE-mice and leads to cognitive impairments. It may exert its effects via controlling astrocyte phenotypic modification. According to some genetic research, constitutive NLRP3 inflammasome activation may be a risk factor for the clinical manifestation of MS [10]. These findings led to the study of inflammasome components as disease-development biomarkers. The inflammasome and TLRs both encourage inflammatory reactions, which cause the release of pro-inflammatory cytokines. Unwanted pro-inflammatory cytokine release, however, can fuel sterile inflammation and heighten oxidative stress, producing a vicious cycle that encourages additional production. Each of these pathways plays a part in how the inflammatory process in MS develops.

Conclusions

Reactive species and antioxidant systems are out of equilibrium, which causes oxidative stress. Increased oxidative stress has the ability to harm cells and even kill tissues. Because the activation of TLRs and the inflammasome could trigger stress, the interaction between inflammation and oxidative state is close. An auto-toxic loop could be created between inflammation and the creation of ROS and RNS, resulting in a pathophysiologic mechanism for disorders like MS.

The main source of ROS is activated microglia, which intensifies the inflammatory milieu until apoptosis, necrosis, or pyroptosis takes place. High levels of ROS may affect mitochondria, preventing the ATP synthesis required for neurons and glia to function normally. Furthermore, RSN can damage the uptake system and cause excitotoxicity by releasing glutamate. By producing pro-inflammatory cytokines and raising oxidative stress, the inflammasome helps to generate an inflammatory state. Each of these pathways contributes to the growth and progression of MS.

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