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NEUROINFLAMMATION: NEUROPATHOLOGICAL AND CLINICAL CORRELATES

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ABSTRACT

Neuroinflammation is central to the common pathology of several acute and chronic brain diseases. The neurotoxic role of microglia-derived inflammatory mediators which are suspected to hasten the death of nigral dopaminergic neurons, in particular the proinflammatory cytokine Tumor Necrosis Factor (TNF) and its downstream signaling pathways. The possibility that chronic microglia activation links proteinopathies to neurodegeneration. This review examines the consequences of excessive and prolonged neuroinflammation, particularly its damaging effects on cellular and brain function, as well as its relevance to disease progression and possible interventions. The evidence gathered here indicates that neuroinflammation causes and accelerates long-term neurodegenerative disease, playing a central role in the very early development of chronic conditions including dementia. The wide scope and numerous complexities of neuroinflammation suggest that combinations of different preventative and therapeutic approaches may be efficacious.

KEYWORDS: Neuroinflammation, microglia, chemokines, parkinson's disease.

1. INTRODUCTION

Inflammation is the process by which an organism responds to tissue injury and involves both immune cell recruitment and mediator release.[1] Inflammation is an important physiological

reaction which occurs in response to wide variety of injurious agents such as bacterial infections or physical trauma, ultimately aiming to perform the dual function of limiting damage and promoting tissue repair. Inflammation is characterized by the following quintet Redness (*rubor*), Heat (*color*), Swelling (*tumor*), pain (*dolor*) and dysfunction of the organs involved (*function laesa*).[2,3] Inflammation is a complex pathophysiological process mediated by a variety of signalling molecules produced by leukocytes, macrophages and mast cells undergoing various cellular responses such as phagocytic uptake and the production of inflammatory mediator such as nitric oxide, prostaglandins E2 and tumor necrosis factor, that bring about edema formation as a result of extravasation of fluid and proteins and accumulation of leucocytes at the inflammatory site.[4][5]

Neuroinflammation is the inflammation of a nerve or of the nervous system. Neuroinflammation is a process in which the brain responds to infections, diseases and injuries through release of proinflammatory molecules. Neuroinflammation is orchesterated by microglia and astrocytes to re-establish homeostasis in the brain after injury mediated disequilibrium of normal physiology. Physiological responses are mediated by two types of immune cells: lymphocytes, monocytes and macrophages of the hematopoietic system and glial cells of the CNS.[6][7]

1.1 Central Nervous System- Neurons

The central nervous system (CNS) represents the largest part of the nervous system, including the brain and the spinal cord. Together, with the peripheral nervous system, it has a fundamental role in the control of behavior.

The neurons are highly specialised cells of the body, posses excitability to respond to a stimulus and convert it into an action potential. A stimulus is any change in the environment that is strong enough to initiate an action potential. An action potential (nerve impulse) is an electrical signal that propagate (travels) along the surface of the membrane of the neuron. Neuron consists of 3 main parts: the cell body, an axon and numerous dendrites.[8][9]

The cell body, also known as the *perikaryon*or *soma*, contains a nucleus surrounded by cytoplasm that includes typical cellular organelles such as lysosomes, mitochondria and a Golgi complex.

The single axon of a neuron propagates nerve impulses toward another neuron, a muscle fiber, or a gland cell. An axon contains mitochondria, microtubules and neurofibrils. The cytoplasm of an axon, called axoplasm**,** is surrounded by a plasma membrane known as the axolemma.

Dendrites are the receiving or input portions of a neuron. Their cytoplasm contains Nissl bodies, mitochondria, and other organelles.

Structurally, neurons are classified according to the number of processes extending from the cell body:

- **Multipolar neurons** usually have several dendrites and one axon. Most neurons in the brain and spinal cord are of this type.
- **Bipolar neurons** have one main dendrite and one axon. They are found in the retina of the eye, in the inner ear, and in the olfactory area of the brain.
- **Unipolar neurons** have dendrites and one axon that are fused together to form a continuous process that emerges from the cell body. These neurons are more appropriately called pseudo unipolar neurons because they begin in the embryo as bipolar neurons.

1.2 Neuroinflammation Causes And Types Of Neuroinflammation

Common causes of Neuroinflammation are

- Toxic metabolites
- Autoimmunity
- Aging
- Microbes
- Viruses
- Traumatic brain injury
- Air pollution
- Passive smoke

There are two types of Neuroinflammation

- **Acute neuroinflammation**

Acute neuroinflammation usually follows injury to the central nervous system immediately, and is characterized by inflammatory molecules, endothelial cell activation, platelet deposition and tissue edema.

Acute neuroinflammation is more of a physiological response either to injury or insult to the CNS. Reactive gliosis entails accumulation of enlarged glial cells, notably microglia and astrocytes, appearing immediately after CNS injury has occurred. Glial reactivity is majorly a passive response to injury whereas glial activation implies a more aggressive role in responding to activating stimuli. Activated glial cells release factors that act on and engender responses in target cells equivalent to the responses of activated immune cells in the periphery; however, peripheral immune cells activation leads to leukocyte infiltration of tissues, which is notably absent in the brain unless there has been destruction or compromise of the blood brain barrier. In the presence of such destruction or compromise, peripheral leukocytes do enter the brain producing a scenario similar to that seen in inflammatory responses in the periphery.[7]

In limited, acute reactions to injury, in the absence of blood-brain barrier breakdown, there is the subtler response of the brain's own immune system, composed largely of rapid activation of glial cells. These responses represent the other end of the spectrum of CNS injury, where limited neuronal insults trigger glial cell activation without breakdown of the blood brain barrier and without concomitant leukocytic infiltration. This form of "pure" glial response occurs in neuronal injury caused by either loss of afferents.

- **Chronic neuroinflammation**

Chronic inflammation is the sustained activation of glial cells and recruitment of other immune cells into the brain. It is chronic inflammation that is typically associated with neurodegenerative diseases.

Chronic inflammation is often associated in the understanding of CNS disease as opposed to acute inflammation which is linked with CNS injury. It is proposed that chronic inflammation is a causative factor to the pathogenesis of neurological diseases and disorders. The immune cells and pro-inflammatory chemicals involved in neuroinflammation would underlie the mechanisms of diseases and neurodegeneration. The activation, or over activation, of immune cells involved in neuroinflammation and release of pro-inflammatory substances would result in reduced neuroprotection and neuronal repair and increased neurodegeneration, leading to neurodegenerative diseases. To elaborate, during disease states (for example, Parkinson's(PD), Multiple sclerosis, Alzheimer's disease the inflammatory responses damage the BBB, increase oxidative stress and release pro-inflammatory and pro-apoptotic cytokines and other neurotoxic factors that affect neuronal damage or dropout. The damage and stress

signals enhance microglial activation, resulting in positive feedback in the release of chemokines and cytotoxic cytokines that cause further ingress of immune cells into the brain and expand inflammatory responses.[12][20]

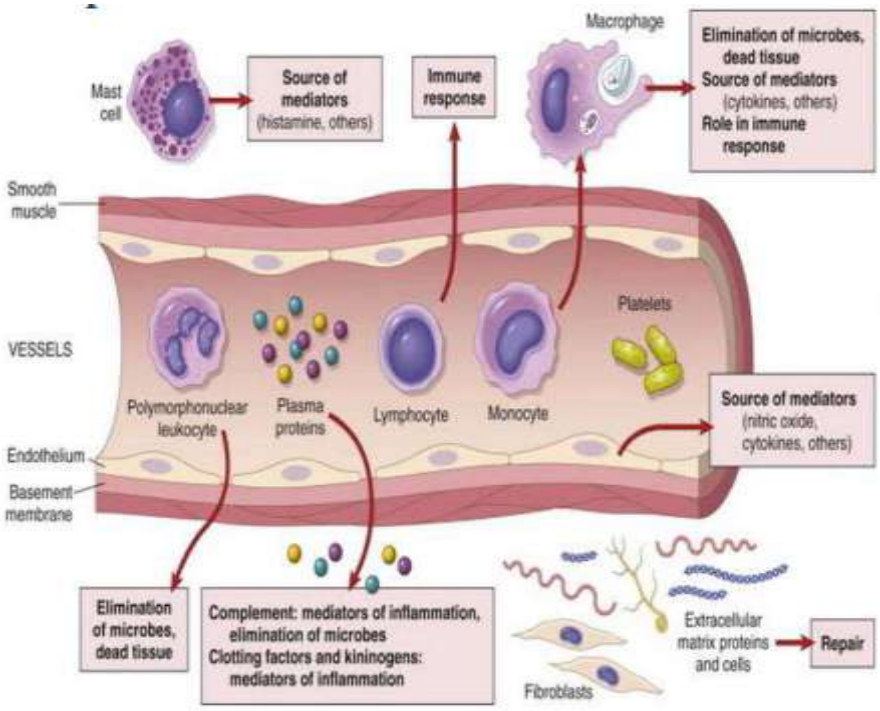

Fig. 1 Components of acute and chronic neuroinflammation.

1.3 CNS immune response

Innate immunity also called natural or native immunity provides the early line of defense against microbes.

It consists of cellular and biochemical defense mechanisms that are in place even before infection and are poised to respond rapidly to infections. These mechanisms react only to microbes (and to the products of injured cells), and they respond in essentially the same way to repeated infections.[13,14]

The principal components of innate immunity are

(1) physical and chemical barriers, such as epithelia and antimicrobial substances produced at epithelial surfaces

(2) phagocytic cells (neutrophils, macro phages) and natural killer (NK) cells

(3) blood proteins, including members of the complement system and other mediators of inflammation;

(4) proteins called cytokines that regulate and coordinate many of the activities of the cells of innate immunity.

Innate immunity serves two important functions

- Innate immunity is the initial response to microbes that prevents, controls, or eliminates infection of the host.
- Innate immunity to microbes stimulates adaptive immune responses and can influenc the nature of the adaptive responses to make them optimally effective against different types of microbes.

Innate immune cell receptor

DCs, macrophages and monocytes all possess both surface and intracellular receptors capable of recognizing pathogen-associated molecular patterns (PAMPs), which are small molecular patterns associated with specific classes of pathogens and microorganisms. These specialized patterns are recognized by different families of pattern recognition receptors (PRRs) and they include TLRs, nucleotide-binding oligodimerization domain (NOD)-like receptors (NLRs) and RIG-like receptors (RLGs). There are several types of TLRs capable of recognizing different PAMPs and these can be found both on the cell surface and within endosomes. Common PAMPs and their receptors include glycolipids and lipoproteins (TLR2), double-stranded RNA (dsRNA) (TLR3), lipopolysaccharide (LPS) (TLR4), flagellin (TLR5), single-stranded RNA (ssRNA) (TLR7) and unmethylated CpGDNA (TLR9). Downstream signalling events of TLR activation are complex, involving several adaptive molecules, kinases and transcription factors. Ultimately, activation of TLRs leads to the transcription of genes that influence inflammatory responses. NLRs are cytosolic receptors and activate similar downstream signaling pathways as TLRs. In mammals, NOD proteins recognize bacterial cell wall proteoglycans and possess CARD domains that can readily recruit caspases, thus activating inflammatory cytokines (e.g.IL1). Mutations in several NOD proteins have been associated with certain inflammatory diseases, including crohn‘s disease.[15]

Key players of immune response.

1.3.1. Microglia

Microglia are key players of the immune response in the central nervous system and, being the resident innate immune cells, they are responsible for the early control of infections and

for the recruitment of cells of the adaptive immune system required for pathogen clearance. Microglia functioning as capability of movement and phagocytosis of pathogens and damaged tissue. Major functions of microglial cells are scavenging, phagocytosis, cytotoxicity, antigenpresentation, synapticstripping, promotion of repair, extracellular signaling.

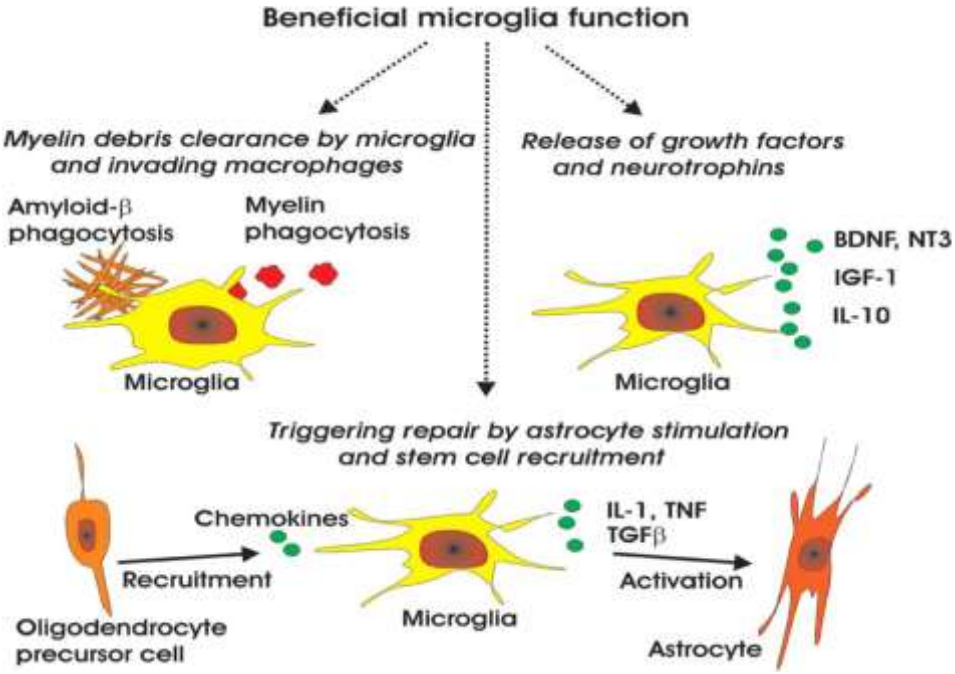

Fig. 2 Microglia with its functions

It has been reported that microglia are essential in the clearance of cellular debris during the development of the foetal brain. Similar to astrocytes, microglia may also play a significant role in the support of axons and the modelling of synapses in the healthy brain. In postnatal development, microglia have been recently shown to participate in activity-dependent synaptic pruning and can engulf presynaptic inputs, which is dependent on both the complement receptor 3 (CR3)–C3 signalling pathway and neural activity. Upon activation, microglia quickly adopt a typical amoeboid morphology and release several cytokines, chemokines, complement proteins, nitric oxide, matrix metalloproteinases (MMPs) and ROS, all of which can influence the innate and adaptive immune responses in the inflamed CNS.[13][15]

The following numerous substances that are secreted when microglia are activated:

- **Cytokines**

Microglia activate the proinflammatory Cytokines IL-1α and IL-1β and TNF-α in the CNS. Cytokines play a potential role in neurodegeneration when microglia remain in a sustained activated state. Direct injection of the cytokines IL-1α, IL-1β and TNF-α into the CNS result in local inflammatory responses and neuronal degradation. This is in contrast with the potential neurotrophic (inducing growth of neurons) actions of these cytokines during acute neuroinflammation.[16]

- **Chemokines**

Chemokines are cytokines that stimulate directional migration of inflammatory cells in vitro and in-vivo. Chemokines are divided into four main subfamilies: C, CC, CXC and CX3C. Microglial cells are sources of some chemokines and express the monocyte chemoattractant protein-1 (MCP-1) chemokine in particular. Other inflammatory cytokines like IL-1β and TNF-α, as well as bacterial derived lipopolysaccharide (LPS) may stimulate microglia to produce MCP-1, MIP-1α and MIP-1β. Microglia can express CCR3, CCR5, CXCR4, and CX3CR1 in vitro. Chemokines are proinflammatory and therefore contribute to the neuroinflammation process.[16]

- **Proteases**

When microglia are activated they induce the synthesis and secretion of proteolytic enzymes that are potentially involved in many functions. There are a number of proteases that possess the potential to degrade both the extracellular matrix and neuronal cells that are in the neighborhood of the microglia releasing these compounds. These proteases include; cathepsins B, L and S, the matrix metalloproteins MMP-1, MMP-2, MMP-3 and MMP-9 and the metalloprotease disintegrin ADAM8 (plasminogen) which forms outside microglia and degrades the extracellular matrix. Both Cathepsin B, MMP-1 and MMP-3 have been found to be increased in Alzheimer‘s disease and cathepsin B is increased in multiple sclerosis. Elastase, another protease, could have large negative effects on the extracellular matrix.[17]

- **Amyloid precursor protein**

Microglia synthesize amyloid precursor protein (APP) in response to excitotoxic injury. Plaques result from abnormal proteolytic cleavage of membrane bound APP. Amyloid plaques can stimulate microglia to produce neurotoxic compounds such as cytokines, excitotoxin, nitric oxide and lipophylic amines, which all cause neural damage. Plaques in Alzheimer's disease contain activated microglia. A study has shown that direct injection of

amyloid into brain tissue activates microglia, which reduces the number of neurons. Microglia have also been suggested as a possible source of secreted β amyloid.[17]

1.4 Major Players of Innate Response

- **Astrocytes**

These star shaped cells have many processes and are the largest and most numerous of the neuroglia. There are two types of astrocytes.

Protoplasmic astrocytes have many short branching processes and are found in gray matter. Fibrous astrocytes have many long unbranched processes and are located mainly in white matter.

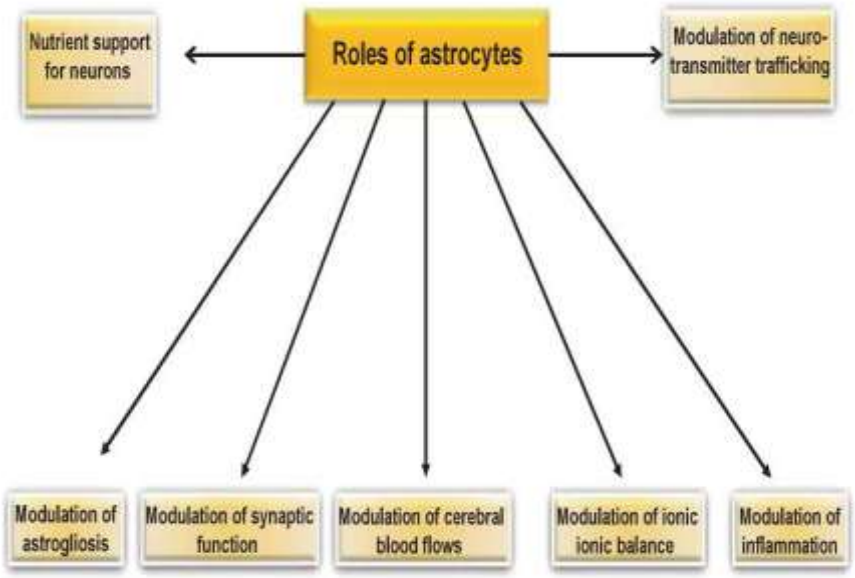

Fig 3 Roles of astrocytes

The functions of astrocytes include the following

(1) Astrocytes contain microfilaments that give them considerable strength, which enables them to support neurons.

(2) Processes of astrocytes wrapped around blood capillaries isolate neurons of the CNS from various potentially harmful substances in blood by secreting chemicals that maintain the unique selective permeability characteristics of the endothelial cells of the capillaries. In effect, the endothelial cells create a blood-brain barrier, which restricts the movement of substances between the blood and interstitial fluid of the CNS.

(3) In the embryo, astrocytes secrete chemicals that appear to regulate the growth, migration, and interconnection among neurons in the brain.
(4) Astrocytes help to maintain the appropriate chemical environment for the generation of nerve impulses. For example, they regulate the concentration of important ions such as K; take up excess neurotransmitters; and serve as a conduit for the passage of nutrients and other substances between blood capillaries and neurons.
(5) Astrocytes may also play a role in learning and memory by influencing the formation of neural synapses.

Astrocytes are complex, highly differentiated cells of the brain. They play several important roles, such as regulating the external environment of neurons, participating in the physical structuring of the brain, providing metabolites to neurons, and maintaining the blood brain barrier (BBB) integrity. The cell body and the major processes of astrocytes are enriched with glial fibrillary acidic protein (GFAP) that forms intermediate filaments, whose recognition by Golgi staining is the reason for the classically star-shaped appearance of astrocytes. Astrocytes not only maintain BBB, regulate cerebral blood flow and modulate synaptic function and plasticity, but also maintain the extracellular balance of ions, modulate neurotransmitter (glutamate) trafficking and recycling and provide nutrient support for neurons. Another transmitter released from astrocytes is ATP, which modulates the functions of gap junction channels. It is proposed that the release of ATP propagates a signal wave via activation of purinoceptors. The purinoceptor activation can stimulate trophic signaling pathways, through the activation of protein kinase or changes in gene expression. Astrocytes also express numerous receptors including G protein-coupled receptors and ionotropic receptors, receptors for growth factors, chemokines and cytokines. Astrocytes display heterogeneity in their pattern of receptor expression and adjust the pattern according to their microenvironment. Astrocytes become highly reactive in response to any insult to the brain. Thus, astrocytes also respond to all forms of injuries including infection, SCI, TBI, ischemic injury and neurodegenerative disease by a process commonly known as reactive astrogliosis. Although, astrocytes are multifunctional housekeeping cells, but their activation is associated with neuronal survival in many different ways. Depending on the type of the stimuli and/or pathological conditions reactive astrogliosis may lead to either neuroprotective or neurotoxic inflammatory responses.[19]

➢ **Cytokines**

Cytokines are produced mainly by the leukocytes (white blood cells). They are potent polypeptide molecules that regulate the immune and inflammation functions, as well as hemopoiesis (production of blood cells) and wound healing. There are two major classes of cytokines: (a) lymphokines and monokines, and (b) growth factors.[16]

Lymphokines and monokines

Cytokines produced by lymphocytes are called lymphokines and those produced by monocytes are termed monokines. Lymphocytes and monocytes are different types of white blood cells. The major lymphokines are interferons (IFNs) and some interleukins (ILs). Monokines include other interleukins and tumor necrosis factor (TNF).

Interferons

There are two types of interferons: Type I, which includes IFN-α and IFN-p and Type II consisting of IFN-y. IFN-α and p have about 30% homology in amino acid sequence. There are two more recently discovered Type I interferons; they are called IFN-w and IFN-t. IFN-α and IFN-p each have 166 amino acids, and IFN-y has 143**.** Both IFN-α and IFN-p are of single chain structure and bind to the same type of cell surface receptors, whereas IFN-y is a dimer of two identical chains and interacts with another type of receptors. All our cells can produce Type I interferons when infected by viruses, bacteria and fungi. However, only T cells and natural killer cells can produce Type II interferon. Type I interferon binds to receptor, which in turn activates tyrosine kinase phosphorylation and the subsequent transcription pathway that induces viral resistance. Similarly, Type II interferon binds to another receptor and activates the immune response. Because of its antiviral and anticancer effects, IFN-α is used in the treatment of hepatitis and various forms of cancer, such as Kaposi‘s sarcoma, non-Hodgkin‘s lymphoma and hairy cell leukemia. Treatment of hepatitis C with IFN-α. IFN-p is used for treating multiple sclerosis, a chronic disease of the nervous system. The medical application of IFN-y is for cancer, AIDS and leprosy.[22][23]

➢ **Interleukins**

Interleukins are proteins produced mainly by leukocytes.

There are many interleukins within this family. Interleukins have a number of functions, but principally in mediating and directing immune cells to proliferate and differentiate. Each interleukin binds to specific receptor and produces its response. IL-2 is possibly the most-

studied interleukin. It is also called T cell growth factor. IL-2 is a 15 kDa glycoprotein produced by CD4+ T helper cells. It has 133 amino acids.

There are four helical regions and a short β-sheet section.

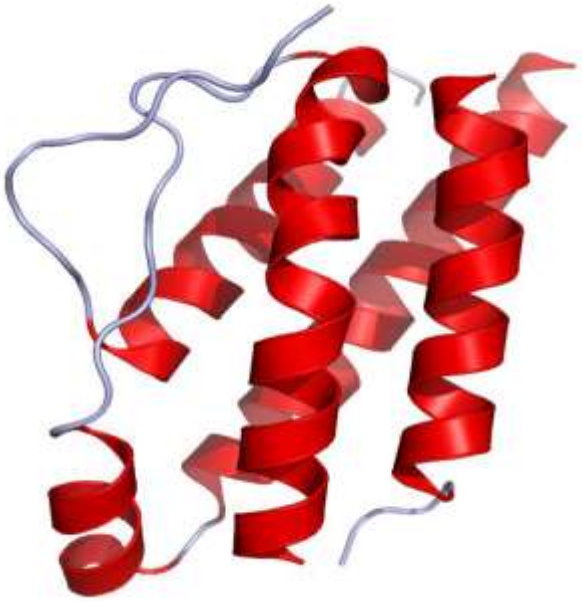

Fig 4 Interleukin 2 (IL-2) molecule

IL-2 promotes the growth of B cells for antibody production and induces the release of IFN-y. It has been approved by the FDA for the treatment of different types of cancer, including metastatic melanoma and metastatic renal carcinoma. Although IL-2 has not been approved to treat HIV/AIDS, many clinical trials using IL-2 are being conducted. The strategy is to complement the anti- HIV therapy by boosting the immune system with IL-2. The replacement therapy of IL-2 administered to AIDS patients increases production of CD4+ T cells and the activities of natural killer cells to combat HIV. Therapeutic IL-2 is manufactured using recombinant technology.

- **Tumor necrosis factor**

There are two types of tumor necrosis factor: TNF-α and TNF-P. Of the two, TNF-α has been studied in more detail. TNF-α is a 157 amino acid polypeptide. It is a mediator of immune regulation, including the activation of macrophages and induction of the proliferation of T cells. Another TNF-α function is its cytotoxic effects on a number of tumor cells. Recent research, however, concentrates on its property in the stimulation of inflammation, particularly in the case of rheumatoid arthritis. Clinical trials are being conducted with drugs to block TNF-α with anti-TNF-α monoclonal antibodies. These antibodies target the

excessive levels of TNF-α in synovial fluids of joints and provide relief to sufferers of rheumatoid arthritis.[16]

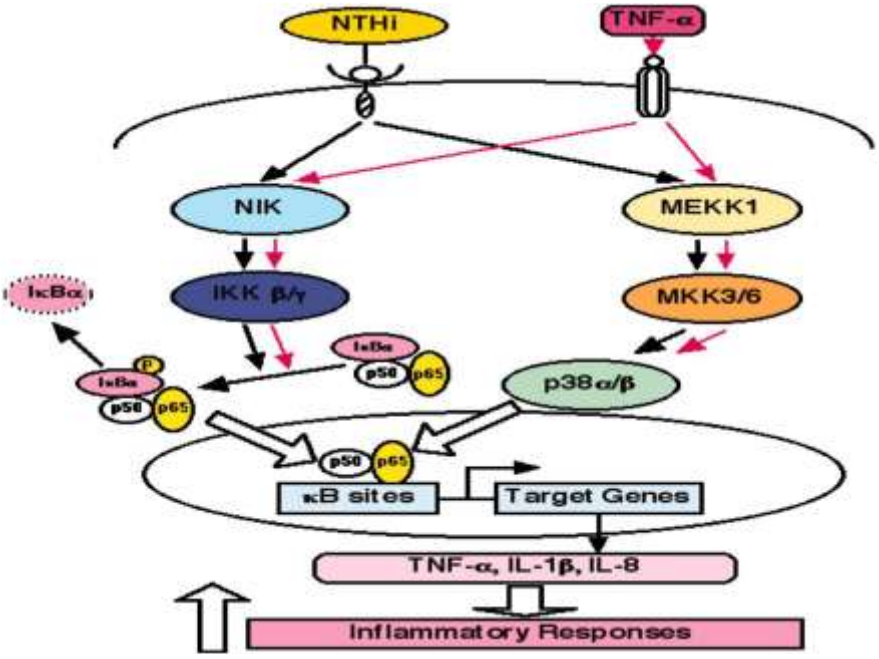

Fig. 5 Tumor necrosis factor release.

- **Growth factors**

As the name implies, growth factors stimulate cell growth and maintenance.

We will discuss the following growth factors:

- **Erythropoietin**

Erythropoietin (EPO) is a glycoprotein produced by specialized cells in the kidneys. It has 166 amino acids and a molecular weight of approximately 36 kDa. EPO stimulates the stem cells of bone marrow to produce red blood cells. It is used to treat anemia and chronic infections such as HIV and cancer treatment with chemotherapy where anemia is induced. Patients feel tired and breathless owing to the low level of red blood cells. EPO can be prescribed instead of blood transfusion. Biopharmaceutical quantities of EPO are produced with recombinant cells. This is achieved through the isolation of the human gene that codes for EPO and transfection of the gene into cell lines such as Chinese hamster ovary cells. The product is called rhEPO-recombinant human EPO. EPO is normally administered subcutaneously and is generally well tolerated by patients. EPO is considered a banned performance-enhancing drug in the sports arena, where athletes use EPO to boost their red blood cells with the expectation of boosting performance.[21][24]

- **Colony stimulating growth factors**

Growth factors such as granulocyte macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF) are involved in the regulation of the immune and inflammatory responses. GM-CSF is a glycoprotein with 127 amino acids and a molecular weight of about 22 kDa. It is produced by macrophages and T cells. Clinically, GM-CSF is used to stimulate production of blood cells, in particular patients who have received chemotherapy. M-CSF is a glycoprotein that can exist in different forms. The number of amino acids ranges from just over 200 to about 500 and molecular weight varies between 45 and 90 kDa. MCSF is being evaluated clinically for its anti-tumor activity.[21]

2. Neuroinflammation

2.1 Neurotropic Factor Released

Neurotrophic factors are a family of proteins responsible for the growth and survival of neurons during development and for the maintenance of adult neurons. They are also capable of promoting damaged axons to regenerate after various peripheral and central nervous system injuries.

Neurotrophic factors (NTFs) are naturally-occurring multifunctional secreted proteins, expressed throughout development and into adulthood and in part serve to promote neuronal survival, to support axonal outgrowth and target innervation and in some cases to modulate synaptic transmission. It is secreted by a target tissue (either neuronal or nonneuronal) and acts on the neurons that innervate that tissue to support their survival or differentiation. Finally, a neurotrophic factor is expressed in the appropriate region and at the appropriate time in development to support the survival of a particular neuronal population.

Neurotrophic factors (NTFs) are secreted peptides that act as growth factors for the phenotypic development and maintenance of specific neuronal populations in developing and adult vertebrate nervous system. These diffusible proteins that act via retrograde signaling from target- neurons and by paracrine and autocrine mechanisms regulate many aspects of neuronal and glial structure and function. Neurons which fail to obtain a sufficient quantity of the necessary neurotrophic factors die by a process called programmed cell-death. Further, in adulthood, neurotrophic factors are required to maintain neuronal functions and specific neuronal phenotype. Neurotrophic factors not only promote the differentiation and growth of developing neurons and phenotypic maintenance and survival of adult mature neurons but

also represent a potential means of modifying neuronal dysfunction, astrocytic activation and inflammatory reactions under pathological conditions.[24][25]

➢ **Families of neurotrophic factors**

Most neurotrophic factors (NTFs) belong to several families of structurally and functionally related molecules:

(1) Nerve growth factor (NGF)- superfamily

(2) glial cell line-derived neurotrophic factor (GDNF) family

(3) neurokine or neuropoietin superfamily

(4) non-neuronal growth factor-superfamily.

All these NTFs signal via specific multicomponent receptor complexes. NGF-super family receptors include p75 and the receptor protein tyrosine kinases (Trk), TrkA, TrkB and TrkC. GDNF family receptors include a receptor complex of Ret and growth factor receptor (GFR). The neurokine superfamily ligands mediate via the receptors gp130 and leukemia inhibitory factor receptor-b (LIFRb).

- **NGF-superfamily**

The NGF-superfamily, originally called the neurotrophins, includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 /5 (NT-4/5) and neurotrophin-6 (NT-6).

- **GDNF family**

The GDNF family, distantly related to the TGF-β superfamily, includes glial cell line-derived neurotrophic factor(GDNF) and three structurally related members called neurturin (NTN), persephin (PSP) and artemin (Art).

- **Neurokine superfamily**

The neurokine family includes ciliaryn eurotrophic factor (CNTF), leukemia inhibitory factor (LIF), interleukin-6 (IL-6), cardiotrophin-1 (CT-1) and oncostatin-M.

- **Non-neuronal growth factors**

Non-neuronal growth factors present in significant concentrations in the nervous system include acidic fibroblast growth factor (aFGF), also called FGF-1; basic fibroblast growth

factor (bFGF), also called FGF-2; epidermal growth factor (EGF), insulin-like growth factor (IGF) and bone morphogenetic protein (BMP).

- **Other neurotropic factors**

Several prominent neurotrophic factor families carry out similar functions as the neurotrophins. Glial-derived neurotrophic factor (GDNF) is an 18-kDa protein, originally isolated from an astrocyte cell line and later shown to be made by many types of neurons. It represents one of the most potent trophic factors for dopaminergic neurons. In both in vitro and in vivo studies, GDNF has been shown to maintain the survival of dopaminergic neurons in the midbrain as well as neurons in the myenteric plexus in the gut. Due to its trophic effects on dopaminergic neurons it has been considered a potential therapeutic agent for Parkinson's disease. GDNF binds to a protein, GFRα1, which is anchored to the plasma membrane by a glycophospholipid. Other ligands have also been discovered, namely, artemin, neurturin and persephin, which recognize specific GFRα receptors. This ligand–receptor complex then associates with Ret, a receptor tyrosine kinase, which, like the Trk receptors, undergoes dimerization and becomes catalytically active. Phosphotyrosine-binding adaptor proteins such as Shc then bind to the Ret receptor and mediate downstream signaling cascades such as the MAP kinase pathway. Mutations in the Ret receptor and GFRα1 have been associated with Hirschprung's disease, a disorder caused by the lack of development of myenteric plexus neurons, leading to abnormal gut motility.

Ciliaryn eurotrophic factor (CNTF) belongs to a family of cytokines, including leukemia inhibitory factor (LIF) and interleukin-6, which maintain the survival of ciliary neurons as well as motor neurons. Due to its ability to rescue motor neurons after axotomy in animal studies, CNTF has been investigated as a therapeutic agent for motor neuron diseases such as amyotrophic lateral sclerosis (ALS). These factors utilize a receptor complex consisting of a plasma-membrane bound CNTF-binding protein (CNTF-α), a glycoprotein (gp130) and a LIF receptor (LIFR) to transduce signals. Upon formation of this complex, a soluble tyrosine kinase, the Janus kinase (JAK), is activated and leads to the activation of a specific family of transcription factors termed STATs.

Therefore, trophic factors exemplified by NGF, CNTF and GDNF and their family members all utilize intracellular tyrosine phosphorylation to mediate neuronal cell survival. CNTF acts through a complex of a CNTF receptor, gp130 and LIFR subunits that are linked to the

JAK/STAT signaling molecules, whereas the GDNF receptor consists of the c-Ret receptor tyrosine kinase and a separate α-binding protein.[24][26]

2.2 Role of Neurotropic factor to promote tissue homeostasis and neuroinflammation

Neurotrophic factors (NTFs) are naturally-occurring multifunctional secreted proteins, expressed throughout development and into adulthood and in part serve to promote neuronal survival, to support axonal outgrowth and target innervation and in some cases to modulate synaptic transmission.

Neurotrophic Factors

The first NTF to be discovered, based on its ability to promote neuronal survival and neurite outgrowth, was nerve growth factor (NGF). NGF is the prototypical member of a family which includes brain-derived NTF (BDNF), neurotrophin 4/5 (NT-4/5) and neurotrophin-3(NT-3).

These molecules act through specific receptors: NGF binds to tropomyosin related kinase A (TrkA), BDNF and NT-4/5 bind to TrkB and NT-3 binds to TrkC. All of these receptors are expressed in dorsal root ganglia and (with the exception of TrkA) motoneurons. All neurotrophins also bind a receptor, p75NTR, which is co-expressed with the Trks but whose role in regeneration remains enigmatic. The neurotrophin sensitivity of DRG neurons is subtypespecificand has been repeatedly demonstrated in vitro and in vivo: half of all nociceptors/thermoreceptors express TrkA (the other half do not express any Trk but do express GDNF receptor components), whereas the majority of mechano/proprioceptors express TrkC and a minority express TrkB. Motoneurons express both TrkB and TrkC. The glial cell line-derived NTF (GDNF) family includes GDNF, neurturin, artemin and persephin. GDNF was isolated based on its ability to promote survival of midbrain dopaminergic neurons and the rest were identified based on sequence homology. All GDNF family members have been shown to augment neurite outgrowth in vitro, but only GDNF and neurturin have proved to enhance regeneration in vivo. GDNF family members signal through receptor complexes which involve a common signaling component and ligand-specific binding components (GFRα1–4). GFRα1–3 are expressed in DRG neurons, mainly among thermo/nociceptors, while GFRα1, 2 and 4 are expressed by motoneurons.

Three members of the interleukin-6 (IL-6) family of neurotrophic cytokines will be considered here: Ciliary NTF (CNTF), leukemia inhibitory factor (LIF) and IL-6. Peripheral

nerve injury increases the exposure of severed axons to all three factors, which are synthesized in nonneuronal cells. IL-6 upregulation also occurs following axotomy in large-diameter DRG neurons and in motoneurons. These molecules share a common receptor component, gp130, but activate it through receptor complexes: IL-6 and CNTF first bind non-signaling receptor components [IL- 6Rα and CNTFRα (Cilary Neurotrophic Factor Receptor)] and then to a gp130 homodimer (in the case of IL-6) or a heterodimer consisting of gp130 and leukemia inhibitory factor receptor (LIFR, in the case of CNTF). LIF signals through LIFR: gp130 heterodimers. All DRG neurons express gp130, IL-6Rα and CNTFRα, while thermoceptors and nociceptors express LIFR. While LIFR, CNTFRα and gp130 are also found in motoneurons, data on motoneuronal IL-6R are lacking.[26]

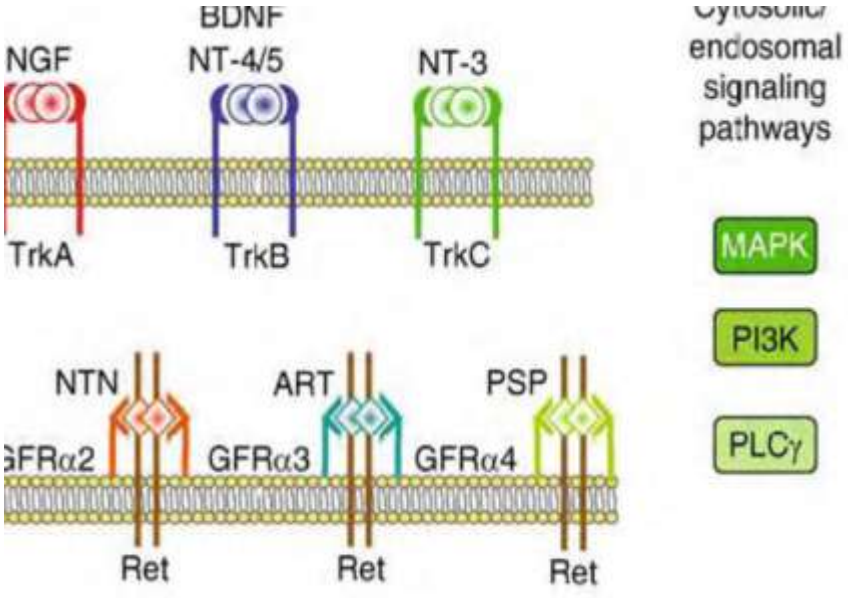

Fig 6 Neurotrophic Factor in Nerve Regeneration

2.3 Role of Neurotrophic factor in disease progression

Neurotrophic factors regulate numerous neuronal functions in development and adult life and in response to injury. As a result, neurotrophins have been implicated in the pathophysiology of a wide variety of neurodegenerative and psychiatric disorders and have been considered as a therapeutic strategy for many neuropsychiatric disorders. It should be emphasized though that few human diseases affecting the nervous system have been shown to be caused by a defect in the neurotrophins or their receptors. Still, the finding that neurotrophic factors modulate neuronal survival and axonal growth was the initial rationale for potential clinical correlates to neurodegenerative disorders and neuronal injury such Alzheimer's disease, Parkinson's disease, Huntington's disease and ALS as well as spinal cord injury. The

additional effects of neurotrophic factors on synaptic connections, synaptic plasticity and neurotransmission have formed the basis for their association with psychiatric disorders such as depression and substance abuse. In these conditions, the response to acute and chronic environmental changes leads to alterations in neuronal function.

The hypothesis underlying these clinical correlations as well as development of therapeutic strategies using neurotrophic factors assumes that these disease states result in either (1) decreased availability of neurotrophins for the affected neurons, (2) a decreased number of neurotrophin receptors on the affected neurons and/or (3) decreased neuronal survival. These deficits can be ameliorated by the addition of neurotrophic factors. In all these disease states the assumption has been that exogenous neurotrophic factors would provide symptomatic treatment for the disease state rather than a cure for the core pathophysiology of these nervous system disorders.[26]

- **Neurodegenerative disorders**

The initial clinical correlation to Alzheimer's disease was made in the 1980s based on studies on aged animals that showed that cholinergic neurons in the basal forebrain could be rescued with intracerebroventricular NGF, resulting in concomitant improvements in memory function. Subsequent animal studies of impaired motor neuron populations demonstrated that other neurotrophins, BDNF, NT-3, NT-4 and CNTF could rescue those neurons in an axotomized facial nerve and sciatic nerve. In addition, mutant mouse models of motor neuron disease, in which there was motor neuron degeneration, demonstrated that BDNF and CNTF could increase the number of motor neurons and improve motor performance. These studies led to the therapeutic strategy to attempt to treat degenerative diseases affecting motor neurons with neurotrophins.

In the 1990s, great effort was focused on studying whether neurotrophic factors could be used as a treatment strategy for ALS, a progressive neurodegenerative disorder that specifically affects motor neurons and leads to death due to respiratory failure with the development of recombinant forms of the neurotrophic factors, namely, BDNF, clinical trials have taken place on patients with ALS. Subcutaneous or intrathecal delivered BDNF had minimal beneficial effect and was associated with side effects such as pain and gastrointestinal symptoms. It was due to these side effects that decreased doses were used as compared to the doses in the animal studies. Similarly, use of another neurotrophic factor, CNTF, also led to even more significant side effects such as fever, pain and anorexia, which also limited the

doses used. These multisite clinical trials highlighted the challenges of delivery of large quantities of these proteins to CNS and PNS neurons. Similar clinical studies using NGF for the treatment of patients with Alzheimer's disease and diabetic neuropathy encountered similar hurdles involving problems of delivery and uncertain pharmacokinetics of the proteins.

- **Correlates to psychiatric disorders**

Many functions of the neurotrophic factors in the adult CNS have been elucidated beyond their effects on survival. These functions include the maintenance of differentiated neuronal phenotypes and the regulation of synaptic connections, activity dependent synaptic plasticity, and neurotransmission. These additional functions have made neurotrophins attractive molecular intermediates that may be involved in the pathophysiology of psychiatric disorders in which environmental inputs can presumably lead to alterations in neuronal circuitry and ultimately behavior. In particular, it has become clear that neurotrophins can produce long-term changes by regulating transcriptional programs on the functioning of adult neurons. This could explain the long delay in therapeutic action of many psychiatric treatments. Again the clinical correlation is based on the assumption that there is a deficit in access or responsiveness to neurotrophic factors contributing to the phenotype of the disease state.

- **Major Depressive disorder**

The strongest evidence for a role for neurotrophins has come from the pathophysiology of depression, especially those associated with stress. For depression, it is believed that there is a fundamental dysregulation of synaptic plasticity and neuronal survival in regions of the brain such as the hippocampus. There are several lines of evidence suggesting a role of neurotrophins in depression. First, in animal models, restraint stress leads to decreased expression of BDNF in the hippocampus. In addition, chronic physical or psychosocial stress leads to atrophy and death of hippocampal neurons especially in the CA3 region in rodents and primates. Also, magnetic resonance imaging (MRI) studies have shown that patients with depressive or posttraumatic stress disorders exhibit a small decrease in hippocampal volume. It is unclear though whether the atrophy and/or death of these neurons is directly related to the decreased availability of BDNF. In addition, not all forms of depression are associated with stress. However, if structural remodeling and synaptic plasticity are involved in the cellular pathophysiology of depression, then BDNF is an attractive candidate molecule to mediate these alterations.

Exogenously administered BDNF in the hippocampus had antidepressant effects in two animal models of depression (i.e., the forced swim and learned helplessness paradigms) comparable to those of chronic treatment with pharmacological antidepressants. In addition, BDNF has also been shown to have trophic effects on serotonergic and noradrenergic neurons in vitro and in vivo. Mutant mice with decreased levels of BDNF have been shown to have a selective decrement in serotonergic neuron function and corresponding behavioral dysfunction consistent with serotonergic abnormalities third, serotonin and norepinephrine reuptake inhibitor antidepressants upregulate CREB, a cyclic adenosine monophosphate (cAMP)- dependent transcription factor and BDNF in a time course that corresponds to therapeutic action (10 to 20 days). The CREB transcription factor is involved in the induction of BDNF gene expression in neurons. This effect on the cAMP pathway provides a link between monoamine antidepressants and neurotrophin actions. These antidepressant treatments also lead to increases in expression of TrkB receptors in the hippocampus in a time course that also parallels the long time course of therapeutic action of these treatments. The effect of prolonged serotonin and norepinephrine reuptake inhibitor treatment involves enhancing neurotrophin signaling. Two other antidepressant treatments, monoamine oxidase inhibitors (MAOIs) and electroconvulsive therapy (ECT), also upregulate BDNF transcription. In rodents, long-term ECT has been shown to elicit the sprouting of hippocampal neurons that was attenuated in mutant mice that express lower levels of BDNF. Conversely, exogenously administered BDNF in the mesolimbic dopamine system appears to have an opposite effect increasing depression like behavior. In addition, removal of BDNF in this dopamine circuit appears to have antidepressant effects on a social defeat paradigm. These findings emphasize the complexity of BDNF's role in mediating aspects of behavior related to depression. Together, these studies provide a framework to examine further the neurotrophin system as a potential therapeutic target for the treatment of depression.

3. Neuroinflammation-neuropathological and clinical correlates

- **Neuropathic pain**

Inflammation is a pathophysiological state associated with pain. The free nerve endings of peripheral nerve fibers in systemic tissues respond directly to inflammatory factors, such as lowered pH, bradykinin, histamine or prostaglandins, by generating electrical activity that is normally interpreted as painful; this beneficial pain state helps to protect us from adverse environments and can be managed by over-the-counter medications. Neuroinflammation is a more restrictive term referring to inflammatory states within the nervous system (NS) that

can give rise to the serious problem of neuropathic pain; the burdensome pain state, for which there is often no effective therapy, that can be debilitating and life-destroying. Stated another way, neuropathic pain is the chronic pain state caused by significant pathological changes in the NS. It can occur secondarily to injury of the central nervous system (CNS) but it occurs most commonly in association with injury to the peripheral nervous system (PNS). These injuries can be caused by tumors compressing peripheral nerves, toxins used as chemotherapy, metabolic or viral diseases, severe ischemic insults and trauma and disc herniation that stretches, compresses or inflames a nerve root.

Neuropathic pain is mediated through neuroinflammatory mechanisms affecting NS tissue that is controlled by inflammatory responses to the initial insult. In fact, ingredients of the so-called 'inflammatory soup' that are associated with systemic tissue injury and acute pain states now include proinflammatory cytokines. Proinflammatory cytokines stimulate the production of the traditional chemical constituents of inflammation, such as prostaglandins. When these factors are upregulated within the NS dire consequences can result.

- **Parkinsons disease**

Although other neurotransmitter systems may also be involved, the primary pathology underlying Parkinson's disease (PD) is damage to and loss of pigmented dopamine (DA) neurons in the lateral and ventral substantia nigra pars compacta (SN). Whether inflammation causes, contributes to, or is a minor consequence of DA degeneration in PD remains undetermined, but there is clear evidence that it occurs, including numerous reports of focal gliosis, which forms extensive SN scars in severe cases of neuron damage, as well as increases in classic markers of inflammatory attack.

The leading hypothesis of Parkinson's disease progression includes neuroinflammation as a major component. This hypothesis, known as "Braak's Hypothesis," stipulates that Stage 1 of Parkinson's disease begins in the gut, as evidenced by a large amount of cases that begin with constipation. The inflammatory response in the gut may play a role in alpha-synuclein (α-Syn) aggregation and misfolding, a characteristic of Parkinson's disease pathology. If there is a balance between good bacteria and bad bacteria in the gut, the bacteria may remain contained to the gut. However, dysbiosis of good bacteria and bad bacteria may cause a "leaky" gut, creating an inflammatory response. This response aids α-Synmisfolding and transfer across neurons, as the protein works its way up to the CNS. The brainstem is vulnerable to inflammation, which would explain Stage 2 of Braak's hypothesis, including

sleep disturbances and depression. In Stage 3 of the hypothesis, the inflammation affects the substantia nigra, the dopamine producing cells of the brain, beginning the characteristic motor deficits of Parkinson's disease. Stage 4 of Parkinson's disease includes deficits caused by inflammation in key regions of the brain that regulate executive function and memory. As evidence supporting Braak's hypothesis, patients in Stage 3 (motor deficits) that are not experiencing cognitive deficits already show that there is neuroinflammation of the cortex. This suggests that neuroinflammation may be a precursor to the deficits seen in Parkinson's disease.

- **Multiple sclerosis**

Multiple sclerosis is a very common neuroinflammatory disease. It is characterized by demyelination and neurodegeneration, which contribute to the common symptoms of cognitive deficits, limb weakness and fatigue. In multiple sclerosis, inflammatory cytokines disrupt the blood brain barrier and allow for the migration of peripheral immune cells into the central nervous system. When they have migrated into the central nervous system, B Cells and plasma cells produce antibodies against the myelin sheath on neurons, degrading the myelin and slowing conduction in the neurons. Additionally, T Cells may enter through the blood brain barrier, be activated by local antigen presenting cells and attack myelin sheath. This has the same effect of degenerating the myelin and slowing conduction. As in other neurodegenerative diseases, activated microglia produce inflammatory cytokines that contribute to the widespread inflammation. It has been shown that inhibiting microglia decreases the severity of multiple sclerosis.

4. Future prospective

- **Drug targets for therapeutic strategy**

Because neuroinflammation has been associated with a variety of neurodegenerative diseases, there is increasing interest to determine whether reducing inflammation will reverse neurodegeneration. Inhibiting inflammatory cytokines, such as IL-1β, decreases neuronal loss seen in neurodegenerative diseases. Current treatments for multiple sclerosis include interferon-B, Glatirameractetate and Mitoxantrone, which function by reducing or inhibiting T Cell activation, but have the side effect of systemic immunosuppression In Alzheimer's disease, the use of non-steroidal anti-inflammatory drugs decreases the risk of developing the disease. Current treatments for Alzheimer's disease include NSAIDs and glutoccorticoids. NSAIDs function by blocking conversion of prostaglandin H2 into other prostaglandins

(PGs) and thromboxane (TX). Prostoglandins and thromboxane act as inflammatory mediators and increase microvascular permeability.

- **Clinical strategies: anti-inflammatory treatment**

With the role of COX pathways in neuroinflammation becoming better established, NSAIDs have been identified as a class of drug with potential therapeutic effects. As COX-1 is expressed in microglia it is thought to play a more significant role in neuroinflammation than COX-2, which is confined to neurons, implying that COX-1 inhibitors may be effective at reducing inflammation. Indeed, aspirin (an irreversible COX-1 inhibitor) reduces neuroinflammatory and oxidative insults by reducing prostaglandins and increasing anti-inflammatory lipoxin. However evidence is lacking for clinical benefit of NSAIDs and selective COX-2 inhibitors in patients with neurodegenerative diseases. Cochrane studies have found no significant improvement resulting from NSAIDs in established AD and Parkinson's disease. The most recent results of a large clinical trial, the Alzheimer disease anti-inflammatory prevention trial (ADAPT), suggest that certain NSAIDs may reduce the chances of an asymptomatic individual developing this disease but these same drugs exacerbate later stage Alzheimer's. The anti-inflammatory properties of some compounds released as by-products of NSAID and other drug activity, however, may present interesting therapeutic possibilities, for example hydrogen sulphide releasing compounds which have recently shown promise in reducing neuroinflammation.

Alongside their well-established role in reducing cholesterol, HMG-CoA reductase inhibiting drugs, statins, have various anti-inflammatory and immunomodulating effects in several effector cells Peripherally, statin pre-treatment dampens TLR4 and TLR2 expression resulting in a decrease in TNF- α and a suppression of innate immunity. The endothelial stabilising properties of statins are also beneficial to maintaining the integrity of the BBB in inflammatory conditions. This is observed in the restriction of the leucocyte migration across the blood brain barrier and impaired migration within the CNS. A further role for statins may lie in glial mediated neuroinflammation as they decrease glial activation and reduce microglial production of TNF-α, IL-1 and IL-6 as well as astrocytic cytokines and iNOS. This production is reduced in microglia stimulated by both IFN- and A and this could prove to be an important benefit of HMG-CoA reductaseas inhibiting microglial activity is an key factor in stemming the tide of chronic neuroinflammation. Protective properties of stains such as atorvastatin have been shown to include neuroprotection through reduction in hippocampal

IL-1 and COX-2 production and inactivation of GSK3. There is clinical evidence supporting the use of statins in reducing cognitive impairment, for example a prospective cohort study showed statin administration significantly reducing post operative delirium, but there is a need for more studies as there is currently a lack of literature concerning the role of statins in neuroinflammation.

5. CONCLUSION

An effective innate immune response in the CNS is crucial for the elimination of pathogens and the clearing of debris and is vital for survival. However, chronic or exaggerated inflammation in the CNS can cause neurodegeneration. Modulation of the innate immune response in the CNS by targeting specific receptors or signaling pathway molecules may be a rewarding therapeutical strategy in the future, particularly in the noninfectious CNS injury found in neurodegenerative diseases.

The neurotrophic factors and their signal transduction cascades represent a complex array of pathways that influence many aspects of neuronal function and survival during development as well as in the adult central nervous system. The characterization of these pathways has provided many new target sites for the development of novel agents that could be used to treat a variety of neurologic and psychiatric illnesses.

Neuroinflammation plays an important role in the toxicity and the progression of the disease process in AD, PD and HD and these similarities in the inflammatory responses could be utilized to develop new therapeutic approaches for their amelioration. However, the underlying cause of the enhanced neuroinflammation in each of these diseases still remains unresolved (i.e. the misfolded proteins), such that these need to be reduced to remove the stimuli associated with the inflammatory responses.

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