Topic: Disruption of the Blood-Brain Barrier by Neuroinflammatory responses: The Hallmark of Neurodegeneration and Demyelination.

Adebisi Benjamin Tèmídayọ

Institute of Anatomy, Cell Biology Brain and Neurodegeneration, Nigeria.

BLOOD-BRAIN BARRIER AND NEUROINFLAMMATION: THE ROLE OF MICROBIAL INFECTIONS IN NEURODEGENERATIVE DISEASES

The BLOOD-BRAIN BARRIER, BBB, is a barrier that prevents passage of particles from the blood stream to the Central Nervous System.

However, it is not completely impenetrable, as some small molecules of oxygen and glucose could diffuse through the barrier.

The barrier is made of several parts namely:

(i) Endothelial cells of the blood vessels close to the brain

(ii) The tight junction that closes the gaps between the endothelial cells.

(iii) The Pericytes surrounding the blood vessels

(iv) Astrocytic foot processes or end feet, that reinforces the barrier.

Astrocytes are supporting cells, or glial cells that provide nutrition for neurons and helps clear waste materials from neuronal extracellular space.

Disruption of the tight junction will apparently stimulate an immunological response.

The immunological response to infection results in the production of T and B cells.

Since the integrity of the blood-brain barrier is compromised, there will be permeation of the B-cells into the central nervous system, and this will invariably, result in amplification of the immune response by the microglia, which is responsible for cerebral immunity.

Microglia release cytokines, chemokines, inflammatory mediators, reactive oxygen species, and reactive nitrogen species.

One of the most important cytokines is the enzyme known as IDO, indolamine oxygenase.

IDO is said to reduce 5HT production, which is responsible for serotonin production and also most importantly, there is increase quinonic acid production.

Quinonic acid production results in glutamate release and reduced Brain Derived Neurotrophic factor, BDNF, production. The former results in excitotoxicity; while the latter results in inhibited synaptogenesis and aberrant protection of the brain neurons.

Triggering of astrocytes by the penetration of B-cells into the Central Nervous system, during disruption of the tight junction, by microbial infections, could also produced Tissue Necrotic Factor, TNF.

TNF kill oligodendrocytes, which is responsible for myelination of the neurons.

Killing the oligodendrocytes is very vital as myelin sheaths are protective coverings of the neurons.

The myelin sheaths also have electrical conductive characteristics across the axons of the myelinated neuron.

TNF produced by the astrocytes could also kill mitochondria, which is the power house of the cell (neuron).

The effect, of this, is responsible for production of reactive oxygen and nitrogen species.

B-cells also produce Brain Reactive antibodies, which could act in four (4) different mechanisms, which are:

(i) Blocking neurotransmitters binding to their receptors on the neural membrane.

(ii) Enhancement of glutamate receptor activity, this culminates in excitotoxicity.

(iii) Blocking of ion channels thereby, compromising electrical activity across neurons.

(iv) Generation of intracellular interference resulting in apoptosis (programmed cell death), this is also connected to damage to oligodendrocytes.

Microbial Infections could result in immunological response due to attack on the mitochondria, the power house of the cell and when this occur, there is usually the formation of Pathogen Associated Molecular Pattern (PAMP).

The formation of PAMP will result in activation of inflammatory response, resulting from binding of the PAMP to the toll-like receptors, TLP.

The TLP binding set up cascade, which ends with the formation of Necrotic Factor kappa Beta (NF-κß).

NF-κß is a transcription factor, that produces cytokines, which are aimed at destroying, the pathogens and these cytokines could destroy brain tissue, if the process is prolonged.

However, there are regulatory factors of T cells (Tregs), which puts the immunological response in check, in order to prevent collateral damage.

Therefore, the research aims to establish:

(i) Production of proinflammatory cytokine, IL-1β, IL-6, IFN-γ, TNF-α. These proinflammatory biomarkers are upregulated in microbial infections.

(ii) Downregulation of IL-10, IL-12p40, TGF-β. These are anti-inflammatory cytokines, which helps in preventing collateral damage of brain tissues, due to prolonged inflammation.

Note

-IL-1β and TNF-α initiate maintenance and persistence of inflammation.

-Tregs have roles in suppressing immune responses stimulation and also in the production of suppressive cytokines. (IL-10 and TGF-β).

The extent/degree of production of pro and anti-inflammatory biomarkers is suggestive of neuroinflammatory response of the blood-brain barrier to microbial infections.

Neuroinflammation is a major event that characterises Neurodegenerative diseases.