Neuroinflammation and its Influence on 'Non-Inflammatory' Neurological Diseases

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Arguably, the development of treatments for neurological diseases is one the most challenging fields in life sciences. This is supported by the very apparent limited success of therapeutics for certain neurological conditions; for example, despite knowing that amyloid plaques are a hallmark of Alzheimer's disease, therapeutics targeted to amyloid clearance have not shown any success in clinical trials.[1] Recent evidence is now indicating that inflammation is involved in all neurological disorders, even those considered to be 'non-inflammatory', such as epilepsy, Alzheimer's disease, stroke, migraine, and many more.[2]

The brain is separated from the rest of the body by the blood-brain barrier, and even has its own immune cells: microglia. When activated, B and T lymphocytes situated in the body release inflammatory markers that pass through the blood-brain barrier and activate the microglia.[2] Because microglia play such a crucial role in the maintenance of a healthy brain, a change in their daily activities, such as alterations in received inflammatory markers or its own aberrant behavior, could result in neurological disorders.

Evidence has already identified such changes; it has been observed that a rapid increase in inflammatory markers occurs minutes after acute injury of the brain, for example from stroke or brain trauma.[2] Furthermore, increased microglia activity has been detected in chronic neurological disorders, including movement disorders, motor neuron disease, and migraines.[2] But one question remains to be answered: is this a curative or causative change, or perhaps even both?

Epilepsy

It is widely accepted that many factors can be attributed to epilepsy-epileptogenesis, for example genetic predisposition.[3] Evidence has identified a role for neuroinflammation in the cause and consequence of epileptic seizures, adding confusion to this complex disorder. IL-1β, TNF, IL-6, prostaglandin E2, and complement cascade are all upregulated in microglia and contribute to seizure generation.[2] Furthermore, their activities are not limited to this initial seizure; consequences of increased inflammatory signaling in the brain can alter synaptic excitability, eventually resulting in chronic epilepsy and the increased likelihood of pharmacoresistance to antiepileptic drugs.[2]

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Alzheimer's Disease

Much evidence suggests that neuroinflammation is involved in the pathogenesis of Alzheimer's disease, causing both negative and positive consequences.[4] Generally, inflammatory mediators aid the eradication of pathogens in the brain. In Alzheimer's disease, the inflammatory mediators that reactive astrocytes secrete can actually break down the amyloid plaques and the astrocytes themselves can ingest amyloid β, leading to its degradation.[5] However, despite this seemingly positive behavior, there are other limitations; reactive astrocytes can secrete enormous quantities of amyloid β, and inflammatory mediators can compromise neuronal function and cause neuronal cell death, adding to the disease burden.[4,5]

Biomarkers

To develop better treatments and improve how disease progression is monitored, biomarkers need to be characterised on a patient level. In epilepsy, viable biomarkers could be used to help predict when a seizure is going to occur and the most likely cause, thus offering the chance to prevent seizure onset and to minimise their long-term effects, ultimately improving patient quality of life. The identification of biomarkers in pre-symptomatic Alzheimer's disease will allow the initiation of interventions earlier to maximise the chance of halting or slowing the disease progression. Not only would this open new avenues of therapeutic research to be explored, but current ineffective therapeutics could have new potential.

Conclusion

Does recent evidence conclude that neurological disorders are the result of unbalanced immune system mechanisms? If so, then current treatments and our understanding of the pathogenesis of neurological disorders need to be rethought. Future research into the relationship between inflammation and neurological disorders could illuminate answers to questions we have been asking for decades, and provide new rationale for potential therapeutics for diseases in which treatment success has not yet been achievable.

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