Neuroinflammatory biomarkers

Neuroinflammatory biomarkers are specific molecules or indicators that are associated with inflammatory processes within the central nervous system (CNS), which includes the brain and spinal cord. These biomarkers are measured in various biological samples such as cerebrospinal fluid (CSF), blood, and brain tissue, and they can provide insights into the presence, severity, and progression of neuroinflammatory conditions. Neuroinflammation is a complex process involving immune cells, cytokines, and other molecules, and its dysregulation is implicated in various neurological disorders.

Examples

C-reactive Protein (CRP): CRP is a general marker of inflammation, and elevated levels in the blood can indicate systemic inflammation. While it's not specific to the CNS, elevated CRP levels might suggest an ongoing inflammatory process that could impact the brain.

Interleukins (ILs): Interleukins are signaling molecules that play a key role in the immune response. Elevated levels of certain interleukins, such as IL-6 and IL-1β, have been associated with neuroinflammation and conditions like multiple sclerosis (MS) and neurodegenerative diseases.

Tumor Necrosis Factor-alpha (TNF-α): TNF-α is another cytokine involved in the immune response. It can contribute to inflammation and has been linked to neuroinflammatory conditions like Alzheimer's disease and Parkinson's disease.

Matrix Metalloproteinases (MMPs): MMPs are enzymes that break down components of the extracellular matrix. Increased levels of MMPs are found in neuroinflammatory conditions like multiple sclerosis and stroke, suggesting their involvement in tissue damage.

S100B: S100B is a protein released by astrocytes (a type of glial cell in the brain) in response to brain injury and inflammation. Elevated S100B levels are associated with various neurological disorders, including traumatic brain injury and some neurodegenerative diseases.

Myelin Basic Protein (MBP): MBP is a protein found in the myelin sheath that covers nerve fibers. Elevated levels of MBP in the CSF can indicate myelin damage, as seen in conditions like MS.

Neopterin: Neopterin is produced by immune cells in response to inflammation and oxidative stress. Elevated neopterin levels in CSF and blood have been found in conditions like HIV-associated neurocognitive disorders and other neuroinflammatory conditions.

Glial Fibrillary Acidic Protein (GFAP): GFAP is a protein found in astrocytes. Elevated levels of GFAP in CSF or blood can indicate astrocytic activation, which occurs in response to CNS injury and inflammation.

Amyloid Beta and Tau Proteins: While primarily associated with Alzheimer's disease, abnormal levels of these proteins in CSF and blood can also reflect neuroinflammation and neuronal damage.

Chemokines: Chemokines are signaling proteins that attract immune cells to sites of inflammation. Some chemokines are implicated in neuroinflammatory disorders like MS.

Reactive oxygen species (ROS): ROS are highly reactive molecules that can cause oxidative damage to cells. Increased levels of ROS have been observed in patients with traumatic brain injury and stroke and have been linked to cerebral autoregulation dysfunction.

Overall, these candidate neuroinflammatory markers may provide insights into the underlying mechanisms of cerebral autoregulation dysfunction in acute brain injury and could potentially serve as targets for therapeutic interventions. However, further research is needed to fully understand the complex relationship between neuroinflammation and cerebral autoregulation dysfunction in these conditions.

Acute activation of innate immune response in the brain, or neuroinflammation, protects this vital organ from a range of external pathogens and promotes healing after traumatic brain injury. However, chronic neuroinflammation leading to the activation of immune cells like microglia and astrocytes cause damage to the nervous tissue, and it is causally linked to a range of neurodegenerative diseases such as Alzheimer's diseases (AD), Multiple Sclerosis (MS), Parkinson's disease (PD), and many others. While neuroinflammation is a key target for a range of neuropathological diseases, there is a lack of effective countermeasures to tackle it, and existing experimental therapies require fairly invasive intracerebral and intrathecal delivery due to difficulty associated with the therapeutic crossover between the blood-brain barrier, making such treatments impractical to treat neuroinflammation long-term. Sharma et al. present the development of an optimal neurotherapeutic using a Nanoligomer Discovery Engine, by screening downregulation of several pro-inflammatory cytokines (e.g., Interleukin-1β or IL-1β, tumor necrosis factor-alpha or TNF-α, TNF receptor 1 or TNFR1, Interleukin 6 or IL-6), inflammasomes (e.g., NLRP1), key transcription factors (e.g., nuclear factor kappa-B or NF-κβ) and their combinations, as upstream regulators and canonical pathway targets, to identify and validate the best-in-class treatment. Using our high-throughput drug discovery, target validation, and lead molecule identification via a bioinformatics and artificial intelligence-based ranking method to design sequence-specific peptide molecules to up- or downregulate gene expression of the targeted gene at will, they used the discovery engine to perturb and identify most effective upstream regulators and canonical pathways for therapeutic intervention to reverse neuroinflammation. The lead neurotherapeutic was a combination of Nanoligomers targeted to NF-κβ (SB.201.17D.8_NF-κβ1) and TNFR1 (SB.201.18D.6_TNFR1), which were identified using in vitro cell-based screening in donor-derived human astrocytes and further validated in vivo using a mouse model of lipopolysaccharide (LPS)-induced neuroinflammation. The combination treatment SB_NI_111 was delivered without any special formulation using a simple intraperitoneal injection of low dose (5 mg/kg) and was found to significantly suppress the expression of LPS-induced neuroinflammation in mouse hippocampus. These results point to the broader applicability of this approach towards the development of therapies for chronic neuroinflammation-linked neurodegenerative diseases, sleep countermeasures, and others, and the potential for further investigation of the lead neurotherapeutic molecule as reversible gene therapy [1)].

Inflammatory response plays a vital role in the pathological mechanism of intracerebral hemorrhage. It has been recently reported that neutrophil to lymphocyte ratio (NLR) could represent a novel composite inflammatory marker for predicting the prognosis of intracranial hemorrhage (ICH).

The inflammatory response in the cerebral cortex serves an important role in the progression of

secondary injury following traumatic brain injury (TBI).

The primary physical effect of the inflammatory response is for blood circulation to increase around the infected area. In particular, the blood vessels around the site of inflammation dilate, permitting increased blood flow to the area. Gaps appear in the cell walls surrounding the infected area, allowing the larger cells of the blood, i.e. the immune cells, to pass. As a result of the increased blood flow, the immune presence is strengthened. All of the different types of cells that constitute the immune system congregate at the site of inflammation, along with a large supply of proteins, which fuel the immune response. There is an increase in body heat, which can itself have an anti-biotic effect, swinging the balance of chemical reactions in favour of the host. The main symptoms of the inflammatory response are as follows.

The tissues in the area are red and warm, as a result of the large amount of blood reaching the site.

The tissues in the area are swollen, again due to the increased amount of blood and proteins that are present.

The area is painful, due the expansion of tissues, causing mechanical pressure on nerve cells, and also due to the presence of pain mediators.

Once the inflammatory process has begun, it continues until the infection that caused it has been eradicated. Phagocytes continue to consume and destroy bacteria, the acquired immune system binds and disposes of harmful toxins. Pus is produced, pus being the debris that is left over from the battle between the invader and the immune system. The colour of the pus depends on the organism causing the infection.

Chronic inflammation has earlier been detected in ruptured intracranial aneurysms. A study detected both dental bacterial DNA and bacterial-driven inflammation in ruptured intracranial aneurysm walls.

Pathogenic inflammation contributes to aneurysm formation by mediating the destruction of the endothelium and the extracellular matrix and promoting pathogenic proliferation of smooth muscle cells. In mouse models, tolerance-inducing regulatory T cell (Treg) cells could significantly reduce the incidence and severity of aneurysms. Hence, it should be investigated why in human intracranial aneurysm (IA) patients, Treg cells failed to provide protection against aneurysm formation. In this study, the frequency and function of Treg cells in IA patients were examined. The frequency of Foxp3+ Treg cells was significantly lower in IA patients than in healthy controls. This downregulation was only specific to the Treg subset of CD4+ T cells, as the frequency of total CD4+ T cell was increased in IA patients. Subsequently, we found that the expressions of Treg-associated molecules, including Foxp3, CTLA-4, TGF-β, and IL-10, were significantly lower in Foxp3+ Treg cells from IA patients than in Foxp3+ Treg cells from healthy controls. In both healthy controls and IA patients, Foxp3+ Treg cells were distinguished into a more potent Tim-3+ subset and a less potent Tim-3- subset. The Tim-3+ subset of Foxp3+ Treg cells was significantly reduced in IA patients. Signaling via IL-2, IL-7, IL-15 and IL-21 was shown to promote Tim-3 upregulation in CD4+ and CD8+ T cells. Interestingly, we found that Tim-3 could be upregulated in Treg cells via the same mechanism, but compared to the Treg cells from healthy controls, the Treg cells from IA patients presented defects in Tim-3 upregulation upon cytokine stimulation. Together, our results demonstrated that Foxp3+ Treg cells in IA patients presented reduced function, which was associated with a defect in Tim-3 upregulation [2)].

Neuroinflammation is inflammation of the nervous tissue. It may be initiated in response to a variety of cues, including infection, traumatic brain injury, toxic metabolites, or autoimmunity.

see Inflammatory response.

In the central nervous system, including the brain and spinal cord, microglia are the resident innate immune cells that are activated in response to these cues.

The CNS is typically an immunologically privileged site because peripheral immune cells are generally blocked by the blood brain barrier (BBB), a specialized structure composed of astrocytes and endothelial cells.

However, circulating peripheral immune cells may surpass a compromised BBB and encounter neurons and glial cells expressing major histocompatibility complex molecules, perpetuating the immune response.

Although the response is initiated to protect the central nervous system from the infectious agent, the effect may be toxic and widespread inflammation as well as further migration of leukocytes through the blood brain barrier.

The onset of aneurysmal subarachnoid hemorrhage (aSAH) elicits activation of the inflammatory cascade, and ongoing neuroinflammation is suspected to contribute to secondary complications, such as vasospasm and delayed cerebral ischemia.

In a review, of Watson et al. analyze the extent literature regarding the relationship between neuroinflammation and cognitive dysfunction after aSAH. Pro-inflammatory cytokines appear to play a role in maintaining normal cognitive function in adults unaffected by aSAH. However, in the setting of aSAH, elevated cytokine levels may correlate with worse neuropsychological outcomes. This seemingly dichotomous relationship between neuroinflammation and cognition suggests that the action of cytokines varies, depending on their physiologic environment. Experimental therapies which suppress the immune response to aSAH appear to have a beneficial effect on cognitive outcomes. However, further studies are necessary to determine the utility of inflammatory mediators as biomarkers of neurocognitive outcomes, as well as their role in the management of aSAH [3)].

Neuroinflammation is a crucial factor contributing to neurological injuries after intracerebral hemorrhage (ICH).

Neuroinflammation has been increasingly implicated as a pathological mechanism in dementia and demonstration that it is a key event accelerating cognitive or functional decline would inform novel therapeutic approaches, and may aid diagnosis. Much research has therefore been done to develop technology capable of imaging neuroinflammation in vivo.

The majority of the studies used positron emission tomography (PET) imaging of the TSPO microglial

marker and found increased neuroinflammation in at least one neuroanatomical region in dementia patients, most usually Alzheimer's disease, relative to controls, but the published evidence to date does not indicate whether the regional distribution of neuroinflammation differs between dementia types or even whether it is reproducible within a single dementia type between individuals. It is less clear that neuroinflammation is increased relative to controls in mild cognitive impairment than it is for dementia, and therefore it is unclear whether neuroinflammation is part of the pathogenesis in early stages of dementia. Despite its great potential, a review of Stefania et al. demonstrates that imaging of neuroinflammation has not thus far clearly established brain inflammation as an early pathological event. Further studies are required, including those of different dementia subtypes at early stages, and newer, more sensitive, PET imaging probes need to be developed [4].

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