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EDITORIAL

Neuroinflammation, the thread connecting neurological disease

Cluster: "Neuroinflammatory mechanisms in neurodegenerative disorders"

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The term neuroinflammation broadly identifies the response of the central nervous system (CNS) to injury and disease. It encompasses cascades initiated by the coordinated action of neural and non-neural cells, all directed towards the ultimate goal of protecting the CNS and preserving its integrity. Because of its complexity and multifactorial nature, it is easy to understand why even a minimal unbalance in any of its components may result in unwanted consequences that hinder CNS recovery, rather than promoting it. Since this maladaptive outcome often prevails, the term neuroinflammation has, over time, taken a negative connotation. However, in recent years, partly due to the failure of highly anticipated clinical trials targeting presumptive pro-inflammatory neurotoxic molecules (e.g., the lenercept trial with a TNF inhibitor for multiple sclerosis [1]), it has become apparent that this one-sided view of the neuroinflammatory process is rather restrictive, if not inaccurate. In vivo studies using gene-targeting approaches and next-generation transcriptomics have uncovered that abolishing or inhibiting signals long considered as the prototypical drivers of neuroinflammation did not necessarily result in CNS protection. On the contrary, it occasionally led to exacerbation of the damage [2, 3]. This has fueled a renewed interest in the field, with a flurry of studies investigating the mechanisms underlying the neuroinflammatory process from different perspectives. What we learned is that the same cascade/molecule may be detrimental or protective to CNS recovery depending upon time and place of action, as well as the cellular source it derives from. Furthermore, the same cell population can adapt its function to the composition of the surrounding environment, thereby sustaining or suppressing the neuroinflammatory response. Given the multiple factors and pathways involved in this process, as well as its various manifestations, some have suggested that the use of the term neuroinflammation may need to be revisited because it is misrepresentative of the pathology of certain CNS disorders [4].

While our understanding of the neuroinflammatory mechanisms is in constant evolution and remodeling, there is little doubt that neuroinflammation is a prominent feature of virtually every neurological/neurodegenerative disorder, the common thread that connects traumatic, neurodegenerative, and psychiatric CNS pathologies. The purpose of the review cluster *"Neuroinflammatory mechanisms in neurodegenerative disorders"* published in this issue of *Acta Neuropathologica* is to provide an overview of the state of the art on neuroinflammation in the context of a broad spectrum of neurological disorders, form traumatic (spinal cord injury (SCI) [5], and traumatic brain injury (TBI) [6]), to chronic neurodegenerative (multiple sclerosis (MS) [7], and amyotrophic lateral sclerosis (ALS) [8]) and ischemic multifactorial (stroke) [9]. The authors paid particular attention to address emerging evidence of the contrasting roles that specific molecules and cell types play in the pathophysiology of each disease. Major recurrent themes across all pathologies are: (1) *cytokines* are center stage: whether in a damaging or protective capacity, or both, they are implicated in all phases of disease, acute and chronic, with long-range effects that span cell death and survival, neuronal damage and repair, demyelination/remyelination, and vascular remodeling; (2) *glial activation* occurs early on and persists chronically; (3) *neuro–immune interactions* between infiltrating peripheral

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immune cells and CNS elements sustain and propagate the neuroinflammatory cascade.

These points are especially evident in MS and its widely adopted animal model experimental autoimmune encephalomyelitis (EAE), discussed by Brambilla [7]. In this review article, Brambilla focused on the contribution of astrocytes to the neuroinflammatory response in MS and EAE, from their temporal profile of activation during disease onset and evolution, to the soluble mediators they release and the cellular processes they affect. The detrimental and beneficial roles of activated astrocytes are analyzed, drawing a parallel between the human condition and the animal model, which has been used quite successfully in aiding our understanding of MS immunopathology. What emerges is that, ultimately, a positive correlation exists between inflammatory astroglial activation and disease severity and progression, suggesting that the protective/reparative properties of activated astrocytes may not be enough to offset their neurotoxic effects. This supports the idea that aiming at an overall suppression of astroglial activation may prove beneficial in MS. Importantly, this review offers a unique perspective on how astroglial activation can be used as a disease biomarker, so that non-invasive measurements of astroglial activation in patients may become a reliable tool to monitor severity, predict progression, and possibly test the efficacy of MS therapeutics.

Cytokines, glial activation and neuro-immune crass-talk emerge as prominent features of ALS and frontotemporal dementia (FTD) reviewed in this issue by McCauley and Baloh [8]. The authors comprehensively addressed the participation of activated microglia and astroglia to ALS/FTD pathology, which occurs in the CNS of patients and in animal models with minimal immune cell infiltration, indicating a more prominent role for the innate, rather than adaptive, immune response in the disease. The theme of a dichotomous role of activated glia emerges once again. Indeed, the authors discussed evidence that activated glia observed in proximity of motor neurons prior to onset of motor symptoms produce detrimental proinflammatory mediators, but is also important for neuronal recovery. Similar to MS, evidence from animal models (particularly the SOD1 model) underscore how glial activity may be viewed as detrimental when considered across the full duration of the disease, but may be supporting protective functions at specific stages and locations.

Neuroinflammation in ischemic stroke is here reviewed by Lambertsen et al. [9]. The focus of their overview is on cytokines, specifically TNF, IL1β, IL6, and IL10, which in human and experimental stroke are produced and released by resident glia and infiltrating immune cells, predominantly neutrophils and macrophages. As these cytokines have pro-inflammatory and immunomodulatory roles, they contribute to infarct expansion but also to its resolution. A comprehensive and in-depth analysis of the ongoing studies, pre- clinical and clinical, with various modulators of these cytokines is presented. Clinical trials with IL1Ra for selective inhibition of IL1β have progressed further and show some promise. However, the mixed outcomes of the vast majority of the studies interfering with cytokine signaling underscore the challenges of targeting neuroinflammation for stroke therapy, a recurrent theme across all neurological diseases.

The role of neuroinflammation in traumatic CNS injury is addressed in the contributions of Morganti-Kossmann et al. [6], and Milich et al. [5]. Although the etiology of traumatic disorders differs significantly from that of the classic chronic neurological syndromes, as they are initiated not by intrinsic CNS dysfunction but external factors acting on an otherwise healthy CNS, the cascades that follow share remarkable similarities. In reviewing the current knowledge in TBI, Morganti-Kossmann et al., delve deeply into the multitude of neuroinflammatory mechanisms initiated by trauma, once again bringing the role of activated glia and their products to the forefront. Astrocytes and microglia are discussed, both in their detrimental and protective capacity, reviewing studies in animal models and in patients. A very important point this review highlights is the concept that latent chronic inflammation, which persists indefinitely in TBI patients, is the culprit, or at least a major component, of the long-term neurological conditions associated with TBI. These include epilepsy, depression, metabolic and neuroendocrine dysfunction, as well as chronic traumatic encephalopathy and Alzheimer's, all comprehensively discussed in this work. Finally, the influence of age and sex on the neuroinflammatory response is tackled.

Rather than classic neuroinflammatory mechanisms of SCI, including astroglia and microglia activation, Milich et al. specifically discussed the role of peripherally derived macrophages. The contribution of macrophages to SCI pathobiology, both in the evolution of the damage and its repair, has received increasing attention recently as it has become apparent that various pools of peripherally derived macrophages exist in the injured spinal cord (splenic, and bone marrow-derived), including possibly a self-renewing population, and they may have different functions. Acutely, macrophages sustain neurotoxic processes by releasing pro-inflammatory cytokines and nitric oxide, but they also eliminate detrimental cellular debris via efficient phagocytosis. Hence, the duplicitous nature of their functions complicates matters when it comes to devising targeted therapeutic strategies, and calls for continuous investigations into the differential cellular properties of each population.

In conclusion, the panoramic overview of neuroinflammation provided by the combined contributions in this review cluster offers key take-home messages. Above all, neuroinflammation is a complex, multifaceted process

accompanying neurological disease where toxic and reparative signals coexist. As a consequence, targeting neuroinflammation for therapeutic purposes is attractive, particularly because of the potential effectiveness across multiple disorders, but challenging. Ultimately, time is of the essence, and inhibition or activation of neuroinflammatory cascades will require precise temporal interventions, tailored to each specific disease. Finally, to favorably alter the neuroinflammatory process a combinatorial approach may be in order, whereby multiple signals are targeted simultaneously to elicit a net beneficial effect.

References

1. Group, T.L.M.S.S.G.a.T.U.o.B.C.M.M.A (1999) TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 53:457–465
2. Liu J, Marino MW, Wong G, Grail D, Dunn A, Bettadapura J et al (1998) TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination. Nat Med 4:78–83
3. Lambertsen KL, Clausen BH, Babcock AA, Gregersen R, Fenger C, Nielsen HH et al (2009) Microglia protect neurons against ischemia by synthesis of tumor necrosis factor. J Neurosci 29:1319–1330
4. Masgrau R, Guaza C, Ransohoff RM, Galea E (2017) Should we stop saying 'Glia' and 'Neuroinflammation'? Trends Mol Med 23:486–500
5. Milich LM, Ryan CB, Lee JK (2019) The origin, fate, and contribution of macrophages to spinal cord injury pathology. Acta Neuropathol. https://doi.org/10.1007/s00401-019-01992-3
6. Morganti-Kossmann MC, Semple BD, Hellewell SC, Bye N, Ziebell JM (2018) The complexity of neuroinflammation consequent to traumatic brain injury: from research evidence to potential treatments. Acta Neuropathol. https://doi.org/10.1007/s00401-018-1944-6
7. Brambilla R (2019) The contribution of astrocytes to the neuroinflammatory response in multiple sclerosis and experimental autoimmune encephalomyelitis. Acta Neuropathol. https://doi.org/10.1007/s00401-019-01980-7
8. McCauley ME, Baloh RH (2018) Inflammation in ALS/FTD pathogenesis. Acta Neuropathol. https://doi.org/10.1007/s00401-018-1933-9
9. Lambertsen KL, Finsen B, Clausen BH (2018) Post-stroke inflammation-target or tool for therapy? Acta Neuropathol. https://doi.org/10.1007/s00401-018-1930-z