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Review

Therapies negating neuroinflammation after brain trauma

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ABSTRACT

Traumatic brain injury (TBI) elicits a complex secondary injury response, with neuroinflammation as a crucial central component. Long thought to be solely a deleterious factor, the neuroinflammatory response has recently been shown to be far more intricate, with both beneficial and detrimental consequences depending on the timing, magnitude and specific immune composition of the response post-injury. Despite extensive preclinical and clinical research into mechanisms of secondary injury after TBI, no effective neuroprotective therapy has been identified, with potential candidates repeatedly proving disappointing in the clinic. The neuroinflammatory response offers a promising avenue for therapeutic targeting, aiming to quell the deleterious consequences without influencing its function in providing a neurotrophic environment supportive of repair. The present review firstly describes the findings of recent clinical trials that aimed to modulate inflammation as a means of neuroprotection. Secondly, we discuss promising multifunctional and single-target anti-inflammatory candidates either currently in trial, or with ample experimental evidence supporting clinical application.

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Contents

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1. Introduction

Inflammatory processes stimulated by traumatic brain injury (TBI) comprise a vast array of cellular and soluble mediator-regulated events. Immune mediators include pro-inflammatory and anti-inflammatory cytokines that initiate, regulate and terminate the inflammatory processes as well as a specific subgroup of chemotactic cytokines named chemokines that play a critical role in stimulating the activation and migration of immune cells towards the injured, inflammatory foci (for review: Semple et al. (2010) and Ziebell and Morganti-Kossmann (2010)). Cytokines are released by peripheral immune cells including leukocytes (macrophages and neutrophils), lymphocytes as well as intrinsic cells of the nervous system such as microglia, the macrophage counterpart of the nervous system, astrocytes, endothelial cells of the cerebrovasculature and even neurons (for more details see: Semple et al. (2010), Bergold (2015), Hellewell and Morganti-Kossmann (2012) and Woodcock and Morganti-Kossmann (2013)). Activated immune cells from the blood stream enter the brain by crossing the blood–brain barrier (BBB) whereas resident glial cells reach the injured site via migration through various brain regions. The complexity of this response is evident by a robust upregulation of almost every measured cytokine after TBI (Ziebell and Morganti-Kossmann, 2010).

In the early 1990s it was unclear whether the brain was capable of mounting its own immune response, and it was believed that both cytokines and leukocytes/lymphocytes arising from the periphery entered the central nervous system (CNS) via the disruption of the BBB. Towards the end of the decade, however, experimental evidence demonstrated that glial cells and even neurons produce a large number of cytokines as communication tools connecting the nervous with the immune system in disease and injury states (Morganti-Kossmann et al., 2002).

Historically, research surrounding the role of brain inflammation following head trauma mostly focused on the acute and sub-acute post-traumatic phases. Cerebrospinal fluid (CSF), drained from the ventricles following implantation of external ventricular devices, provides a rich resource to monitor cytokine changes in patients with severe brain injuries. In early human studies, we and others found elevated cytokine and chemokine levels (including Interleukin (IL)-6, tumor necrosis factor (TNF), Transforming Factor (TGF) 1, IL-10, CCL2 and IL-8) in matched serum and CSF samples after severe TBI, typically peaking within the first 24–48 h and decreasing over several weeks (Csuka et al., 1999; Semple et al., 2010a; Kossmann et al., 1997). From these studies, it was evident that CSF cytokine concentrations abundantly surpassed the levels measured in matched serum samples; a strong indicator of intrathecal cytokine synthesis (Kossmann et al., 1997, 1996). A robust cytokine production after TBI was more recently confirmed by examination of postmortem human brains from individuals who deceased as a consequence of TBI. In these samples, an elevation of both protein and mRNA levels of key cytokines was detected within minutes after the accident, lasting up to 5 days post-trauma/mortem, the latest available time point in our patient cohort (Frugier et al., 2010). This demonstrated cytokine spike correlated with tissue changes including increased GFAP