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Overcoming trivialization: The neuroimmune response after acute central nervous system injury

Neuroimmunology has classically been focused on chronic inflammatory central nervous system (CNS) disease. Only more recently have neuroimmune interactions after acute CNS injury become the subject of more systematic investigations. The underlying reasons can be traced back to oversimplifications fueled by attempts to classify neuroinflammation into a binary of good versus bad. Traditionally, acute injury to the CNS was considered a condition primarily characterized by neuroaxonal injury caused by direct trauma or loss of trophic support. Local immune responses were long considered to be a bystander phenomenon.

However, perplexing effects such as the promotion of axon outgrowth/regeneration with concurrent neurotoxicity were already being reported in the *Journal of Neuroimmunology* more than 20 years ago (Hirschberg et al., 1994) and blurred a clear perspective with regard to a therapeutic use. Propagated nerve fiber outgrowth contrasted by larger tissue damage (Gensel et al., 2009) represented an obstacle for immunomodulatory therapy until today (Fig. 1). The failure of unselective immunomodulatory therapy, such as high-dose steroids in larger traumatic brain injury (TBI) and spinal cord injury (SCI) phase III trials, further supported the notion of a response that was difficult or even futile to treat.

Additionally, neuroimmunological and neuropathological textbooks understated neuroimmune interactions. Neuropathological textbooks long upheld the view that the local inflammatory response elicited after an acute CNS injury was self-limiting and resolved within a short period of time, and was therefore unlikely to follow an active neuroimmunopathological process. However, in the early 2000's neuropathological studies have provided evidence that the inflammatory response is not short-lived and is characterized by a sustained plateau of accumulated inflammatory cells that can be detected at the lesion site for months and even years in patients after stroke, traumatic brain injury, or spinal cord injury (Fleming et al., 2006; Schwab et al., 2000; Schwab et al., 2002). This sterile local inflammation is mostly composed of activated, lipid-laden microglia/macrophages engrafting at the lesion site, behind the blood-brain/spinal cord barrier (BB/SCB). Facilitated by an incompletely closed BB/SCB, allowing for late infiltration of blood-derived immune cells, these lesional cells are able to sense and respond to systemic humoral stimuli even long after injury.

A fundamental discovery characterizing CNS-immune interaction as becoming maladaptive after acute CNS injury relates to the systemic immune system function. Acute CNS lesions trigger a CNS injury-induced immune deficiency syndrome (CIDS) (Meisel et al., 2005). This neurogenic immune deficiency is mediated by the decentralized autonomic nervous system (Zhang et al., 2013) and a sympathetic-endocrine reflex (Prüss et al., 2017). It is functionally relevant, blunts host defense, and thereby facilitates the development of infections (Brommer et al., 2016), which in turn drives mortality and disability (Kopp et al., 2017).

This special issue focusing on the *Neuroimmunology of acute CNS lesions* outlines several key aspects of the emerging maladaptive immune responses. One report investigates the application of a putative CIDS treatment using an FDA-approved drug established for other secondary immune deficiency syndromes (Dames et al., 2018); another provides novel angles focusing on the spleen as the largest secondary immune organ becoming decentralized due to pre-ganglionary sympathetic injury after high thoracic complete spinal cord injury (T5 and rostral; Noble et al., 2018). The discovery of CIDS serves as an example of the clinical relevance of neuroimmune interactions after acute CNS injury contributing to post-CNS injury disease. This special issue also illustrates additional important aspects with regard to microthrombus formation in and beyond the penumbra (Albert-Weissenberger et al., 2019), cellular immunology relating to the innate and adaptive immune system (Needham and Menon, 2019) and their respective effector cells (such as T cells; Cramer et al., 2019), infiltrating monocytes (David et al., 2018), and granulocytes (Hermann et al., 2018). The diversification of a dynamic inflammatory response, being less pronounced in the lesion core compared with the penumbra is also illustrated (Horváth et al., 2018). Differences in the immune response between rodent models and human specimens after ischemic CNS injury are highlighted (Wimmer et al., 2018) and serve as a guidepost for the translation of future immunomodulatory interventions toward clinical testing. Endothelial dysfunction represents an early and decisive hallmark driving propagating sterile inflammation after acute CNS injury (Ludewig et al., 2019). Reports surveying ischemic and traumatic CNS injury paradigms are complemented by findings on the acute inflammatory lesion originating from CNS vessels. This primary vasculitis affects the brain, spinal cord, and meninges, resulting in ischemic and hemorrhagic injury (Strunk et al., 2018).

Deciphering the intricate and interdependent aspects of the neuroimmunology, neurobiology, and neurophysiology of acute CNS lesions (Fig. 1) constitutes a logical pathway to develop more mechanistic and target-specific interventions. Here, investigation of the neuroimmune response after acute CNS injury, linearized approaches in order to better investigate the sequence of immunopathological events and their interdependencies, which offers an important advantage when trying to disentangle cause from effect.

While it would be impossible to cover all aspects related to the *Neuroimmunology of acute CNS lesions,* we are confident that we have compiled a selection of interesting and informative articles relevant to a large audience including scientists and clinicians.

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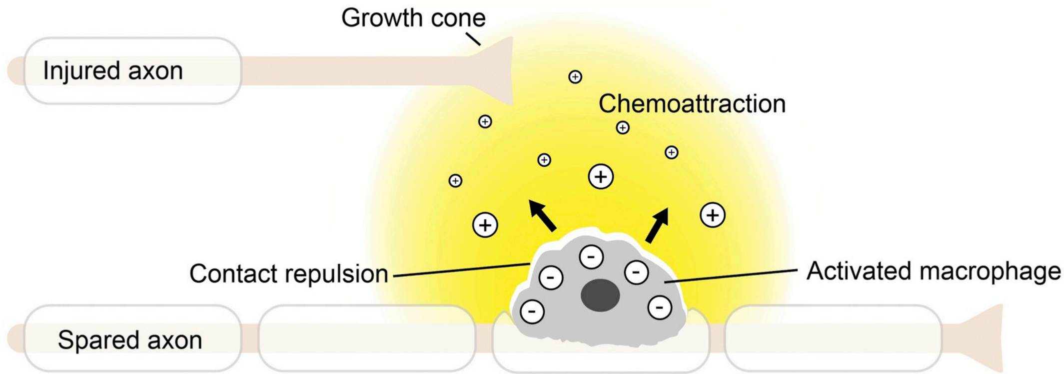

Fig. 1. The inflammatory response exerts a drastic change on the neuroaxonal milieu after acute CNS injury and has been traditionally oversimplified and framed by a "good versus bad" binary. The macrophage response provides a tangible dichotomous example with regard to injury and repair. On one side, activated macrophages provide a milieu conducive to axonal outgrowth (chemoattraction) through the expression of a variety of neurotrophins, including brain-derived neurotrophic factor (BDNF) and Neurotrophin 3 (NT-3; Dougherty et al., 2000; Elkabes et al., 1996). By contrast, at the same time, activated macrophages operate as inflammatory scalpels, causing injury to intact axon fibers (Popovich et al., 2002); for example, being spared from the initial injury. Hence, the classification of the effect depends largely on the read-out. Outgrowth as a measure of repair is propagated ('beneficial'), while injury/damage is exacerbated ('detrimental'). The paradox of macrophage-propagated repair and injury has been recapitulated in vivo (Hirschberg et al., 1994: Gensel et al., 2009). A closer look at activated macrophages and their effect on neuroaxonal outgrowth in CNS lesions offers a more detailed and differential view with relevance to axon elongation in an inflammatory milieu. Whereas macrophage-derived soluble neurotrophins (BDNF, NT3) provide a *chemo*-attractive cure for outgrowth, contact with activated macrophages will result in growth cone collapse and axon retraction (*contact* repulsion; Horn et al., 2008; Busch et al., 2009). Hence, activated macrophages can be classified exerting *chemo*attractive and *contact*repulsive properties for axonal outgrowth (Tessier-Lavigne and Goodman, 1996). Approaches that focus on validated molecular targets, taking into account the rapidly changing neuropathological context, will be required to better decipher the aspects that drive tissue remodeling/repair from concomitant neuro- or glial toxicity. Functional outcomes will be insightful to evaluate net effects and attribute functional relevance to concurrent neurobiological mechanisms. The growing field studying neuroimmune interactions after acute CNS injury offers intriguing paradigms and findings of complementary value to classical autoimmune CNS disease.

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