INVITED COMMENTARY

Targeting “Natural Born Killers” to Modulate Immune Suppression in Neurocritical Care

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Acquired immune suppression is common after acute brain injury [1]. In theory, this may benefit patients by preventing harmful autoimmunity and promoting a pro-regenerative phenotype in the central nervous system (CNS) [2]. Systemic immune suppression leading to opportunistic infection, however, puts patients with acute brain injury at risk of complications, such as prolonged mechanical ventilation and increased length of hospitalization. In addition, the immune response to infection may itself exacerbate brain injury and impair recovery [2–6]. In the current issue of *Neurocritical Care*, Scott et al. [7] address a novel facet of systemic inflammation in patients across the neurologic intensive care unit (ICU): invariant natural killer T (iNKT) cells.

Invariant natural killer T cells are innate lymphoid cells with an invariant T cell receptor- α chain (V α 24–J α 18) that recognizes lipid and glycolipid antigens bound to CD1d on antigen-presenting cells. Although typically making up less than 1% of circulating T lymphocytes, iNKT cells are quickly activated by antigenic stimulation or proinflammatory cytokines to release large quantities of proinflammatory and antiinflammatory mediators, with secondary activation of other cellular targets thereby influencing the nature of the immune response. The cytokine profiles produced by iNKT cells are used to define subtypes that mirror the classical T helper 1 (T_H1) (interferon- γ [IFN γ]), T helper 2 (T_H2) (interleukin-4 and interleukin-10), and T helper 17 (interleukin-17)

classifications of T helper cells. The role of iNKT cells in shaping the immune response has led to investigations of targeted inhibition or reprogramming with specific lipid antigens, checkpoint inhibitors, and cytokines to drive a proinflammatory or antiinflammatory phenotype in diseases such as cancer, sepsis, and asthma [8]. Thus, there is an intriguing potential therapeutic opportunity by manipulating this aspect of the inflammatory response.

Within the ICU population, the immunity of patients with brain injury against infection may be particularly dependent on the proinflammatory or antiinflammatory activity of iNKT cells. In previous work by this group, using a middle cerebral artery occlusion model of stroke in mice, the authors observed an expansion of interleukin-10 producing iNKT cells via a catecholamine-dependent mechanism that predisposed the mice to develop pneumonia and increased mortality [9]. The development of pneumonia could be prevented by β -adrenergic blockade or stimulation of iNKT cells with their canonical glycolipid ligand, α -galactosylceramide, to promote IFN γ secretion. In subsequent studies of adults with traumatic brain injury (TBI), spontaneous subarachnoid hemorrhage (SAH), and stroke, the authors obtained blood samples within 24 h of injury and observed decreased surface expression of human leukocyte antigen-DR on monocytes and B cells but increased expression of the antigen expression molecule for iNKT cells, CD1d. Unlike conditions such as sepsis, however, in which there is expansion of iNKT cell populations, the number of circulating iNKT cells was reduced after TBI and SAH but remained stable after stroke. The percentage of iNKT cells that was activated, determined by CD69 positivity, was increased in these conditions.

In the current study, Scott et al. [7] sought to further characterize iNKT cells and their relationship to circulating T_H1 and T_H2 cytokines in patients with brain injury by prospectively enrolling patients with acute brain

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injury and performing serial blood sampling over 28 days after admission. The cohort of 20 patients included those with TBI, SAH, intracerebral hemorrhage, and ischemic stroke. ICU-relevant controls were enrolled for comparison, along with age-matched healthy volunteers. The authors report that the total number of iNKT cells is decreased in acute neurological injury (it is unclear whether this reflects loss of these cells from the whole body system or sequestration into tissues) and that the percentage of activated iNKT cells by CD69 positivity is increased. Several differences of the cytokine profile, suggesting greater suppression of the T_H1 cytokine response (IFN γ and tumor necrosis factor), were seen in patients with brain injury compared with the ICU control group. Surprisingly, an anticipated increase in T_H2 cytokine levels was not seen in the neuro-ICU patients. Only modest suppression of the T_H2 cytokine, interleukin-4, was noted.

Several limitations of this exploratory analysis should be noted. The small sample size, further complicated by multiple diagnoses, results in there being few patients in each of the diagnostic groups. The differences between the neuro-ICU and general ICU populations regarding iNKT cell numbers and iNKT cell activation were also fairly modest. Although the directionality suggested in the correlation of a T_H2/T_H1 cytokine ratio and the percentage of CD69-positive iNKT cells is interesting, much larger sample sizes will be needed to test hypotheses appropriately regarding potential differences between these groups, such as the impact of β -adrenergic blockade, norepinephrine use, raised intracranial pressure, and craniectomy. Direct measurement of cytokine expression to phenotype in circulating iNKT cells by flow cytometry, rather than cell surface markers, would also strengthen the evidence of iNKT cell polarization contributing to systemic immune suppression.

Studies of iNKT cells in the neuro-ICU might aid in future therapy development to modulate the immunosuppression that follows critical acute CNS insults. Treating patients with iNKT cell antigens, such as α -galactosylceramide to promote NKT1 cytokine production in vitro, has been investigated in the oncology field [10]. However, the impact of promoting systemic production of T_H1 cytokines on secondary brain injury should be considered. Early reports examining the T_H1/T_H2 response in CNS injury suggested a T_H1 -predominant profile [11]. Many proinflammatory cytokines are likely to have concentration-dependent effects in the CNS, in which at lower levels, they promote tissue repair and production of neurotrophic factors, but at higher concentrations, they may exacerbate neurologic damage [2, 12]. As studies like the one by Smith et al. [7] demonstrate, there is clearly a need to

define tissue-specific, as well as systemic inflammatory, phenotypes in our patients with acute brain injury and identify interventions that may optimize the immune response both within and outside of the CNS.

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