A great deal of progress has been made over the past decade in understanding the role of secondary injury in the progression of brain and spinal cord injury, and the innate immune response has emerged as an important potential therapeutic target (e.g. Beattie, 2004; Donnelly and Popovich, 2008). The microglial response to CNS damage and subsequent invasion of the lesion by peripheral macrophages are associated with the production of pro-inflammatory cytokines and related immune effector molecules that can induce cell death through necrosis and apoptosis both in neurons and oligodendrocytes. Brain and spinal cord injury can initiate a long-lasting cascade of oligodendrocyte death that may lead to chronic demyelination, adding to the dysfunction (e.g. Crowe et al., 1997; Beattie et al., 2002), and this cascade is driven at least in part through the actions of immune mediators including pro-inflammatory cytokines (Donnelly and Popovich, 2008). Thus, neuroinflammation has been identified as a target for pharmacological therapies, with some evidence of success in animal models of acute spinal cord injury. For example, the anti-inflammatory antibiotic minocycline has been shown to reduce oligodendrocyte apoptosis and spare function in acute cervical spinal cord injury (Stirling et al., 2004). Neuroinflammation has also been identified as a contributor to cell death in ischaemic stroke and chronic neurodegenerative disorders; and these findings point to the potential commonality of mechanisms underlying cell damage and death in both acute neural injury and slow-developing pathologies like those seen in Alzheimer’s disease and amyotrophic lateral sclerosis. Now, in this issue of *Brain*, Yu et al. (2011) provide evidence that cerebral spondylotic myelopathy, a slow progressive compression injury to the cord and arguably the most prevalent form of spinal cord injury, also involves innate immune responses that contribute to neuronal and oligodendrocyte death, similar to that seen in acute spinal cord injury. Further, they demonstrate that the immunological injury is mediated at least in part by Fas (also known as CD95 or APO-1 receptors) and Fas ligand, components of the immune response known to induce apoptosis. These new results focus attention on the clinical importance of cerebral spondylotic myelopathy, and provide a rationale for targeting cell death by pharmacological neuroprotection in addition to treatment by the usual route of surgical decompression (reviewed in Fehlings and Skaf, 1998).

Cervical spondylotic myelopathy is characterized by progressive stenosis of the cervical canal and compression of the spinal cord due to degenerative changes in the spine, including degeneration of the intervertebral discs, joints and ligaments. Symptoms usually begin after the age of 50 years with slowly progressive neck stiffness, numbness and myelopathy. Human pathological findings include cord flattening, loss of anterior horn cells, demyelination and axonal degeneration (Fehlings and Skaf, 1998). Functional loss has been thought to be due to mechanical disruption of the cord, especially with hyperextension injuries, as well as compression-induced ischaemia.

Fas/CD95 is a receptor that is a member of the tumour necrosis factor (TNF)-α receptor superfamily; it initiates cell death via Fas ligand binding-dependent attraction of Fas-associated protein-containing death domain (FADD) to the CD95 death domain to drive caspase-mediated apoptosis (reviewed in Letellier et al., 2010). In addition to a role in peripheral inflammation, a number of previous studies have implicated this signalling pathway in cell death following spinal cord injury (Casha et al., 2004; Demjen et al., 2004; Ackery et al., 2006). Fas is present on neurons and oligodendrocytes, and may be up-regulated after injury (Ackery et al., 2006), as has been reported for other members of the TNF-α receptor superfamily (e.g. the p75 neurotrophin receptor; Beattie et al., 2002; and TNF receptor 1). Further, Fas ligand may initiate pro-inflammatory cytokine production by binding to Fas on microglia or astrocytes, which could also lead to cell death in the lesion zone.

Yu et al. (2011) found evidence for both Fas ligand and Fas in human cervical spinal cords from patients with significant cervical spondylotic myelopathy that also exhibited the classical pathological signs of neuronal loss and axon degeneration. They also identified ongoing apoptosis of neurons, oligodendrocytes and microglial cells, and these cells often also expressed Fas ligand. Given the similarity of these findings to those of acute spinal cord injury, the authors hypothesize that blockade of Fas ligand might also be a therapeutic strategy in cervical spondylotic myelopathy. While this might seem obvious at first, there are many potential differences in the innate immune response to acute concussion injuries versus the kind of chronic, slow compression seen in cervical spondylotic myelopathy. In order to test the hypothesis, they took advantage of a hyperostotic mouse mutant that...
endogenous oligodendrocyte progenitor cells (Setzu and inflammatory cytokines can have effects not only on oligo-and remyelination in dysfunction in spinal cord injury, and cer-
dendrocyte and neuronal loss. Indeed, the role of demyelination driven by chronic progressive cord compression in cervical spond-
dylotic myelopathy. It would have been interesting to see whether the treated mice had spared myelinated tracts and reduced oligo-
dendrocyte and neuronal loss. Indeed, the role of demyelination and remyelination in dysfunction in spinal cord injury, and cer-
tainly in cervical spondylotic myelopathy, is not fully resolved; and inflammatory cytokines can have effects not only on oligo-
dendrocyte death, but on the proliferation and differentiation of endogenous oligodendrocyte progenitor cells (Setzu et al., 2006). Thus, as in wound healing, the key to optimizing repair may lie in a balance between pro- and anti-inflammatory processes (Kigerl et al., 2009). Further studies of compressive myelopathies in this and other models may help to further our understanding of the roles of oligodendrocyte death and regeneration in recovery from spinal cord injury. For example, studies of oligodendrocyte pro-
genitor cell proliferation and remyelination in models of compres-
sive spinal cord injury are needed in order to determine whether anti-inflammatory drugs might help or hinder endogenous repair. The Yu et al. (2011) results do suggest that even in slow progressive injuries, reduction of inflammation leads to less apoptosis, and so perhaps, less demyelination and consequent axonal damage. However, there is much more to learn about this progressive dis-
order and the role of the innate and adaptive immune responses in the development of myelopathy.

Finally, it is interesting to consider the mechanisms driving Fas ligand and Fas involvement in the slow decay of function in cervical spondylotic myelopathy. Yu et al. (2011) suggest that Fas ligand may be produced by injury-induced inflammation within the injured cord, and that binding of Fas ligand to Fas on neurons and oligo-
dendrocytes can trigger apoptosis. In addition, they provide evidence for microglial activation, which has been shown to produce pro-inflammatory cytokines including TNF-α, interleukin (IL)-1β and IL-6 in acute spinal cord injury. Indeed, many of the apoptotic cells that they labelled were microglia, and activated microglia, are known to undergo apoptosis in response to pro-
inflammatory signals (Miller et al., 2007). Interestingly, another recent study of cervical spondylotic myelopathy in the twy mouse showed increased expression of TNF and TNFR1 correlated with increased apoptosis and cord compression (Inukai et al., 2009). Of course, this expression could be a consequence of Fas ligand activation of microglia; and unfortunately, these authors did not evaluate the effects of blocking TNF or its receptor on cell death or neuro-
logical outcome. However, other recent work also provides evidence for an important role of TNF in cell death after spinal cord injury (e.g. Ferguson et al., 2008). Clearly, multiple aspects of the innate immune response to CNS injury, even if restricted within the TNFR superfamily, provide a multitude of potential therapeutic targets.

A recent examination of the role of Fas ligand/CD95L in myel-
loid cell migration after CNS injury suggests that the story may be even more complicated. In an elegant study of neutrophil and macrophage migration and expression after spinal cord injury, cited by Yu et al. (2011), Letellier et al. (2010) provide convincing evidence that a major source of Fas ligand after spinal cord injury is likely to be from invading immune cells rather than from en-
dogenous CNS microglia or neural cells. Further, these authors suggest that CNS damage may be mediated more by pro-inflammatory cytokines produced in response to peripheral Fas ligand rather than by Fas-mediated apoptosis. Studies of human spinal cord injury agree with animal studies that neutro-
phils are the earliest invaders after spinal cord injury, followed by macrophages (Fleming et al., 2006; Donnelly and Popovich, 2008). The blood-brain barrier is known to be destroyed in acute spinal cord injury, but whether this is true in cervical spondylotic myelopathy is not yet known. In any event, the role of peripheral innate immune responses versus endogenous immune cells in the early secondary injury cascade, and thus the best stra-
gies for anti-inflammatory interventions, remain elusive.

The incidence of cervical spondylotic myelopathy is increasing as the population ages, and the presence of spinal stenosis is a risk factor for more acute contusion injuries to the cord caused by falls in the elderly. Yet, the special features of cervical spondylotic myelopathy versus other causes of spinal cord injury and dysfunc-
tion are relatively unstudied. Thus, the work by Yu et al. (2011) represents a promising trend in translational neuroscience: the de-
velopment of animal models of CNS injury that are driven by unmet needs for information on the aetiology and treatment of growing clinical problems. The twy/twy mouse is one approach, but other translational models of slow compressive injury to the cord will also be needed to provide means for evaluating therapeu-
tic strategies for this increasingly important clinical entity.

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Germinal matrix haemorrhage: destroying the brain’s building blocks

The most skilled stonemasons cannot construct a cathedral without an ample supply of fine granite blocks. Likewise, the human brain cannot be built properly if stocks of neuroglial progenitors (the building blocks of the brain) are depleted by injury during the critical period of progenitor cell proliferation and migration, as occurs in germinal matrix haemorrhage in prematurity.

The article by Prof. Marc Del Bigio (2011), representing the analysis of a career-spanning autopsy cohort of preterm infants with and without germinal matrix haemorrhage, he addresses a persistent clinical concern facing paediatric specialists caring for survivors of prematurity: what are the consequences of germinal matrix haemorrhage on normal brain development at the microanatomic level, and do they explain observed neurodevelopmental and neuroimaging outcome data?

As a serious complication of prematurity, germinal matrix haemorrhage and its frequent accompaniment, intraventricular haemorrhage, have been recognized in the medical literature since the turn of the last century (Corvelaire, 1903). In the period from 1940 to 1970, population studies identified the maternal, obstetric and neonatal risk factors for development of germinal matrix haemorrhage, including vaginal delivery, low birth weight, low Apgar scores, hypoxia and hypercapnea (Bassan, 2009; Ballabh, 2010). Improvements since the 1970s in neonatal intensive care have reduced the incidence of cardiorespiratory complications and increased survival following preterm delivery; however, the overall incidence of intraventricular haemorrhage in very low birth weight infants has remained static over the last two decades (Jain et al., 2009). Thus, intraventricular haemorrhage is still a significant problem affecting >12,000 infants per year in the USA alone (Guyer et al., 1999). The extent of haemorrhage and ventricular dilatation, as detected by cranial ultrasound, continue to predict morbidity and mortality, with ultrasonographic grades III (intraventricular haemorrhage with ventricular dilatation) and IV (intraventricular haemorrhage complicated by periventricular haemorrhagic infarction) having survival rates of 40 and 67%, respectively; of those surviving, 50 and 75% ultimately develop definite neurological sequelae (Volpe, 2008). These sequelae are related to progressive post-haemorrhagic hydrocephalus and the need for shunt placement and maintenance, as well as destruction of projection and association axons traveling through the periventricular zone ipsilateral to a periventricular haemorrhagic infarction (Bassan, 2009). In addition, direct cortical injury, periventricular leukomalacia, and secondary impairment of overlying cerebral cortical development may be significant contributors to a complex constellation of destructive and development-altering influences in the sick preterm neonate (Volpe, 2009b). Subarachnoid blood