

Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade

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The pathophysiology of acute spinal cord injury (SCI) involves primary and secondary mechanisms of injury. Though both mechanisms are involved in the neurological dysfunction in SCI most research however has focused on understanding the pathophysiology of the secondary damage and reducing the amount of delayed cell loss following SCI. Research has revealed extensive therapeutic windows in secondary injury mechanisms that could be manipulated by appropriate exogenous interventions. In contrast, primary injury to the cord happens unexpectedly, and it is associated with inevitable delays; ranging from several hours to days before specialized care is administered. Therefore, apart from achieving patient's stabilization, the therapeutic window in the primary phase of injury is essentially obliterated, and consequently inaccessible for specialized intervention. Coupled to this, the exacerbating effect of secondary injury mechanisms has generally commenced before the specialist intervention. Hence, knowledge of secondary injury mechanisms and their intricacies are invaluable requisite for any tailored therapeutic strategy in the persistent search for a cure of SCI. There are about 25 well-established secondary injury mechanisms in SCI, and are found in bits or clusters in literature. A vast number of these articles are not open access. Besides, articles with a comprehensive catalog of these mechanisms are not readily available. This article has cataloged over twenty five identified secondary mechanisms of injury in the spinal cord in an open access portal, and is particularly versatile for starters in spinal cord injury research.

Key words: pathophysiologic mechanisms, secondary injury, spinal cord injury

INTRODUCTION

Worldwide, an estimated 2.5 million people live with spinal cord injury (SCI), with more than 130 000 new injuries reported annually (Thuret et al. 2006). Spinal cord injury (SCI) is one of the most debilitating pathologies, leading to huge rehabilitation challenges (Campagnolo et al. 2000, Wu and Ren 2009). SCI is not only debilitating to the affected individual but also drastically impinge on quality of life of an affected family. The cost of a SCI is enormous emotionally, socially and financially. Treatment, including acute-care hospitalization and rehabilitation, as well as lifetime medical costs and lost earnings is in the range of ten million US dollars (Fehlings and Nguyen 2010). The cost of enrollment in a clinical trial is currently

\$50 000 to \$100 000 per person in the United States and Europe, and the projected cost of phase 2 preliminary efficacy trials in humans are no less than \$5 - 10 million per candidate drug (Tator 2006). Despite this immense cost, clinically available treatments provide modest benefit; therefore current research is aimed at developing more effective therapies for spinal cord repair and regeneration (Kwon et al. 2004, Baptiste and Fehlings 2007, Fehlings and Nguyen 2010, Ali and Bahbahani 2010). SCI research is remarkable for the high number of treatment trials in humans but sadly till date, in spite of the huge resources that have been expended in research and human trials none has produced a major improvement in neurological recovery or a meaningful increase in function (Tator 2006, Simon et al. 2009, Wang et al. 2009, Jablonska et al. 2010). The complex pathophysiology of SCI, consisting of primary and secondary mechanisms may explain the difficulty in finding a suitable therapy (Blesch and Tuszynski 2008). The primary (mechanical) injury

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serves as the nidus from which secondary mechanisms of injury extend; which involves a cascade of vascular, cellular and biochemical events (Ray et al. 2002, Simon et al. 2009). However, our knowledge of the exact apparatus through which primary injury initiates secondary injury is not very precise (Simon et al. 2009). Nevertheless, it is known that the severity of the primary injury, in large part, determines a given patient's neurologic grade on admission and consequently is the strongest prognostic indicator. Nonetheless, for a large majority of patients with SCI, the extent of secondary injury evokes further damage, limits restorative processes, and predicts their long-term morbidity (Dumont et al. 2001). This is due in part, to the fact that mild injury elicits fewer inflammatory and secondary sequels than the moderate or severe types (Kloos et al. 2005, Siegenthaler et al. 2007). Primary injury to the cord happens unexpectedly, and it is associated with inevitable delays; ranging from several hours to days before patients are handled in a specialized neurological centre (Guly et al. 2008). Therefore, apart from achieving patient's stabilization, the short and practically vague therapeutic window which intuitively existed for combating or reducing the extent of injury in the primary phase sequel to a primary injury is essentially obliterated, and therefore clinically inaccessible for definitive specialized care (Liverman et al. 2005, Guly et al. 2008). Coupled to this, the exacerbating effect of secondary injury mechanisms, which are hallmarks of the sub-acute phase of SCI, has generally commenced prior to expertise interventions. Therefore, strategies have focused mainly on combating the cascading myriad of secondary injury mechanisms unleashed soon after a cord was traumatized (Dumont et al. 2001, Hall and Traystman 2009, Fehlings and Nguyen 2010). Hence, comprehension of secondary injury mechanisms and their complexities in SCI are invaluable requisite for planned therapeutic strategies: to stimulate axonal regrowth (regeneration), to arrest the self-perpetuating degeneration (neuroprotection), and the generation of new neurons and glia that will repopulate the site of injury and functionally integrate into the surviving neural tissue.

There are approximately 25 well-established secondary injury mechanisms in SCI (Tator 1998, Ramer et al. 2005). These secondary mechanisms are scattered in bits or in clusters in literature (Bunge et al. 1993, Profyris et al. 2004, Maier and Schwab 2006,

Baptiste and Fehlings 2007, Fehlings and Nguyen 2010). However, articles that provide a comprehensive catalog of the secondary injury mechanisms are not readily available. Though they are available in bits in some articles, nonetheless they describe the various aspects of SCI pathogenesis and, are generally not open access. This restricted access to relevant literature puts constraint on researcher from developing countries that are very often saddled with some cost of running their research. This article endeavors to provide a check list of the secondary mechanisms in SCI in an open access portal, and would be particularly useful for starters in spinal cord injury research and for researchers that may require this basic at a grasp.

PHASES OF SPINAL CORD INJURIES

Traumatic SCI results from either endogenous or exogenous trauma. Regardless of the cause, the resultant pathology is caused by two separate mechanisms: primary injury mechanisms (the initial mechanical damage), and secondary injury mechanisms (secondary change due to vascular and biochemical effects; Ray et al. 2002, Rossignol et al. 2007). The initial impact leads to immediate hemorrhage and rapid cell death at the impact site, followed by multiple secondary injury cascades that cause further tissue loss and dysfunction. Primary injury to the spinal cord has four morphologic types: impact plus persistent compression, impact alone with transient compression, distraction, and laceration or transection. Morphologic injury on a cord not only instantly injures or destroys resident cells, but also causes delayed damage and death to cells that survive the original trauma. The biological response to a spinal cord injury is divided into three phases (Table I) that follow a distinct but somewhat overlapping temporal sequence: acute (seconds to minutes after the injury), secondary (minutes to weeks after the injury), and chronic (months to years after the injury). In the acute phase, primary damage occurs as a direct result of trauma when structural thresholds are surpassed, leading to immediate physical and biochemical cellular alterations. It begins within seconds of the injury, is marked by systemic as well as local events (Tator et al. 1998, Hulsebosch 2002). These include systemic hypotension, spinal shock, vasospasm, ischemia, plasma membrane compromise, derangements in ionic homeostasis, and accumulation of neurotransmitters. Diverse groups of cells and mol-

Table I

Major features of the three phases of spinal cord injury

ACUTE	SUB-ACUTE	CHRONIC
Systemic hypotension and spinal shock		
Vasospasm	Vasospasm	
Cell death from direct insult	Cell death from direct insult	
Ischemia	Ischemia	
Oedema	Oedema	
Derangements in ionic homeostasis	Derangements in ionic homeostasis	
Accumulation of neurotransmitters	Glutamatergic excitotoxicity	
Plasma membrane compromise	Plasma membrane compromise / permeability	
	Free-radical production	
	Lipid peroxidation	
	Nitrous oxide excess	
	Conduction block	
	Excess noradrenaline	
	Energy failure and decreased ATP	
	Immune cells invasion and release of cytokines	
	Inflammatory mediated cell death	
	Neurite growth-inhibitory factors	
	Central chromatolysis	
	Vertebral compression / column instability	
	Demyelination of surviving axons	Continued demyelination
	Apoptosis	Continued apoptosis
	Initiation of central cavitation	Continued central cavitation
	Astroglial scar launch	Glial scar / syrinx formation
		Alteration of ion channels and receptors
		Regenerative processes, including sprouting by neurons
		Altered neurocircuits
		Syringomyelia

Upper rectangular shade: events common to acute and secondary phase

Lower rectangular shade: events common secondary phase and chronic phase

ecules from the nervous, immune, and vascular systems are involved in each phase. Most participating cells reside in the spinal cord, but others are summoned to the site of injury from the circulatory system (Liverman et al. 2005). Some acute phase events continue into the sub-acute phase, and also some sub-acute phase events continue into the chronic phase (Table I).

SECONDARY (SUB-ACUTE) PHASE

The secondary mechanism sets in minutes after injury and lasts for weeks or months (Tanhoffer et al. 2007). During this phase the area of trauma distinctly enlarges. The secondary phase features a continuation of some events from the acute phase - electrolyte shifts, oedema, and necrotic cell death - as well as novel ones, including the formation of free radicals, delayed calcium influx, immune system response or inflammation, and apoptotic cell death (Liverman et al. 2005). Some classic secondary injury mechanism of the spinal cord that has been identified in this field is presented (Table II). *A priori*, it must be stated that these mechanisms are interconnected in a self-propagating cycle that perpetuates each other once initiated by trauma. An injurious mechanism may perpetuate another or several others, or vice versa forming a deleterious network. A detailed review of individual mechanism is not the focus of this article. However, the following highlights may be helpful.

IMMUNE SYSTEM MEDIATED CNS INJURY

The immune system reactions to acute SCI are broadly cellular and molecular; and are intricately interwoven. In an injured cord, the cumulative effect of the immune cells (cellular), and regulatory proteins (molecular) is inflammation. Inflammation, a key event in the secondary injury cascade, occurs immediately and persists for several weeks or months following SCI (Fehlings and Nguyen 2010). The immune cells secrete proinflammatory cytokines, including interleukin (IL)-1 β , interleukin-6, and tumor necrosis factor- α (TNF- α), all of which increase the extent of inflammation. The inflammatory response is critical for the clearance of cellular debris, which can prevent the regeneration of surviving neurons. However, over-activation of the inflammatory response can damage healthy tissue and exacerbate the injury. The role of the

immune system in SCI is generally controversial. However, it is plausible that an uncontrolled immune system mediates cell death and inhibits axonal growth in SCI; and requires an exogenous control to be of net benefit (Rossignol et al. 2007). The healthy CNS houses the resident microglia, the innate immune cells of the CNS. It is now clear, however, that these cells have a wide range of functions that vary with context and time (Schwartz et al. 2006). Far back in 1998, Rapalino and coauthors reported that effect of blood-borne monocytes (macrophages) on the injured spinal cord is distinct from that of resident microglia. They demonstrated that exogenously applied macrophages possessing well controlled activities, unlike destructive microglia, could promote recovery of the completely transected spinal cord. This finding was received with a high degree of skepticism. The negative view of immune-cell activity in the CNS was supported by reports of beneficial effects, in both animal models and patients, of high-dose steroidal treatment at the hyperacute phase of SCI (Young 2002). Rossignol and coworkers (2007) reported that beneficial results were reported in research in which SCI was followed by experimental depletion of macrophages (Popovich et al. 1999) or blocking of neutrophil infiltration (Ditor et al. 2006). In contrast to these and other studies, and in opposition to the generally negative reputation ascribed to immune cells in the CNS, the work of Schwartz and his colleagues (2006), and by other groups over the past decade has brought to light the seminal finding that a well controlled innate and adaptive immune response is pivotal for repair (Hammarberg et al. 2000, Turrin and Rivest 2006, Hendrix and Nitsch 2007). Inflammation resulting from SCI attracts four major categories of immune cells: neutrophils, monocytes, microglia, and T-lymphocytes (Schnell et al. 1999, Bareyre and Schwab 2003). The neutrophils are the first immune cells to arrive at the site of injury. They are conscripted from the circulatory system, especially by vascular endothelial cells, which up-regulate and express adhesion molecules on their cell membranes to help guide neutrophils to the site of injury. Neutrophils in the spinal tissue, removes microbial intruders and tissue debris. Neutrophils also release cytokines, proteases, and free radicals, all of which activate other inflammatory and glial cells for the inflammatory cascade that can ultimately lead to neuron injury or death (Liverman et al. 2005). It has also been shown that the inhibition of neutrophil adhe-

Table II

A list of secondary injury mechanisms	
SECONDARY INJURY MECHANISMS	SOURCE
Apoptosis	Liu 1997, Beattie et al. 2000, Casha et al. 2001, Paterniti et al. 2009
Astroglial scar launch	Allan and Rothwell 2003, Herrmann et al. 2008, Buss et al. 2009
Calcium influx in cells	Stys et al. 1992b, Imaizumi et al. 1997, Xiong et al. 2007
Central cavitation	Balentine 1978, Zhang et al. 1997, Fehlings and Nguyen 2010
Central chromatolysis	Kikukawa et al. 1998, Vranken et al. 2006, Callegari et al. 2008
Compression and vertebral column instability	Shimada and Tokioka 1995, Wenger et al. 2003, Rossignol et al. 2007
Conduction block and spinal shock due to leakage of fast K ⁺ into the ECF	Shi and Borgens 2000, Hiersemenzel et al. 2000, McTigue 2008
Deficient expression of myelin associated genes after SCI	Martini et al. 1995, Grill et al. 1997, Rossignol et al. 2007
Demyelination of residual axons and demyelination of subpial rim of surviving axons	Casha et al. 2001, Liverman et al. 2005, McTigue 2008
Derangements in ionic homeostasis	Whalen et al. 2007, Simon et al. 2009
Energy failure and decreased ATP production	Xiong et al. 1999, Domont et al. 2001, Peng et al. 2009
Excessive noradrenaline secretion	Tator 1995, Satoe et al. 2001, Lucin et al. 2007
Fluid accumulation / oedema at the lesion site	Tator and Fehlings 1991, Kaymaz et al. 2005, Choo et al. 2007
Glutamatergic excitotoxicity	Xu et al. 2005, McTigue 2008
Hemorrhage	Tator and Fehlings 1991, Choo et al. 2007
Immune cells invasion and release of cytokines	Hammarberg et al. 2000, Schwartz et al. 2006, Hendrix and Nitsch 2007
Inflammation	Allan and Rothwell 2003, Fehlings and Nguyen 2010
Ischemia / reperfusion-induced endothelial damage	Xu et al. 1990, Toaka et al. 1998, Lee et al. 2003
Lipid peroxidation / oxidative stress	Xiong et al. 2007, Sullivan et al. 2007

Neurite growth-inhibitory factors e.g., Nogo-A, Rho-A, oligodendrocyte myelin glycoprotein (OMgp) myelin-associated glycoprotein (MAG), and chondroitin sulfate proteoglycans	Liverman et al. 2005, Rossignol et al. 2007
Neurogenic shock	Sekhon and Fehlings 2001, Guly et al. 2008
Nitrous oxide excess	Stagi et al. 2005, Guix et al. 2005, Wu et al. 2009
Oligodendrocytes to secondary apoptotic death	Domont et al. 2001, Grossman et al. 2001
Plasma membrane compromise / increases in plasma membrane permeability	Shi et al 2000, LaPlaca et al 2007, Whalen et al 2007, Simon et al. 2009
Systemic hypotension due to sympathetic loss	Guha et al. 1988, Gondim et al. 2004, Krassioukov and Claydon 2006
TNF- α production at the site of SCI	Yakovlev and Faden 1994, Taoka et al. 1998, Pan et al. 2003, Can et al. 2009
Vasospasm and microcirculatory inconsistencies	Tator 1995, Tator and Koyanagi 1997, Xu et al. 2005

sion to the endothelial cell surface markedly reduces the severity of the SCI induced by compressive trauma (Taoka et al. 1997). Soon after the mechanical injury, monocytes infiltrate into the spinal cord and differentiate into macrophages. Activated resident microglia and macrophages also secrete numerous cytokines, free radicals, and growth factors, which, in turn, affect nearby cells in positive and negative ways (Lindholm et al. 1992, Schnell et al. 1999, Anderson 2002). The growth factors are critical for neuron survival and tissue repair. However, free radicals and pro-inflammatory cytokines contribute to expansion of the lesion, worsening the impact of the injury. The role of lymphocytes in spinal cord injuries is rather controversial. Some argue that one type of lymphocyte (autoreactive T-lymphocytes) have destructive properties: according to this schema they exacerbate injury to axons and induce demyelination, leading to functional loss (Popovich and Jones 2003). Others argue that this lymphocyte is not pathological but, rather, confers protection to the myelin-insulated neurons (Schwartz and Kipnis 2001, Kipnis et al. 2002). Protection of myelin also protects the integrity of the axon that it insulates. To summarize, the exacerbating effect of the uncontrolled immune system on the injured spinal cord is to a large extent both inflammatory and free radical mediated. The immune system would only be of net benefit if exogenously controlled.

LIPID PEROXIDATION

A well characterized pathological process occurring early after SCI is the formation of reactive oxygen (ROS) and reactive nitrogen species (RNS; Azbill et al. 1997, Xiong et al. 2007). This is sequel to increased intracellular calcium levels, mitochondrial dysfunction, arachidonic acid breakdown and activation of inducible nitric oxide synthase (iNOS; Hall and Springer 2004, McTigue 2008). ROS and RNS cause lipid peroxidation as well as oxidative and nitrative damage to proteins and nucleic acids (Xu et al. 2005). Apart from cell membrane lysis; leading to neuronal loss, free radicals invoke other types of damage particularly on the cytoskeleton and organelles. In lipid peroxidation, free radicals absorb an electron from a lipid molecule, which in turn becomes less stable, thus launching a chain reaction that ultimately leads to lysis of the membrane and death by necrosis. In addition, oxidative damage exacerbates mitochondrial dysfunction (Sullivan et al. 2007) and contributes to intracellular calcium overload which activates proteases resulting in breakdown of cytoskeletal proteins (Xiong et al. 2007). Thus, the collective damage induced by ROS and RNS is widespread and may be central in the etiology of cellular death (necrotic and apoptotic) and functional loss after SCI.

GLUTAMATE EXCITOTOXICITY

Glutamate, the major excitatory neurotransmitter of the central nervous system (CNS) is released excessively after injury. Soon after trauma to the spinal cord, extracellular glutamate levels rise within and around the injury site (McAdoo et al. 1999), and it is known to produce direct damage to the cord, and indirect damage from production of reactive oxygen and nitrogen species and from alterations in microcirculatory function and secondary ischemia (Dumont et al. 2001). The resultant influx of Ca^{2+} into neurons causes neuronal death by necrosis or apoptosis through a process known as excitotoxic cell death (Xu et al. 2005). Glutamate, however, must first bind to receptor proteins that also act as potassium and calcium gates before influx of these ions into the neurons. Neurons and oligodendrocytes are particularly vulnerable to glutamate excitotoxicity because they express a full complement of glutamate receptors. Excitotoxic injury to oligodendrocytes and neurons results in demyelination of axons and loss of neurons around the injury site, leading to a drastic reduction or complete halt of axonal transmission (conduction block), thereby enhancing the disconnect between the brain and spinal segments below the level of injury, and thus contributing to motor and sensory deficits. Consequently, glutamate excitotoxicity markedly exacerbate the functional problems encountered after SCI. Researchers have studied drugs that block glutamate receptors in the hope of preventing excess potassium and calcium from entering and destroying the neuron (Lea and Faden 2003) or inhibiting the injurious interaction between excitotoxicity and inflammation (Yune et al. 2007).

APOPTOTIC CELL DEATH

During the acute phase, the mechanical trauma to the spinal cord causes cells death instantaneously by necrosis, a process of cell inflammation and then cell membrane rupture. Within hours, another type of cell death assumes center stage: apoptosis. With apoptosis, cells are not inflamed prior to death; rather, they condense and break apart into small fragments in a programmed pathway that requires energy and protein synthesis (Liverman et al. 2005). This programmed pathway of neuronal

death has been implicated in the pathobiology of multiple neurologic disorders including SCI (Dumont et al. 2001, Paterniti et al. 2009). The apoptotic cascade in SCI is activated in neurons, oligodendrocytes, microglia, and perhaps, astrocytes (Liu et al. 1997, Beattie et al. 2000). A major trigger appears to be the injury-induced rush of calcium into cells (Happel et al. 1981, Imaizumi et al. 1997, Xiong et al. 2007). Calcium influx activates key enzymes inside the cell - the caspases and calpain - that break down proteins in the internal cytoskeleton and membrane of the cell, leading to cell death (Ray et al. 2003). Yet, apoptosis of cortical motor neurons can occur after the axons centimeters away are severed by spinal cord injury, too far for the calcium to diffuse (Hains et al. 2003a). It is believed that this may be due to a variety of insults including cytokines, inflammatory injury, free radical damage, and excitotoxicity (Domont et al. 2001, Amemiya et al. 2005).

DEMYELINATION OF SURVIVING AXONS

Sequel to the death of oligodendrocytes triggered by glutamate excitotoxicity and exacerbated by a cascade that include; apoptosis, free radical assaults, activities of pro-inflammatory/inflammatory mediator and cytokines, is the demyelination of axons that survive the initial trauma. Demyelination is due to loss of oligodendrocytes, which are destroyed at the injury epicenter within hours of the injury and continue to undergo apoptosis in rostral and caudal white matter for many weeks after SCI (Cash et al. 2001, Grossman et al. 2001). This pathological process is particularly evident in the sub- acute and chronic phases of SCI (Guest et al. 2005, Liverman et al. 2005). With the loss of myelin, axons are now directly exposed to the damaging effects of free radicals and inflammatory cytokines, leading to neuronal loss via necrosis or/and apoptosis. Demyelination leads to conduction delays or/and conduction block (McTigue 2008, Hall and Traystman 2009). Given that axons traversing the injury site are the sole remaining connection between the brain and caudal spinal neurons, inefficient communication through these axons is a significant clinical issue (McTigue 2008). Hence demyelination and neuronal loss sequel to oligodendrocytes death aggravates the damage in a traumatized cord and thus limiting the potentials for a cure.

AXONAL REGENERATION INHIBITORY CELLS AND MOLECULES

The inherent limited capacities of regeneration after SCI aggravate the initial trauma. Several resident cells and a few recruited cells release factors that inhibit neuronal regeneration (Table III). By inhibiting regeneration, the net effect of degeneration may likely be amplified in a traumatized spinal cord. Several cells and molecules up or down regulates in SCI. Their overall activities are detrimental to the *milieu intérieur* of the spinal cord.

LOCAL VASCULAR DERANGEMENTS

The contribution of vascular mechanisms, including: ischemia / reperfusion, impaired autoregulation, systemic hypotension (neurogenic shock), hemorrhage (especially gray matter), and microcirculatory derangements in the pathophysiology of human SCI is well reviewed by Tator and Koyanagi (1997). Traumatized spinal cords show severe hemorrhages predominantly in gray matter, leading to the hemorrhagic necrosis and subsequent central myelomalacia at the site of injury (Sekhon and Fehlings 2001). Studies in both the human situation and experimentally, confirm that the large arteries remain patent but that a major change occurs in the local microcirculation (mainly capillaries and venules) in the area of the injury. Immediately after SCI, a major reduction in blood flow at the lesion occurs (Senter and Venes 1978, Fehlings et al. 1989, Tator and Fehlings 1991). This ischemia becomes progressively worse over the first few hours (Fehlings et al. 1989). The precise mechanisms behind this ischemia are unclear. Vasospasm secondary to mechanical damage or a vasoactive amine may be partially responsible (Tator and Fehlings 1991). Hemorrhages may promote ischemia (Wallace et al 1986) or thrombosis may occur *via* platelet aggregation (Nemecek 1978, Torre 1981). Ischemia has been implicated in the formation of local cord oedema (Tator and Koyanagi 1997). The accumulation of fluid in the site of injury is injurious to the cord (Kaymaz et al. 2005, Choo et al. 2007). Loss of microcirculation, direct disruption of small vessels and hemorrhage, failure of autoregulation, glutamate-mediated excitotoxicity (Xu et al. 2005) and ischemia particularly is a

direct linear dose-response association, with the severity of the injury becoming progressively worse a few hours after SCI. Apart from direct disruptions on microcirculation of the cord by trauma, there are evidences that ischemia and reperfusion induced endothelial damage in vessels of damaged spinal segment; and that this damage contributes to the exacerbating cascade already at work (Taoka et al. 1998, Lee et al. 2003). Ischemia and reperfusion induced endothelial damage are mediated through free radicals and other toxic byproducts (Cuzzocrea et al. 2001). Oxygen- derived free radicals (including superoxide, hydroxyl radicals, and nitric oxide and other high-energy oxidants (including peroxynitrite) are produced during ischemia (Lewen et al. 2000, Bao et al. 2005) with a most pronounced rise during the early reperfusion period (Zini et al. 1992, Nagel et al 2008). These highly reactive oxygen and nitrogen species contribute to oxidative stress, a pathological mechanism that contributes to the secondary injury of spinal cord trauma. Although the precise mechanisms of vascular events in SCI are still subject of investigation, it is however known that endothelial damage occurs early, with the formation of craters, adherence of non-cellular debris, over-riding of endothelial cell junctions, and formations of microglobular (Sekhon and Fehlings 2001), and that alterations in endothelial cell function cause an increase in vascular permeability and oedema formation (Kaymaz et al. 2005, Benton et al. 2008). In summary, oxidative stress resulting from compromises in the microcirculation of a damaged spinal segment contributes to SCI and is intimately related to other mediators of secondary injury.

NEUROGENIC SHOCK

Spinal cord injury may result in neurogenic shock. Uncontrolled neurogenic shock perpetuates further damage on a traumatized cord. Its systemic effects include ischemia of the spinal cord and other organs (Dumon et al. 2001). Neurogenic shock is manifested by the triad of hypotension, bradycardia, and hypothermia (Kiss and Tator 1993). It is known that SCI causes hypotension due to loss of sympathetic tone and decreased peripheral vascular resistance. The resultant hypotension is further exacerbated by neurogenic shock; and intra-abdominal pathology is more difficult to diag-

Table III

Cells and molecules that inhibit axon regeneration	
Cell Type	Inhibitory Molecule
Activated microglia	Arachidonic acid derivatives Cytokines Free radicals Nitric oxide
Astrocyte	Brevican (a proteoglycan) Neurocan (a proteoglycan) NG2 (a proteoglycan) Tenascin
Meningeal cell	NG2 Semaphorins
Neutrophils	Cytokines Free radicals Neutrophils Proteases
Oligodendrocyte	Myelin-associated glycoprotein (MAG) NI-250 (Nogo-A) Oligodendrocyte myelin glycoprotein (OMGP) Tenascin-R
Oligodendrocyte precursor	DSD-1 or phosphacan (a proteoglycan) NG2 (a proteoglycan) Versican (a proteoglycan)

SOURCE: Fawcett and Asher 1999, Liverman et al. 2006

nose in the presence of an SCI (Dumon et al. 2001). Bradycardia may occur due to unopposed vagal activity in a high cord lesion that disrupts the sympathetic supply to the heart (Guly et al. 2008). Bradycardia is exacerbated by hypoxia and endobronchial suction (Piepmeyer et al. 1985). In high cervical injuries, safeguarding the integrity of airway is fraught with difficulty; without infrequent respiratory failure. The aforesaid cascade has a cumulative effect of exacerbating nervous tissue damage (Guly et al. 2008) and, thus worsening the outcome from SCI; both in terms of mortality and morbidity (Sekhon and Fehlings 2001). There is no universally accepted definition of neurogenic shock. It has been defined as a systolic BP < 100 mm Hg and a heart rate < 80 BPM in a patient without other obvious cause, or as a systolic BP < 90 mm Hg (Guly et al. 2008). Ignoring definitions, an essentially silent question is whether neurogenic shock is an integral part of the secondary injury mechanisms or an epiphenomenal event that plausibly precipitate a spinal injury?

PRODUCTION OF TNF- α AT THE SITE OF SCI

Tumor necrosis factor-alpha (TNF- α) is one of the best characterized cytokines. To date there is no clear consensus on the role of endogenous TNF- α in CNS acute injury. Studies strongly suggest that the production of tumor necrosis factor α (TNF- α) at the site of SCI is involved in secondary tissue damage in SCI (Yakovlev and Faden 1994, Wang et al. 1996, Taoka et al. 1998, Pan et al. 2003, Paterniti et al. 2009). Wang and others (1996) showed the presence of TNF- α at the sites of traumatic spinal cord lesions but did not detect this factor in cerebrospinal fluid or in serum. Earlier, Yakovlev and Faden (1994) demonstrated that spinal cord impact in rats caused an elevation of TNF- α mRNA levels at the site of trauma 30 min after the injury; the severity of injury was proportional to the level of the TNF- α message. In leukocytopenic rats, where the level of TNF- α was not increased at the site

of trauma exhibited a significant reduction in motor disturbances, indicates that increased levels of TNF- α at the site of injury may be a cause, rather than an effect, of the SCI induced by compressive trauma (Taoka et al. 1998). Interestingly, contrary to most report, there are certain documented evidences of its ameliorating potentials in CNS injury (Hurtado et al. 2002, Pradillo et al. 2005, for review see: Figiel 2008). A recent study however, ascribed to it, a dual role; depending on the phase of injury: overexpression of TNF- α is deleterious in the acute phase, but beneficial in the chronic phase in the response to SCI (Chi et al. 2010). It is now clear that TNF- α receptors mediates distinct cellular responses, and there is an increasing evidence of considerable overlap of their signaling capabilities in mediating biological effects (Declercq et al. 1998, Quintana et al. 2005). The differential patterns of localization of TNF- α receptors in neuronal and glial cells, their state of activation and the downstream effectors, all are thought to play an important role in determining whether TNF- α will exert a beneficial or harmful effect on CNS (Fontaine et al. 2002, Figiel 2008). Additionally, TNF- α contributes to the tissue injury induced by neutrophils by directly activating them (Klebanoff et al. 1986, Genovese et al. 2005b, Paterniti et al. 2009) as well as by increasing the expression of such molecules as E-selectin, which cause the activated neutrophils to adhere to the surface of the endothelial cells (Mulligan et al. 1991, Genovese et al. 2005a, b). It has also been shown that the inhibition of neutrophil adhesion to the endothelial cell surface markedly reduces the severity of the SCI induced by compressive trauma (Taoka et al. 1997, Dona et al. 2003). In addition to the direct damage of TNF- α on traumatized cord; these observations indicate that the interaction of activated neutrophils with the surface of the endothelial cells is important in the secondary tissue damage.

PLASMA MEMBRANE COMPROMISE / DERANGEMENTS IN IONIC HOMEOSTASIS

One direct result of the mechanical impact in traumatic CNS injury is the formation of non-specific breaches in the neuronal plasma membrane (Simon et al. 2009). Simon and coauthors also emphasized that this phenomenon has been observed in many models of neuronal injury and is postulated to be detrimental to post-injury outcomes (Shi et al. 2000, Choo et al.

2007, LaPlaca et al. 2007, Whalen et al. 2007). The temporarily or permanently destroyed barrier between the cytosol of neuron / glia and the ECF results in derangements in ionic and molecules homeostasis. This unregulated ionic / molecular flux is detrimental to cell function and survival (Simon et al. 2009). Sequel to this, surviving cells may experience downstream debilitating consequences of plasma membrane compromise (Barbee 2005, Farkas and Povlishock 2007). Compromised cell membrane permeability is also associated with protease activation. Protease activities are connected with tissue loss and apoptosis secondary to acute CNS injury (Farkas et al. 2006, Whalen et al. 2007).

INCREASED CALCIUM INFLUX

Another key element in secondary injury mechanism is an excessive intracellular level of Ca²⁺ ions. Calcium influx is triggered by acute injury and continues for hours to weeks afterwards (Liverman et al. 2005). Although, the initial calcium influx into neuron at the time of injury contributes to the acute phase of damage, an additional influx of calcium is triggered by the acute injury and continues for hours afterwards (Liverman et al. 2005). Calcium influx down its concentration gradient could result in mitochondrial damage, aberrant enzyme activation, changes in gene expression, and apoptosis (Simon et al. 2009). Once inside, calcium ions not only activate caspases and calpains to degrade the local axoplasm, but also diffuse and exceed the threshold of calpain activation in the immediately adjacent region; which leads to further axoplasmic and membrane breakdown and further calcium influx (Ray et al. 2003, Beirowski et al. 2005). A particularly powerful mode of calcium influx within injured axons in white matter involves an initial inward leakage of sodium due to the acute injury, which drives the sodium-calcium exchanger to import damaging levels of calcium; this multistage cascade has been demonstrated within myelinated axons of the optic nerve (Stys et al. 1992b) and the spinal cord (Imaizumi et al. 1997). Delayed calcium blocking is a viable therapeutic strategy that could reduce the degree of secondary damage to spinal cord axons (Liverman et al. 2005).

CENTRAL CHROMATOLYSIS

It is a process that occurs after an injury to the neuron is sustained and or irreparable. It is characterized

by tumefaction of cell body and the disappearance of Nissl bodies from the central portion of the cell. Accompany by a relocation of the nucleus peripherally (Callegari et al. 2008). It is an axonal reaction where changes appear to reflect reversible changes in cell metabolism that include ischemia; these changes are interpreted as a state of heightened metabolic activity that favors axonal regeneration (Kreutzberg 1996, Errando et al. 1999). Chromatolysis and inflammation are characteristic of neuronal cells with compromised microcirculation. These changes can disrupt communication in many portions of the central nervous system (Guyton and Hall 2006). Chromatolysis also causes degeneration of myelin sheaths and neuronal death in both the peripheral nerves and the central nervous system. These and associated conduction block markedly aggravate damage and neurological dysfunction in SCI (McTigue 2008).

CENTRAL CAVITATION

A phenomenon that adds to the complexity of regenerative failure is the process of progressive central cavitation in which, after days to weeks, a SCI can expand in size leading to scar-encapsulated cavity many times the size of the initial lesion (Balentine 1978, Rossignol et al. 2007, Fehlings and Nguyen 2010). Various studies suggest that this secondary process of cavitation is related to ischemia (Balentine 1978, Shan et al. 2010), hemorrhage (Ducker et al. 1971, Wallace et al. 1987), lysozyme activity (Kao et al. 1977), pulsatile hydrodynamics (Williams et al. 1981), or macrophage infiltration and inflammation (Blight 1994, Zhang et al. 1997). Inflammatory processes alone initiate a cascade of secondary tissue damage, progressive cavitation and glial scarring in the CNS (Allan and Rothwell 2003, Fehlings and Nguyen 2010). The physical process of cavitation leads to astrocyte abandonment of neuronal processes, neurite stretching, and secondary injury. The macrophage mannose receptor and the complement receptor type 3 $\beta 2$ integrin are implicated in the cascade that induces cavity and scar formation (Fitch et al. 1999, Von Boxberg et al. 2006).

CONTROLLING SECONDARY INJURY

Primary injury to the cord can not be prevented. It happened unexpectedly in normal daily life. However,

repetitive or sustained mechanical insult that may exacerbates damage sequel to the primary mechanical injury are minimized through surgical decompression of the spinal cord and, or stabilization of vertebrae. The debilitating effects of secondary injury mechanisms are far reaching, however, therapies aimed at controlling them offer the potential to reduce the extent of injury and thus enhance the prospect of recovering. To this end, various therapeutics strategy, have been tried. A variety of approaches have been studied to alter neuroinflammation (administration of immunomodulator drugs such as minocycline or antibodies against leukocyte adhesion molecules; Popovich et al. 1999, Wells et al. 2003, Gris et al. 2004, Schwartz and Yoles 2006), reduce free radical damage (administration of glucocorticoids, iron chelators, and glutathione promoters; Hall and Braughler 1982, Schultke et al. 2003, Golding et al. 2006, Liu-Snyder et al. 2007), reduce excitotoxic damage to neurons (administration of N-methyl-D-aspartate (NMDA) receptor antagonists; Hirbec et al. 2001), improve blood flow (administration of opioid antagonists or calcium channel blockers; Faden et al. 1981), seal damaged membranes (systemic administration of surfactants; Luo et al. 2002, Lavery et al. 2004), and counter the effects of local ionic imbalances (administration of sodium and calcium channel blocker; Winkler et al. 2003, Hains et al. 2004, Kaptanoglu et al. 2005, Nehrt et al. 2007; for a detailed review see Baptiste and Fehlings 2006). Similarly, an array of cellular therapeutic interventions has shown impressive results after SCI. The strategies were generally: to bridge any cysts or cavities; to replace dead cells (by providing new neurons or myelinating cells), and to create a favourable environment for axon regeneration (Thuret et al. 2006). Efforts aimed at these includes: transplantation of peripheral nerve (Levi et al. 2002), transplantation of Schwann cells (Papastefanaki et al. 2007), transplantation of olfactory unsheathing cells (Li et al. 2003), transplantation of embryonic stem/progenitor cells (Teng et al. 2002, Jablonska et al. 2010, Szymczak et al. 2010), transplantation of adult stem/progenitor cells (Koda et al. 2005, Karimi-Abdolrezaee et al. 2006, Sypecka et al. 2009, Jablonska et al. 2010), transplantation of engineered stem/progenitor cells (Chen et al. 2006, Ali et al. 2009, Buzanska et al. 2009; for a detailed review see Thuret et al. 2006, Ali and Bahbahani 2010). Molecular therapeutic interventions that inhibit the activities of some secondary injury mechanisms in

SCI have been assessed in animals and in human with impressive outcome. The therapeutic strategies were generally: to protect neurons from secondary cell death; to promote axonal growth; and to enhance conduction (Thuret et al. 2006). Efforts aimed at these includes: neuroprotective therapies (Fehlings and Baptiste 2005), conduction enhancing (Guest et al. 2005), delivery of growth factors (Zhou and Shine 2003, Bartkowska et al. 2010), modulation of interactions with myelin inhibitors (Fouad et al. 2004), extracellular matrix modifiers (Klapka et al. 2005; for a detailed review see Thuret et al. 2006). However, none of these therapeutics strategies has produced any clinically satisfactory intervention. The biological processes involved in regaining sensory or motor functions, preventing or eliminating pain, and retraining and relearning motor tasks are so diverse that treatment strategies aimed at obstructing several of the secondary injury mechanisms in a tailored combination therapies will certainly be required (Liverman et al. 2005, Thuret et al. 2006, Webb et al. 2010). Optimal recovery of function will require a combination of effective and safe therapeutic interventions. However, determining which interventions would best combine in a multimodal therapy for SCI, that would provide satisfactory and meaningful locomotive or neurological improvement remain critical.

CONCLUSION

This article has cataloged some key secondary injury mechanisms that exacerbate a SCI. These mechanisms are intricately interconnected in a self-propagating destructive cascade; nonetheless, individual mechanisms are capable of exacerbating a traumatized spinal cord. Additionally, several distinct precursors can further perpetuate a particular mechanism; which in-turn induces the release or generation of more quantity of several secondary injurious elements, forming a deleterious network. Owing to its complexity, a spinal cord injury is unlikely to be cured by a single therapy. And given the complexity of the factors that are involved, research into multimodal therapies will require many years of investigation to identify an appropriate therapy that is unequivocally safe and effective, that could be tested in human clinical trials. Nevertheless, there are concerted efforts to identify and develop appropriate and efficacious multimodal therapy for SCI.

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