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Mesenchymal Stem Cell Therapy for Apoptosis After Spinal Cord Injury

Venkata Ramesh Dasari[1], Krishna Kumar Veeravalli[1], Jasti S. Rao[1,2], Dan Fassett[2,3] and Dzung H. Dinh[2,3]
[1]*Departments of Cancer Biology and Pharmacology,*
[2]*Neurosurgery*
[3]*Illinois Neurological Institute*
University of Illinois College of Medicine at Peoria, Peoria, Illinois, USA

1. Introduction

Spinal cord injury (SCI) is a devastating clinical problem that has irreversible consequences, results in permanent functional loss, and life time disability (Sekhon and Fehlings, 2001). This debilitating condition often affects young and healthy individuals at the prime of their life, creates enormous physical and emotional cost, and places a significant financial burden to society at large (Ackery et al., 2004). Even though years of research have led to a better understanding in the pathophysiology of permanent neural injuries at the cellular level, much of the mechanism and processes of secondary injury at the molecular level remain to be elucidated. With modern molecular strategies and techniques, breakthroughs in the understanding of neuronal injury and neural regeneration provide new promises for reversal of spinal cord injury that once was thought to be permanent and irreversible (Carlson and Gorden, 2002).

Spinal cord injury involves an initial mechanical or primary injury followed by a series of cellular and molecular secondary events that amplify the extent of the initial damage and results in the progressive destruction of spinal cord tissue. After acute contusion, the spinal cord undergoes a sequential progression of pathologic changes, including micro hemorrhage, cytotoxic edema, neuronal necrosis, axonal fragmentation, demyelination, further secondary cellular destruction and eventually cyst formation (Balentine, 1978; Balentine and Greene, 1984; Coutts and Keirstead, 2008). Damage to the spinal cord results in extensive proliferation of microglia and macrophages in and around the injury epicenter. This acute inflammatory response at the injury site is at least partly responsible for secondary spinal cord injury (Popovich et al., 1997; Carlson et al., 1998; Taoka et al., 1998). The inflammatory cells (particularly macrophages/microglia) mediate tissue damage by producing a variety of cytotoxic factors including interleukins (Rice et al., 2007) and tumor necrosis factor-alpha (TNF-α) (Beattie et al., 2002). White matter breakdown begins at the grey-white matter junction with progressive edema (Dohrmann et al., 1972). Axoplasmic stasis and axonal swelling that contains multiple organelles, mitochondria, neurofilament, and smooth endoplasmic reticulum eventually undergo glandular dissolution and myelin

disruption (Bresnahan et al., 1976; Balentine, 1978; Bresnahan, 1978; Balentine and Greene, 1984). Within 4h of injury, neuronal and oligodendroglial cell loss is apparent in the lesion epicenter, and extends rostrally and caudally (Grossman et al., 2001). Within days after the injury polymorphonuclear cells and macrophages begin to infiltrate the injured region (Blight, 1985; Means and Anderson, 1983). And within one week, the central necrotic region begins to show cystic changes. By four weeks, chronic changes have occurred, and a cystic cavity remains with astrocytic gliosis and demyelination of the remaining axons (Wagner et al., 1971). Even years after initial trauma, neuronal and oligodendroglial apoptotic cell death processes continues to contribute to demyelination and Wallerian degeneration (Hagg and Oudega, 2006; Taoka and Okajima, 1998). The wave of post-traumatic tissue destruction, as initiated by secondary injury mechanisms, include disruption of spinal cord vasculature and ischemia, glutamatergic excitotoxicity, oxidative cell stress, lipid peroxidation and inflammation (Nashmi and Fehlings, 2001; Tator and Fehlings, 1991)—all of which alone or in concert can trigger apoptosis, contribute to the permanency of functional motor and sensory deficits (Hagg and Oudega, 2006; Taoka and Okajima, 1998).

Apoptotic cell death has been observed to occur for weeks after injury at distance remote from the point of mechanical impact (Crowe et al., 1997; Emery et al., 1998; Springer et al., 1999). Neurons and oligodendrocytes are especially vulnerable to the toxicity of the acute lesion microenvironment after SCI for several reasons (Choi, 1988). Neurons have a high rate of oxidative metabolism that makes them susceptible to injury by reactive oxygen species (ROS) following ischemia (Juurlink and Paterson, 1998). Compared to their supporting astroglial cells, neurons have lower levels of antioxidant levels (e.g., glutathione) and respond differently to molecular mechanisms involving the activation of Phase II enzymes, which are responsible for neutralization of damaging free radicals (Eftekharpour et al., 2000). Oligodendrocytes are also very susceptible to ROS due to their higher iron content and lower levels of glutathione and its related antioxidant enzymes, (Juurlink and Paterson, 1998). The oxidative stress by induction of ROS and pro-inflammatory cytokines initiates a cascade of oxidative events that lead to cell death due to a combination of necrosis and apoptosis (Crowe et al., 1997). Loss of oligodendroglia causes demyelination, impairs axonal function and survival. In the days to weeks after injury, disrupted neuronal axons and extracellular elements of the necrotic core at the site of injury are removed by recruited inflammatory cells and phagocytes (Dusart and Schwab, 1994), leaving in place fluid-filled cystic cavities at the site of injury (Greitz, 2006).

2. Apoptosis after SCI

Apoptosis is a genetically controlled cell death that is characterized by intact membrane integrity, cytoplasmic and nuclear condensation, loss of cellular volume, membrane bleb formation and nuclear disintegration (Yakovlev and Faden, 2001). The cell eventually fragments into apoptotic bodies, which are then engulfed and degraded by neighboring cells. During apoptosis, morphological changes are often accompanied by internucleosomal cleavage of genomic DNA (Wyllie et al., 1980). In the secondary injury process after SCI, apoptosis has been well documented. Emery *et al*., (1998) analyzed the spinal cords of 15 patients who had died after traumatic SCI and described evidence of apoptotic cells at the edges of the lesion epicenter and in the adjacent white matter. Apoptotic mechanisms of cell death have been implicated in delayed Wallerian degeneration of white matter after spinal cord injury (Crowe et al., 1997). Oligodendrocytes, microglia, and neurons are susceptible to

apoptosis. After SCI, some cellular demise was directly related to post-traumatic necrosis, whereas others die due to apoptosis (Crowe et al., 1997; Emery et al., 1998; Shuman et al., 1997; Springer et al., 1999; Keane et al., 2001; Warden et al., 2001; Beattie et al., 2002). Spinal cord trauma activates upregulation of caspases and calpain and the apoptotic machinery, leading to increased expression of death receptors and their ligands (Banik et al., 1997; Casha et al., 2001; Keane et al., 2001; Springer et al., 1999). However, there are conflicting reports as to the role of cell death in SCI— probably a reflection of the known dual capacity of TNF to be both pro- and anti-apoptotic. Fas/CD95, TNFR1 and TNFR2 have been mainly characterized in the immune system and are primarily involved in regulating inflammatory and apoptotic responses. However, these receptors and their ligands are also detectable in CNS tissue (both normal and traumatized), implicating their roles in neuronal maturation as well as in neurological trauma and disease. Apoptotic pathways triggered after SCI are depicted in Figure 1.

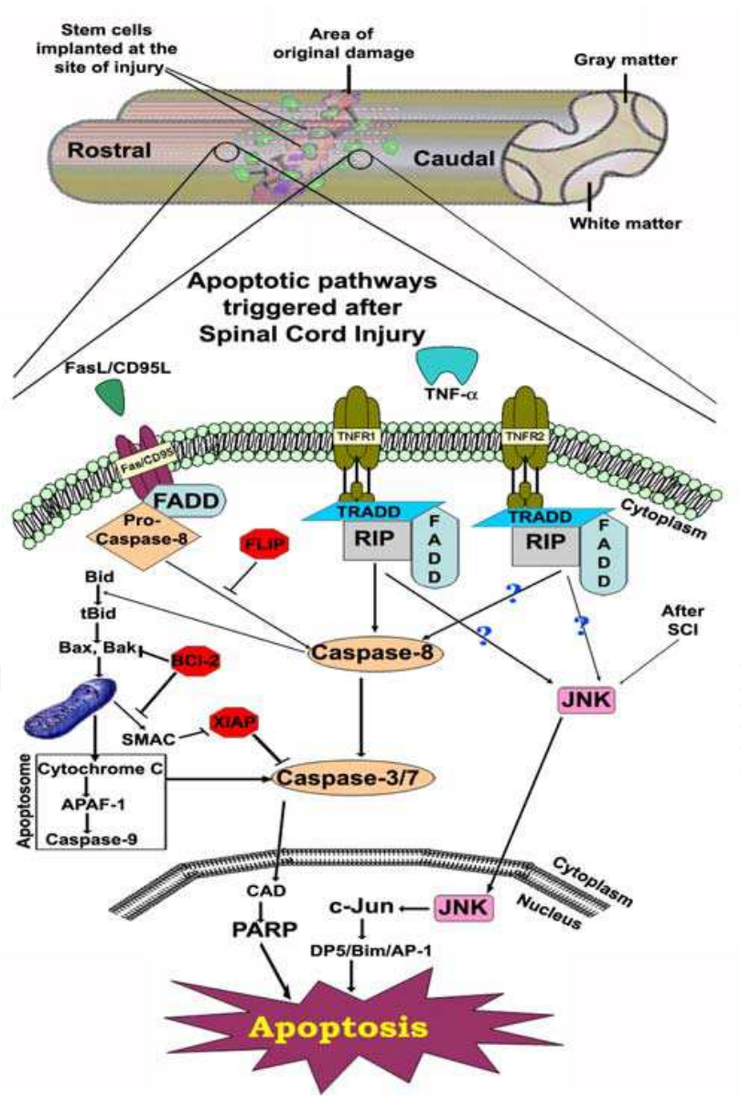


Fig. 1. Apoptotic pathways triggered after SCI

Apoptosis of the cells takes place either rostral or caudal to the area of original damage. These are mainly either Fas-activated or TNF-α or JNK-activated pathways. In Fas-mediated pathway, Fas is activated by Fas ligand, whereby Fas-associated death domain (FADD) and caspase-8 are recruited to Fas to form the death-inducing signaling complex (DISC). Subsequently, caspase-8 can autoactivate and trigger cell death by cleavage of Bid and activation of effector caspases- 3 and -7. The activation and involvement of mitochondria in apoptosis appears to be the main pathway responsible for cell death. In tumor necrosis factor receptor 1 (TNFR1/TNFR2) signaling, early after trauma, increased levels of TNFR1/TNFR2 are activated where they associate with the adaptor protein TRADD, Fas-associated death domain (FADD), TRAF2, TRAF1, and RIP. In later stages after injury, RIP and cIAP-1 appear to dissociate from the TNFR1 complex by an unknown mechanism and this complex signals death by activating caspase-8. In either case, activated caspase-3 translocates to nucleus, and activates CAD resulting in cleavage of PARP leading to apoptotic cell death. In JNK mediated pathway, JNK gets activated after SCI, and translocated to nucleus where it activates c-Jun leading to apoptotic cell death. In mesenchymal stem cell treatment for apoptosis, mesenchymal stem cells are injected at the site of injury or rostral or caudal to the site of injury.

2.1 Apoptosis involving FAS/CD95 and caspases

Fas (CD95 or Apo-1) is a member of the TNFR superfamily and is one of six known death receptors. Fas exists as a 45-kDa, type 1 transmembrane protein with an elongated extracellular domain. This extracellular region contains three cysteine-rich domains (CRDs), which are typical of TNF receptors (Keane et al., 2006). This receptor contains a death domain and plays a central role in the physiological regulation of programmed cell death, and has been implicated in the pathogenesis of various malignancies and diseases of the immune system. The interaction of this receptor with its ligand generates the formation of a death-inducing signaling complex that includes Fas-associated death domain protein (FADD), caspase-8, and caspase-10. The autoproteolytic processing of the caspases in the complex triggers a downstream caspase cascade, and leads to apoptosis. The typical ligand for Fas is FasL (CD95L, Apo-1L, Cd178, TNFSF6), which is a 281–amino acid protein produced as a type 2 transmembrane protein and is highly restricted to immune cells and cells of the CNS. In the nervous system, Fas/CD95 activation can lead to cell death involving neurons and glial cells (D'Souza et al., 1995; Raoul et al., 2002). Activation of Fas/CD95 can also lead to enhanced axonal growth (Desbarats et al., 2003). Fas and FasL are expressed in the normal CNS, and are upregulated in inflamed and degenerated brains (Choi and Benveniste, 2004). Fas and FasL levels have been found to be elevated after SCI (Casha et al., 2001; Dasari et al., 2008; Demjen et al., 2004; Li et al., 2000a). Yoshino *et al*., (Yoshino et al., 2004) investigated Fas/CD95-mediated apoptosis after SCI using Fas-deficient mutant mice. Mice lacking Fas/FasL showed improved functional recovery, decreased lesion size, and fewer apoptotic cells in the injured cord than control littermates. It appears that Fas-FasL induce apoptosis via both intrinsic and extrinsic pathways. The extrinsic pathway involves Fas-FasL mediated activation of caspase-8, which then directly activates caspase-3 (Salvesen and Dixit, 1999; Stennicke et al., 1998). There was evidence to support the regulation of intrinsic mitochondrial apoptotic pathways by the Bcl-2 family proteins, which consists of both pro-apoptotic (Bid and Bax) and anti-apoptotic (Bcl-2 and Bcl-xL) members (Kim et al., 2000). In addition, the intrinsic pathway can be initiated by the

extrinsic pathway, thereby amplifying the apoptotic process. In this scenario, Caspase-8 cleaves Bid into truncated tBid, which translocates from the cytosol into the mitochondria, releasing cytochrome c and activating caspase-3 and -9 (Kuwana et al., 1998; Li et al., 1998; Scaffidi et al., 1998; Stennicke et al., 1998; Verhagen et al., 2000). Also, a mitochondrial apoptotic protein, Apoptosis-inducing factor (AIF), was found capable of inducing neuronal apoptosis when translocated from mitochondria to the nucleus via a caspase-dependent pathway (Tsujimoto, 2003; Tsujimoto and Shimizu, 2000; Yu et al., 2006; Yu et al., 2009).

Strategies to inhibit Fas-FasL cascade may provide effective neuroprotective approaches for mollifying apoptosis after SCI. In one experiment, neutralization of FasL, but not TNF, significantly decreased apoptotic cell death after SCI (Demjen et al., 2004). Mice pretreated with FasL-specific antibodies were capable of initiating active hind-limb movements several weeks after injury with upregulation of growth-associated protein Gap-43 and more abundance in regenerating fibers. Thus, neutralization of FasL appears to diminish apoptotic cell death and promote axonal regeneration and functional improvement in injured adult animals (Demjen et al., 2004). Other experiments have demonstrated that blocking Fas activation using soluble Fas receptors for competitive inhibition or neutralization using anti-FasL antibody diminished brain injury volume and improved outcome in a stroke model of mouse (Gao et al., 2005). The neuroprotective effect of anti-FasL in animal models of SCI, stroke and multiple sclerosis has stimulated considerable interest in elucidation of the role of the Fas/CD95/FasL system in CNS neurons (Demjen et al., 2004; Martin-Villalba et al., 1999; Waldner et al., 1997). However, a true understanding of how FasL antibodies reduce cell death and enhance recovery requires more detailed knowledge. It is not clear if CNS cells exhibit differences in the efficiency of Fas/CD95 signaling and thus can be categorized as type I or type II cells (Keane et al., 2006). The cellular source and target of the ligand in damaged CNS tissue need to be identified, and strategies need to be developed for effective delivering antibodies to the lesion. Recent experimental evidence has provided some knowledge about receptor submembrane localization and the formation of alternative signaling complexes that can alter the fate of cells *in vitro*, but whether these principles hold true *in vivo* remained to be explored. Thus, activation of these signaling pathways might result in promising therapeutic targets for the acute treatment of neurological trauma and disease.

In addition to FasL/CD95 involvement in apoptosis, caspases are also known to be powerful mediators of programmed cell-death in CNS injury and disease processes. All caspases are translated initially as inactive zymogens that are then activated after specific cleavage. They have the following structural features in common: an N-terminal pro-domain of variable length (22 to >200 amino acids), a large subunit (~ 17-20 kDa), a short inter-subunit region (~10 amino acids), and a small subunit (~10—12 kDa). The C-terminal portion of the large subunit contains the catalytic cysteine residue. Flanking this are other conserved residues that, together, form the semiconserved pentapeptide sequence QACXG at the active site (Alnemri et al., 1996; Thornberry and Lazebnik, 1998). Pro-caspases are processed by limited proteolysis into their active form, which consists of a large and small subunit dimer. *In vivo*, however, caspases are more conformationally stable as tetramers consisting of two large/small subunit dimers (Eldadah and Faden, 2000). Once activated by specific cleavage to active forms, caspases can activate other procaspases via extrinsic pathway directly or intrinsic pathway by mitochondrial-dependent mechanisms, thereby amplifying the programmed cell death process (Li et al., 1998; Scaffidi et al., 1998; Slee et al., 1999; Yakovlev and Faden, 2001; Yu et al., 2009). Based on their putative functions and

sequence homologies, caspases are often categorized into three groups: apoptotic initiators (caspase-2, 8, -9 and -10), apoptotic executioners (caspase- 3, -6, and -7), and inflammatory mediators (caspase -1, -4,-5, -11, -12, and -13) (Alenzi et al., 2010; Thornberry and Lazebnik, 1998). The apoptotic initiators, act at upstream positions within apoptotic pathways; that is, the cell surface and mitochondria. They have in common long N-terminal pro-domains that contain six anti-parallel α-helices with complementary binding capability. Caspases-8 and -10 have two such domains at their N-termini known as death effector domains (DEDs). Caspases-2 and -9 have only one of these domains, which, in the case of these members, are known as caspase recruitment domains (CARDs). These sequences play an important role in localization and activation of specific procaspases. The apoptotic executioners mediate some of the morphological and biochemical manifestations of apoptosis: plasma membrane blebbing, nuclear membrane dissolution, chromatin condensation and margination, and DNA fragmentation. Executioner caspases have short N-terminal pro-domains whose function remains unclear (Eldadah and Faden, 2000). The third group of caspases is inflammatory mediating proteases that are poor substrates for other caspases and their activation pathways are not well understood.

Numerous studies have demonstrated the presence of multiple caspases and apoptosis following SCI (Beattie et al., 2000; Citron et al., 2000; Crowe et al., 1997; Eldadah and Faden, 2000; Keane et al., 2001; Liu et al., 1997; Lou et al., 1998; Springer et al., 1999; Yong et al., 1998). Emery *et al.*, (1998) have reported substantial labeling of active caspase-3 around the injury site in histological study of injured spinal cords from 15 patients who died after traumatic SCI. The involvement of caspase-3 as a major effector in injury-induced neuronal apoptosis was established by using specific caspase inhibitors in various models of ischemic or traumatic injury (Clark et al., 2000; Gillardon et al., 1997; Gottron et al., 1997; Namura et al., 1998; Yakovlev et al., 1997). Caspase-3 can be activated by caspases-8, -9, -11, and -12 (Kang et al., 2000; Wang et al., 1998). Caspases-11 and -12 in turn can be activated by Calpain and Cathepsin B (Nakagawa and Yuan, 2000; Schotte et al., 1998; Yamashima, 2000). Apoptosis therefore plays an important role in the secondary injury processes following traumatic injury to the CNS (Crowe et al., 1997; Keane et al., 2001; Li et al., 1996; Lu et al., 2000). The permanent neurological deficits after spinal cord injury may be due in part to widespread apoptosis in regions distant from and relatively unaffected by the initial injury (Crowe et al., 1997). Caspases were one of the viable therapeutic targets for modulating apoptosis and remain the viable approach to blocking apoptotic cell death (Nicholson, 2000). A number of caspase inhibitors such as z-VAD fmk (N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketones) have been developed to avert apoptotic chain events. X-linked inhibitor of apoptosis proteins (XIAP) has been identified as one of the mammalian homologues in the IAP family, and has been demonstrated to inhibit cell death (Ekert et al., 1999). During apoptosis, XIAP is cleaved to generate fragments with distinct specificity for caspases (Deveraux et al., 1999). However, caspase inhibition has yet to be used in clinical setting despite demonstrated efficacy in treatment of various CNS insults of *in vivo* models (Braun et al., 1999; Hara et al., 1997; Li et al., 2000b; Yakovlev et al., 1997). Several SCI experiments using caspase inhibitors have been reported (Li et al., 2000a; Lou et al., 1998; Springer et al., 1999) to mitigate injury-induced programmed cell death.

2.2 Apoptosis involving TNF-α mediated pathway

Tumor necrosis factor (TNF)-α, also known as cachexin or cachectin, is a pro-inflammatory, pro-apoptotic cytokine that elicits diverse biological actions, including the induction of

apoptosis (Tracey, 2011). TNF-α is a trimeric protein primarily produced by the brain resident immune cells such as monocytes and macrophages (the microglia cells) in response to various stimuli (Leung and Cahill, 2010). TNF-α is initially synthesized as a 26-kD cell surface-associated molecule (membrane-bound form) which is then cleaved into a soluble 17-kD form by TNF-converting enzyme (Grewal, 2009). The known roles of TNF-α have extended from the immune system to neuro-inflammatory domain in the nervous system (Leung and Cahill, 2010). TNF-α induces central sensitization and hyperalgesia by increasing excitatory synaptic transmission (Kawasaki et al., 2008). TNF-α initiates the activation of several cytokines and growth factors, as well as the recruitment of some immune cells. Cytokines exist in 'cascades' and interrupting one cytokine can disrupt the cascade. For example, blocking TNF-α reduces the activity of IL-6 and IL-1b (Fong et al., 1989); whereas blocking IL-1b reduces IL-6 (Goldbach-Mansky et al., 2006); and blocking IL-12 and IL-23 reduces IFN-γ. It is this 'master role' in cytokine function that makes TNF-α an attractive target in SCI and other disorders involving inflammation and apoptosis. TNF-α interacts with two distinct receptors – TNFR-55 (TNFR1, p55, CD120a) and TNFR-75 (TNFR2, p75, CD120b). TNF-α can either bind directly to TNFR1 and TNFR2 through cell-to-cell contact or undergo cleavage and binds in its soluble form (Vandenabeele et al., 1995). All nucleated cells express TNF receptors. TNFR1 is expressed constitutively on most cell types, whereas expression of TNFR2 can be induced by TNF-α, interleukin (IL)-1, and interferon (IFN)-α in rat primary astrocytes (Choi et al., 2005). In addition, TNFR2 expression is restricted to hematopoetic cells and can discriminate between murine and human forms of TNF-α (Tartaglia et al., 1991). The receptors also differ significantly in their binding affinity for homotrimeric TNF-α. Although both receptors can be considered high-affinity, the on–off kinetics of the two differs dramatically. Binding of homotrimeric TNF-α to TNFR1 seems to be essentially irreversible, whereas binding to TNFR2 is associated with rapid on–off kinetics (Choi et al., 2005).

Evidence showed that proinflammatory and proapoptotic cytokines, including TNF-α, IL-1γ, and FasL regulate cellular events and contributes to neuronal damage and functional impairment associated with SCI (Harrington et al., 2005; Lee et al., 2000; Martin-Villalba et al., 1999; Streit et al., 1998). TNF-α levels become elevated in human spinal cord after SCI, reaching a peak within 1h after the initial trauma (Dinomais et al., 2009). The expression of TNF-α is upregulated rapidly at the lesion site after SCI (Hayashi et al., 2000; Streit et al., 1998; Wang et al., 1996; Wang et al., 2002; Yan et al., 2001). TNF-α can induce apoptosis of oligodendrocytes and neuronal cell line *in vitro* (D'Souza et al., 1995; Sipe et al., 1996). Rapid accumulation of TNF-α may act as an external signal initiating apoptosis after SCI in neurons and glial cells (Lee et al., 2000; Shuman et al., 1997). Neutralization of TNF-α reduced the number of apoptotic cells after SCI (Lee et al., 2000). Apoptosis induced by TNF-α after SCI could be mediated in part by nitric oxide via upregulation of inducible nitric oxide synthase (iNOS) (Yune et al., 2003). Although, few studies indicate a neuroprotective role of TNF-α and NOS expression in SCI, several investigators support a neurodestructive role of these agents in spinal cord pathology (Bethea et al., 1999; Bethea and Dietrich, 2002; Dolga et al., 2008; Gonz'alez Deniselle et al., 2001; Sharma et al., 1995; Sharma, 2007; Sharma, 2008; Sharma, 2010; Stalberg et al., 1998).

Apoptosis of oligodendrocytes *in vivo* was shown to be induced by the overexpression of TNFR1 (Akassoglou et al., 1998). Following SCI, TNFR1 and TNFR2 expression is elevated in the injured spinal cord and localized on neurons, astrocytes and oligodendrocytes (Yan et

al., 2003). TNFR1 and TNFR2 are elevated as soon as 15 min after traumatic SCI in adult rats, reaches the peak at 4h for TNFR2 and 8h for TNFR1, and declines markedly after 1 day and 3 days (Yan et al., 2003). TNFR1 immunoreactivity was demonstrated on cells and afferent fibers of dorsal root and dorsal root ganglia, dorsal root entry zone and within lamina I and II of dorsal horn, whereas TNFR2 expression was absent in these regions (Holmes et al., 2004). These two receptors might work individually or synergistically to mediate the biological activity of TNF-α. It has been suggested that TNF receptors are involved in anti-apoptotic activities through the TNFR1-nuclear factor kappa B (NFκB) signal transduction pathway, which activates a recently identified endogenous caspase inhibitory system that is mediated by cellular inhibitor of apoptosis protein 2 (c-IAP2) (Kim et al., 2001). After TNF binding to TNFR1, a TNFR1 receptor–associated complex (complex-I) forms and contains TRADD, RIP1, TRAF1, TRAF2, and cIAP-1. Complex-I transduce signals that lead to NF-κB activation through recruitment of the IκB kinase 'signalsome' high-molecular-weight complex (Poyet et al., 2000; Zhang et al., 2000). TNFR1$^{-/-}$ mice had greater numbers of apoptotic cells, larger contusion size, and worse functional recovery after SCI. TNFR2$^{-/-}$ mice had similar, although not as pronounced, consequences as the TNFR1$^{-/-}$ mice. However, when new protein synthesis is inhibited prior to TNF stimulation, TNFR1 can initiate apoptosis by activation of apical caspases (Varfolomeev and Ashkenazi, 2004). TNFR1-mediated apoptosis signaling is induced in which TRADD and RIP1 associate with FADD and caspase-8 to form a cytoplasmic complex (complex-II) that dissociates from TNFR1. When complex-I triggers sufficient NF-κB signaling, anti-apoptotic gene expression is induced and the activation of initiator caspases in complex-II is inhibited. If NFκB signaling is deficient, complex-II transduces an apoptotic signal. Thus, early activation of NFκB by complex-I serves as a checkpoint to regulate whether complex-II induces apoptosis at a later time point after TNF binding.

2.3 Apoptosis involving JNK mediated pathway

The mitogen-activated protein kinases (MAPKs) are a family of evolutionally conserved molecules that play a critical role in cell signaling and gene expression. MAPK family includes three major members: c-Jun N-terminal kinase (JNK), p38 and extracellular signal regulated kinase (ERK), representing three different signaling cascades. The JNK pathway is considered as a key mediator of stress-induced apoptosis (Davis, 2000). Examples include neuronal apoptosis induced by NGF withdrawal (Eilers et al., 1998; Park et al., 1996; Xia et al., 1995), excitotoxic stress (Yang et al., 1997b) and UV radiation (Tournier et al., 2000; Tournier et al., 2001), thymocyte apoptosis induced by anti-CD3 antibody (Rincon et al., 1998; Sabapathy et al., 1999) and endothelial cell apoptosis caused by diabetes-associated hyperglycemia (Ho et al., 2000). JNK pathway activation may also contribute to neuronal death in neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's Diseases and stroke (Gao et al., 2005; Okuno et al., 2004; Yang et al., 1997b). However, the mechanism by which JNK activation triggers apoptotic processes remains to be fully elucidated. Substrates of JNK, including the Bcl-2 family proteins, regulate cytochrome c release which is an important event in apoptosis secondary to mitochondrial dysfunction. After SCI, JNK3 activity itself is induced by the injury, regulating cytochrome C release by phosphorylating Mcl-1, and thereby facilitating the degradation of Mcl-1, which is necessary for induction of apoptosis of oligodendrocytes (Li et al., 2007). Although JNK3 is also activated in neurons after SCI, it did not induce neuronal apoptosis. A potential role for

JNK3 in neurons is regulation of autophagic death instead of apoptotic death as observed in oligodendrocytes (Li et al., 2007). Several studies demonstrated that the anti-apoptotic proteins Bcl-2, Bcl-xL and Mcl-1 are phosphorylated by JNK *in vitro* and *in vivo* (Inoshita et al., 2002; Maundrell et al., 1997; Yamamoto et al., 1999), there by suppressing the anti-apoptotic activity of these proteins. Another possibility is that JNK phosphorylates the transcription factor c-Jun which might in turn mediate the induction of proteins regulating cytochrome c release in apoptosis (Behrens et al., 1999). Indeed, JNK has been found to regulate some pro-apoptotic BH3-only proteins via transcription-dependent mechanisms (Tournier et al., 2000). Two genes in this subfamily, DP5 and Bim, have AP-1 binding sites on their promoters, and transcription appears to be regulated by JNK activity (Davis, 2000; Harris and Johnson, Jr., 2001; Putcha et al., 2001; Putcha et al., 2003; Whitfield et al., 2001; Yang et al., 1997a; Yin et al., 2005).

Substantial increases in p-JNK expression were noticed after SCI (Esposito et al., 2009; Yin et al., 2005). Activated form of JNK was expressed in the apoptotic cells that were stained by oligodendrocyte antibodies 1–3 days after SCI (Nakahara et al., 1999) and both p-JNK and DP5 colocalization were found in neurons and oligodendrocytes undergoing apoptosis after SCI (Yin et al., 2005). Similarly, the transcription factor, c-Jun (which is an exclusive substrate of JNK), was also phosphorylated shortly after traumatic injury. Furthermore, DP5 is also induced after SCI in a JNK-dependent manner. Suppression of JNK activity by SP600125, a JNK inhibitor, or jnk1 knockdown by an antisense oligodeoxynucleotide (ODN) attenuated SCI-induced DP5 upregulation and caspase-3 activation. Following traumatic SCI, JNK activation contributes to activation of caspase 3, and apoptosis of glia and neurons (Yin et al., 2005). Based on these discoveries, it appears that JNK/c-Jun/DP5/Caspase 3 signaling pathway could represent a potential target for therapeutic interventions in SCI.

3. Stem cell therapy for apoptosis after SCI

During the first few days after injury, there are many microenvironmental features that are detrimental to the survival and integration of transplanted stem cells (Hausmann, 2003). The pathophysiologic processes initiated after acute spinal cord injury are extremely complex, and our limited understanding is reflected in the utilization of i.v. steroid trauma protocol as the only currently available neuroprotective strategy. The limited success of pharmacologic treatment has shifted the focus of medical research away from these traditional treatments to other more promising areas such as cell-based therapy, particularly, the application of stem cell biology (Hipp and Atala, 2004; Stanworth and Newland, 2001). Thus, various cellular transplantation strategies have been utilized in different models of SCI (Eftekharpour et al., 2008). The adult spinal cord harbors endogenous stem/progenitor cells, collectively referred to as NPCs, which might be responsible for normal cell turnover. However, the proliferative activity of endogenous NPCs is too limited to support significant self repair after injury. As such, stem cell transplantation has become a very attractive and viable treatment option for not only CNS injury but also other neurodegenerative disease processes such as Parkinson disease, MS, stroke and ALS (Malgieri et al., 2010). The rationale for cell replacement approach for the treatment of SCI are (1) regeneration, which seeks to replace lost or damaged neurons and induce axonal regeneration or modulate plasticity; and (2) repair, which seeks to replace supportive cells such as oligodendrocytes in order to prevent progressive myelin loss and induce remyelination (Totoiu and Keirstead, 2005). Additionally, stem cell transplantation may promote protection of endogenous cells

from further cell loss by attenuation of secondary injury process. Non-embryonic sources of adult stem cells, free from many of the ethical and legal concerns associated with embryonic stem cell research, may offer great promise for the advancement of medicine (Moore et al., 2006). At present, the only non-embryonic stem cells easily available in large numbers are found in the bone marrow, adipose tissue and human umbilical cord blood. These multipotent adult stem cells are ideal vehicles for gene therapy, and genetic engineering for therapeutic treatment of various genetic disorders (Pessina and Gribaldo, 2006). Recent studies have shown that transplanted adult stem cells, including mesenchymal stem cells, human umbilical cord blood stem cells into injured spinal cord promote endogenous myelin repair and modulate immune response, stirring the hope of applying their efficacy to other demyelinating diseases such as MS and stroke.

3.1 Mesenchymal stem cells

Mesenchymal stem cells (MSC) are stromal cells from the bone marrow (BM) and appear as spindle-shaped cells in culture (Friedenstein et al., 1974). Human mesenchymal stem cells are multipotent cells that are present in adult marrow, can replicate as undifferentiated cells and have the potential to differentiate to lineages of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle, and marrow stroma (Pittenger et al., 1999). Even though not immortal, they have the ability to expand many folds in culture while retaining their growth and multilineage potential. MSC are identified by the expression of surface markers including CD105 (SH2) and CD73, and are negative for hematopoietic markers such as CD34, CD45 and CD14. MSC attracted interest for their ability to migrate to the injured site and differentiate into multiple cellular phenotypes *in vivo* (Uccelli et al., 2011). The heterogenity of MSC, and their expression of a large number of regulatory proteins, may explain their wide therapeutic features and capacity to respond differently to injuries depending on the microenvironment, despite their low engraftment *in vivo* (Phinney and Prockop, 2007). MSC produce cytokines and a variety of soluble factors regulating several biological activities as demonstrated by their transcriptome analysis (Phinney et al., 2006). They play a major role in the maintenance of local homeostasis via their supporting activity in the survival of non-proliferating hematopoietic stem cells (HSC) niche in the bone marrow (Mendez-Ferrer et al., 2010). These mesenchymal stem cells are derived from the embryonic mesodermal layer and retain the cardinal abilities of stemcellness for self-renewal and multipotentiality to differentiate into various tissue cell types.

MSCs are attractive candidates for cellular therapies because they are easy to isolate, have a broad differentiation potential, and proliferate *in vitro* (Barry, 2003). Bone Marrow and umbilical cord blood are rich sources of these cells, but MSC have also been isolated from fat (Gronthos et al., 2001), skeletal muscle (Jankowski et al., 2002), human deciduous teeth (Miura et al., 2003), and trabecular bone (Noth et al., 2002). In addition, recent data demonstrated that MSC can give rise to cells of non-mesodermal origin such as hepatocytes, epithelial and neural cells (Chagraoui et al., 2003; Ma et al., 2006; Spees et al., 2003; Woodbury et al., 2000). The choice of the tissue source is governed by availability, as well as by the degree of characterization of the cells and the consistency of the preparations. MSCs from bone marrow and umbilical cord blood have been reasonably well defined in terms of surface markers and differentiation pathways. These donor sites provide a readily available autologous source for cell transplantation, alleviating the need for long-term immunosuppression. Mesenchymal stem cells have been used in experimental models of

SCI and in preliminary clinical trials for SCI (Himes et al., 2006; Sykova et al., 2006) with apparent improvement of behavioral outcome. Stem cells are likely to be therapeutically valuable both in providing permissive substrates for axonal regeneration and as 'cellular minipumps' delivering trophic factors that could enhance white matter sparing and/or axonal regeneration (Enzmann *et al*., 2006). The functional benefits of MSC transplantation in CNS injuries can be explained by their ability to provide the host tissue with growth factors or modulate the host immune system (Garbuzova-Davis et al., 2006). One of the major goals for the therapeutic use of stem cells is to prevent apoptosis or to replace lost cells, particularly oligodendrocytes, in order to facilitate the remyelination of spared axons. Details showing application of unengineered mesenchymal stem cells from various sources and their applications after SCI are provided in Table 1.

3.1.1 Bone marrow derived mesenchymal stem cells

Human MSCs are isolated from a bone marrow (BM) aspirate, which is often harvested from the superior iliac crest of the pelvis. They represent a very minor fraction of the total nucleated cell population in marrow, but can be plated and enriched using standard cell culture techniques. Frequently, the marrow sample is subjected to fractionation on a density gradient solution, such as Percoll, after which the cells are plated. Primary cultures are usually maintained for 12–16 days, and are then detached by trypsinization and subcultured. Morphologically, the cells resemble adherent fibroblasts (Barry, 2003). Under physiological settings bone marrow derived MSC (BMSC) main function is to regulate hematopoiesis. However, when these cells are grown away from their natural environment, they can be readily and effectively propagated and manipulated genetically into cells of the mesodermal lineage but also, under certain experimental circumstances, into cells of the neuronal and glial lineage (Clark and Keating, 1995). The advantages of using bone marrow as a source for stem cells are numerous: they are relatively easy to isolate, the cells grow and expand well in tissue culture. BMSC may be used in autologous transplantation protocols, and these have already received FDA approval for treatment of hematopoietic diseases (Sykova et al., 2006). BMSC therapeutic value relies on their significant anti-proliferative, anti-inflammatory and anti-apoptotic features. These properties have been demonstrated in the treatment of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis where inhibition of the autoimmune response resulted in a significant neuroprotection.

BMSC transplantation results in neuroprotection and increased endogenous neuronal survival in experimental brain ischemia, traumatic brain and spinal cord injury models (Uccelli et al., 2011). There is increasing evidence that MSCs possess immunosuppressive features (Bartholomew et al., 2002; Corcione et al., 2006; Di Nicola et al., 2002; Jiang et al., 2005). These immunosuppressive properties in combination with their restorative functions reduce the acute inflammatory response to SCI, minimize cavity formation, as well as diminish astrocyte and microglia/macrophage reactivity (Abrams et al., 2009; Himes et al., 2006; Neuhuber et al., 2005). BMSC administered 1- week post-SCI had better rates of survival since the microenvironment has become less hostile by then. MSC transplantation in an experimental SCI model has been shown to enhance tissue protection and cellular preservation via reduction in injury-induced sensitivity to mechanical trauma (Abrams et al., 2009). These studies indicated that transplanted MSC attenuates acute inflammation and promote functional recovery following SCI (Hofstetter et al., 2002). Clinically, Park *et al*. (2005)

References	Source of Mesenchymal stem cells	Experimental Animals	Route/site of administration	Treatment timing	Treatment outcome
Cízková *et al*., 2006	Human bone marrow	Rats	Into right femoral vein	7 days after thoracic SCI	Remyelination of spared white matter tracts, enhancing axonal growth and functional recovery
Dasari *et al*., 2007a	Rat bone marrow	Rats	Injury epicenter	7 days after thoracic SCI	Downregulation of caspase mediated apoptosis, functional recovery of rats
Dasari *et al*., 2008	Human umbilical cord blood	Rats	Injury epicenter	7 days after thoracic SCI	Downregulation of Fas mediated apoptosis, functional recovery of rats
Dasari *et al*., 2009	Human umbilical cord blood	Rats	Injury epicenter	7 days after thoracic SCI	Downregulation of TNF-α mediated neuronal apoptosis
Deng *et al*., 2006	Rhesus monkey bone marrow	Rhesus monkey	Injury epicenter	7 days after thoracic SCI	*de novo* neurogenesis and functional recovery
Gu *et al*., 2010	Rat bone marrow	Rats	1mm rostral and caudal from injury epicenter	7 days after thoracic SCI	Reduction in lesion volume; axonal regrowth of injured spinal cord.
Hu *et al*., 2010	Human umbilical cord blood	Rats	2mm rostral and caudal from injury epicenter	24h after thoracic SCI	Increased length of neurofilament positive fibers and increased numbers of growth cone-like structures around the lesion site, functional recovery
Lee *et al*., 2007	Human bone marrow	Rats	Injury epicenter	7 days after thoracic SCI	Functional recovery
Lim *et al*., 2007	Umbilical cord blood of canine fetuses	Dogs	Injury epicenter	7 days after balloon compression at the first lumbar vertebra.	Significant improvement in the nerve conduction velocity based on the somatosensory evoked potentials. Functional recovery.
Osaka *et al*., 2010	Rat bone marrow	Rats	Intravenous (through the femoral vein)	6h, 1d, 3d, 10d, 14d, 21d, 28d after thoracic SCI	Cavitation in the contused spinal cords was less; functional recovery
Parr *et al*., 2008	Rat bone marrow	Rats	Injury epicenter	9 days after clip compression injury at the thoracic region	Potential axonal guidance through guiding strands of matrix generated by the bone marrow stromal cells
Satake *et al*., 2004	Rat bone marrow	Rats	Stem cells injected into the subarachnoid space	3, 5, 7 days after thoracic SCI	MSCs differentiated into Nestin-positive, immature neurons or glial cells
Yang *et al*., 2008	Wharton's jelly of the human umbilical cord	Rats	2mm rostral and caudal to injury epicenter	After complete transection at the thoracic region.	Functional recovery, regenerated axons in the corticospinal tract and neurofilament-positive fibers around the lesion site.
Zeng *et al*., 2011	Rat bone marrow derived mesenchymal stem cells grown on 3D gelatin sponge (GS) scaffolds	Rats	Injury epicenter	7 days after thoracic SCI	Attenuating inflammation, promoting angiogenesis and reducing cavity formation.

Table 1. Table showing different authors using mesenchymal stem cells for treatment after SCI

evaluated the therapeutic efficacy of combining autologous BMSC transplantation, administered directly into the spinal cord lesion site, with granulocyte macrophage- colony stimulating factor (GM-CSF), given subcutaneously, in six patients with complete SCI. At the 6-month and 18-month follow-up periods, four of the six patients showed neurological improvements by two ASIA grade (from ASIA A to ASIA C), while another improved from ASIA A to ASIA B. Moreover, BMSC transplantation together with GM-CSF was not associated with increased morbidity or mortality. In another clinical trial, safety of autologous bone marrow cell implantation was tested in 20 patients (Sykova et al., 2006). Motor evoked potential, somatosensory evoked potential, magnetic resonance imaging, and ASIA scores were measured in patient follow-up. This study demonstrated that BMSC transplantation is a relatively safe procedure and BMSC-mediated repair can lead to modest improvements in some injured patients. Thus, it is anticipated that a Phase II clinical trial designed to test the efficacy will be initiated in the near future. In another study using human mesenchymal stem cells (hMSCs) derived from adult bone marrow, the transplanted cells were found to infiltrate mainly into the ventrolateral white matter tracts, spreading to adjacent segments rostro-caudal to the injury epicenter, and facilitate recovery from SCI by remyelinating spared white matter tracts and/or by enhancing axonal growth (Cizkova et al., 2006). In our laboratory, we used mesenchymal stem cells from rat bone marrow to evaluate the therapeutic potential after SCI (Dasari et al., 2007a). Immunohistochemistry confirmed a large number of apoptotic neurons and oligodendrocytes in caudal segments 2 mm away from the lesion site. Expression of caspase-3 on both neurons and oligodendrocytes after SCI was significantly downregulated by BMSC. Treatment with BMSC had a positive effect on behavioral outcome and better structural integrity preservation as seen on histopathological analysis. BMSC secrete protective factors that prevent neuronal apoptosis through stimulation of endogenous survival signaling pathways, namely the PI3-K/Akt and the MAPK/Erk1, 2-cascade (Isele et al., 2007). The potential of bone marrow cell transplantation as a method of repair in the injured CNS may serve a number of different purposes that span various therapeutic targets. Animal studies have demonstrated that transplanted MSCs mollify the inflammatory response in the acute setting and reduce the inhibitory effects of scar tissue in the subacute/chronic setting to provide a permissive environment for axonal extension. In addition, grafted cells may provide a source of growth factors to enhance axonal elongation across spinal cord lesions (Wright et al., 2011). Moreover, SCI initiates an innate immune response that participates not only in secondary pathogenesis but also in wound healing (Trivedi et al., 2006). Even though the present data are promising, further research is needed to establish whether bone marrow cell treatments can serve as a safe and efficacious autologous source for the treatment of the injured SCI (Wright et al., 2011). Downregulation of TNF-α expression in macrophages/microglia was observed at an early stage after SCI in rats transplanted with a gelatin sponge scaffold impregnated with rat bone marrow-derived mesenchymal stem cells at the site of injury (Zeng et al., 2011).

3.1.2 Human umbilical cord blood derived mesenchymal stem cells

Human umbilical cord blood collected from umbilical vein following birth is a valuable source of mesenchymal stem cells (hUCB or hUCBSC) and has been used as an alternative source of allogenic donor cells to treat a variety of hematologic, immunologic and oncologic disorders (Broxmeyer et al., 1989; Gluckman et al., 1997; Han et al., 2003; Kim et al., 2002).

Human umbilical cord blood contains a heterogeneous population of cells enriched in hematopoietic stem cells and display a high proliferative capacity (Mayani and Lansdorp, 1998). These mesenchymal multipotent progenitor cells possess the capability of differentiating into diverse functional progenitors, including hematopoietic cell lineages, dendritic cells, cardiomyocytes, mesenchymal stem cell (MSC) progenitors, neural stem cell (NSC) progenitors, keratinocytes, hepatocytes, pancreatic β-cells, and endothelial cells in specific culture conditions *in vitro* and *in vivo* (Brunstein et al., 2007; Hemmoranta et al., 2006; Mimeault and Batra, 2006; Weiss and Troyer, 2006). Complex interactions between adult stem cells, host cells and the specialized microenvironment may influence their behavior (Arai and Suda, 2007; Barrilleaux et al., 2006; Bryder et al., 2006; Moore et al., 2006; Wilson and Stice, 2006). More specifically, the reciprocal interactions of adult stem cells with neighboring cells *via* the formation of adherens junctions and the secretion of diverse soluble factors might contribute to their restricted mobility and the adoption of a quiescent or activated state within niches (Mimeault and Batra, 2006). There are many advantages of human umbilical cord blood as a source of MSC as compared to bone marrow or adipose tissue. First, the collection of cord blood is easy and painless. The cord blood can be stored for later use. Second, hUCBSC are more primitive than MSCs isolated from other tissue sources (Can and Karahuseyinoglu, 2007; Lu et al., 2006; Sarugaser et al., 2005; Wu et al., 2007). Third, hUCBSC have a higher proliferative capacity and a faster population doubling time that remains unaltered after 30 passages. In contrast, BMSC showed significantly slower doubling time which became even longer after 6 passages (Malgieri et al., 2010). Finally, hUCBSC has lower immunogenicity and graft-versus-host reactivity when compared to BMSC (Malgieri et al., 2010). There are four different methods for isolation and purification of hUCBSC: density gradient centrifugation, flow cytometry isolation, attachment screening and two-step enzymatic digestion (Zhang et al., 2006). In our laboratory, the cord blood is subjected to fractionation on a density gradient solution, such as Ficoll, after which the cells are plated. Primary cultures are usually maintained for 12–16 days, and are then detached by trypsinization and subcultured. As such, umbilical cord blood bank represents a rich source of multipotent stem cells that are readily available for transplantation or for generating diverse tissue-specific adult stem/progenitor cells and their further differentiated progeny for cellular therapies of various disorders in humans (Barrilleaux et al., 2006; Brunstein et al., 2007; Mimeault and Batra, 2006).

Human umbilical cord blood stem cells offer great potential for novel therapeutic approaches targeted against many CNS diseases. The therapeutic potential of hUCBSC may either be attributed to the inherent ability of stem cell populations to replace damaged tissues outright, or alternatively, to their ability to repair damaged tissues through neural protection and secretion of neurotrophic factors by various cell types within the graft (Park et al., 2011; Sanberg et al., 2005). Previous studies have reported that hUCBSC are beneficial in reversing the deleterious behavioral effects of spinal cord injury, even when infused 5 days after injury (Saporta et al., 2003). Transplanted hUCBSC differentiate into various neural cells and induce motor function improvement in SCI rat models (Kuh et al., 2005). However, to date, very few reports have utilized hUCBSC in SCI. More thorough experiments are needed to evaluate how hUCBSC modulates improvement after SCI and whether it possesses the potential of tissue plasticity (Enzmann et al., 2006). In our laboratory, using SCI injury model in rats, we transplanted hUCBSC one week after SCI to evaluate neural cell differentiation and functional improvement. We have shown that

hUCBSC transdifferentiated into neurons and oligodendrocytes, and downregulated Fas-mediated apoptosis (Dasari et al., 2007b; Dasari et al., 2008). The hUCBSC-transdifferentiated oligodendrocytes facilitate the secretion of neurotrophic hormones NT3 and BDNF and synthesize MBP and PLP, promoting the remyelination of demyelinated axons in the injured spinal cord (Dasari et al., 2007b). Furthermore, apoptotic pathways mediated by both Fas and TNF-α were downregulated by hUCBSC (Dasari et al., 2008). Our findings confirmed that mesenchymal stem cells were able to downregulate apoptotic pathways mediated by Fas and Caspase-3 (Figure 2) (Dasari et al., 2007b; Dasari et al., 2008). In hUCBSC-treated rats, the PI3K/Akt pathway was also involved in anti-apoptotic actions. Further, the structural integrity of the cytoskeletal proteins α-tubulin, MAP-2A and -2B and NF-200 has been maintained with hUCBSC treatments. The locomotor scale scores in hUCBSC-treated rats were significantly improved compared to those of the injured group. Taken together, hUCBSC-mediated down-regulation of Fas and caspases may lead to functional recovery of the hind limbs of rats after SCI. With extension of this study, using RT-PCR microarray and analyzing 84 apoptotic genes, we identified the genes that render the injured spinal cord harmful and the hUCBSC-treated spinal cord conducive to regeneration and repair at 3 weeks (Dasari et al., 2009). We observed that the genes involved in inflammation and apoptosis were up-regulated (phospho-p53 and Bax) in the injured spinal cords of rats (Kotipatruni et al., 2011), whereas the genes involved in neuroprotection were up-regulated in the hUCBSC-treated rats (Dasari et al., 2008). Changes in the expressions of TNF-α, TNFR1 and TNFR2 were detected over 3 weeks after SCI and after transplantation with hUCBSC cells. The expression of P50 and P65 on neurons after SCI was efficiently inhibited by application of hUCBSC. Both the *in vivo* and *in vitro* studies support our hypothesis that the therapeutic mechanism of hUCBSC is inhibition of the neuronal apoptosis during the repair of injured spinal cord. Veeravalli *et al*. (2009a) reported the involvement of tissue plasminogen activator (tPA) after SCI in rats and the role of hUCB stem cells. The tPA expression and activity were studied *in vivo* after SCI in rats and *in vitro* in rat embryonic spinal neurons in response to injury with staurosporine, hydrogen peroxide and glutamate. The expression of tPA increased after SCI and reached peak levels at 3 weeks post-SCI. The MBP expression was minimal at the time of the peak tPA activity and *vice versa*. By contrast, infusion of hUCBSC stem cells down-regulated the elevated tPA activity *in vivo* in rats as well as *in vitro* in the spinal neurons. Further, MMP-2 is upregulated after hUCBSC treatment in spinal cord injured rats and in spinal neurons injured either with staurosporine or hydrogen peroxide. Also, hUCBSC-induced upregulation of MMP-2 diminished formation of the glial scar at the site of injury along with reduced immunoreactivity to chondroitin sulfate proteoglycans. This upregulation of MMP-2 levels and reduction of glial scar formation by hUCBSC treatment after SCI created an environment more favorable for endogenous repair mechanisms (Veeravalli et al., 2009b). There have been an increasing number of studies suggesting that these hUCB derived-$CD34^+$ cells can induce angiogenesis and endo/exogenous neurogenesis in stroke (Taguchi et al., 2004) and SCI (Kao et al., 2008). In addition, Chen *et al*. (2008) recently showed that hUCB cells have the ability to secrete multiple neurotrophic factors. Their study demonstrated elevation of neuroprotective cytokine serum IL-10 levels and depression of TNF-α levels after hUCB cell infusion. Moreover, both GDNF and VEGF could be detected in the injured spinal cord after the transplantation of hUCB cells, promoting angiogenesis and neuronal regeneration.

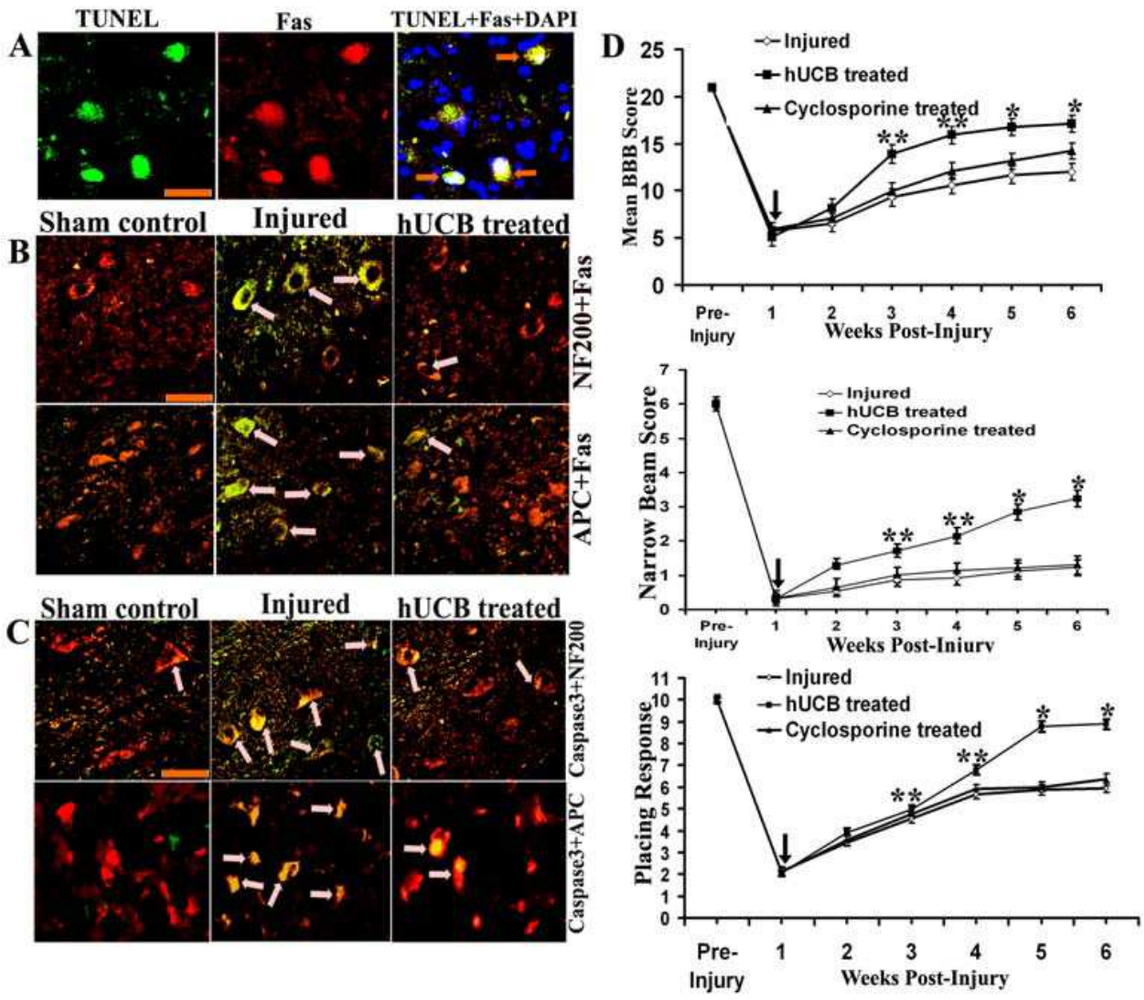


Fig. 2. Fas expression after SCI and treatment with hUCBSC: (A) Fas immunoreactivity on TUNEL positive cells. Expression of Fas (Texas-red conjugated) on TUNEL positive cells (green) from injured sections. (B) Cryo-sections showing co-localization of Fas and NF-200 (specific for neurons) and Fas and APC (mature marker for oligodendrocytes) showing expression of Fas on neurons and oligodendrocytes (↑) undergoing apoptosis. Fas is FITC-conjugated and NF-200 and APC are Texas-red conjugated. Results are from 3 sections between 1 and 2mm caudal to the injury epicenter after 3 weeks SCI (n≥3). (C) Confocal images of cryo-sections illustrate co-localization (yellow) of activated caspase-3 (FITC-conjugated) with NF-200 (Texas-red conjugated) and APC (Texas-red conjugated) within the dorsal region(↑), following spinal cord contusion. For panels A, B and C Bar = 100µm.
(D) Top panel shows BBB scores of rats with SCI before and after hUCB transplantation. Repeated-measures of ANOVA followed by Bonferroni's post hoc tests showed that BBB scores in hUCB-grafted animals were significantly higher than those in injured-untreated animals. Each point represents the highest locomotor score achieved each day. Middle panel shows Narrow beam scores of injured and treated rats over a period of 6 weeks and bottom panel shows number of placing responses of injured and treated animals. Arrow (↓) indicates hUCB transplantation point. Error bars indicate ±SEM (n≥5/group) (*p<0.01 and **p<0.05)

4. Conclusions

Transplantation of mesenchymal stem cells into the injured spinal cord and therapeutic applications of mesenchymal stem cells represent exciting new approaches to managing spinal cord injury. Improvements in molecular techniques and strategies along with the availability of modified stem cell lines have fostered our understanding in the mechanism of SCI and advanced the application of stem cell transplantation for treatment of other neurological disorders beyond traumatic brain and spinal cord injury. However, cell-based therapy for SCI is still at an early stage and faces numerous challenges: among them safety problem, patient's genetic diversity and variability, differences in the extent of injury, translational clinical issues, regulatory and ethical concerns. There are numerous ongoing clinical trials utilizing MSC transplantation for treatment of various genetic and neurological disorders. However, the ultimate value of cell-based therapy will need continued expansion of basic scientific knowledge of disease processes and proven therapeutic efficacy via rigorous controlled, randomized, double blind clinical trials.

5. Acknowledgements

This research was supported by a grant from Illinois Neurological Institute to DHD. We also thank Shellee Abraham for manuscript preparation and Diana Meister and Sushma Jasti for manuscript review.

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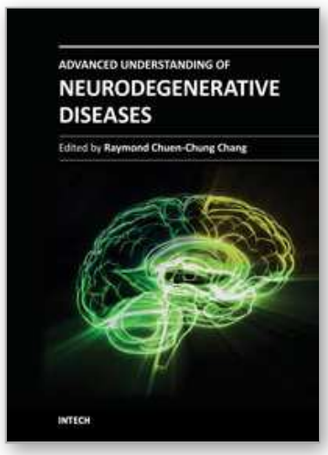
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Advanced Understanding of Neurodegenerative Diseases

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-529-7
Hard cover, 442 pages
Publisher InTech
Published online 16, December, 2011
Published in print edition December, 2011

Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

How to reference

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Venkata Ramesh Dasari, Krishna Kumar Veeravalli, Jasti S. Rao, Dan Fassett and Dzung H. Dinh (2011). Mesenchymal Stem Cell Therapy for Apoptosis After Spinal Cord Injury, Advanced Understanding of Neurodegenerative Diseases, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-529-7, InTech, Available from: http://www.intechopen.com/books/advanced-understanding-of-neurodegenerative-diseases/mesenchymal-stem-cell-therapy-for-apoptosis-after-spinal-cord-injury

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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Phone: +86-21-62489820
Fax: +86-21-62489821

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