



Review Article

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Long Non-Coding RNAs in Spinal Cord Injury

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Abstract

Non-coding RNAs whether short (such as microRNAs) or long >200 nucleotides, are implicated in a wide array of physiological and pathological processes including spinal cord injury. In this review, we will focus specifically on long non-coding RNAs and their involvement in spinal cord injury. We will first provide a background on the cellular and molecular mechanisms involved in spinal cord injury and emphasize the need to better understand these processes for developing effective therapeutics. Next, we will review the long non-coding RNAs reported to be changed by injury to the spinal cord, the study models and the techniques used, as well as the outcomes of injury when the expression of these transcripts is modified. We will finally discuss what can be done in the future for the experimental application of long noncoding RNAs in spinal cord injury.

Introduction

Spinal cord injury (SCI) and paralysis can be the result from: (I) a non-traumatic etiology such as viral infections (e.g. poliovirus can trigger poliomyelitis causing motor neuron death [1]), arthritis, and autoimmune disorders (e.g. multiple sclerosis in which white matter demyelination results in several neurological symptoms including gait ataxia, weakness, and optic neuritis [2]); (II) a traumatic injury (for example a motor vehicle accident); or (III) an ischemic event, caused by ischemic conditions imposed on the spinal cord during surgical interventions [3]. This review will only be focused on traumatic and ischemic spinal cord damage and long-noncoding RNAs.

A-Spinal Cord Injury

In traumatic SCI, the injury is sustained from a traumatic event (e.g. car accidents, falls, violence) [4] and can result in contusion [5], vertebral fracture and dislocation [6], or transection [7]. The damage caused by the initiating traumatic event is referred to as the primary injury; secondary injury refers to the biochemical reactions that follow the primary insult and exacerbate the injury to the spinal cord [8]. Secondary injury involves ionic imbalances and glutamate excitotoxicity, inflammation and inflammatory cytokine signaling, lipid peroxidation (LP), demyelination, axonal dieback,

cell death, and gliosis and fibrosis [8]. The mechanical forces imparted by the primary injury disrupts the local vasculature and damages cells thus yielding higher amounts of extracellular debris including glutamate [8]; higher concentrations of extracellular glutamate dysregulates ionic homeostasis which ultimately promotes cell death [9]. Deleterious enzymes such as nitric oxide synthase and phospholipase A, activated by glutamate excitotoxicity [9], produce free radicals which initiates LP, a process that yields toxic 4-hydroxynonenal and 2-propenal [10] and produces protein adducts [11]. Free radicals generated from nitric oxide synthase and LP protein adducts also contribute to DNA damage which can result in neuronal death [12-14]. Vascular disruption results in neutrophil extravasation which, along with microglial activation, propagates inflammatory signaling through elevated inflammatory cytokine and chemokine secretion. Reports indicate that these processes exert some regenerative/neuroprotective signals at the synapse but due to the high intensity of the immune response at this point it is rather the detrimental signals that dominate the secondary effects in the injured spinal cord [15,16]. This inflammatory milieu further exacerbates the damage caused by the primary insult via activation of cell death programs (e.g. apoptosis, necroptosis), astrogliosis, glial scar formation, and extracellular matrix remodeling [8].

Ischemic SCI (ISCI) involves an ischemic etiology such as atherosclerotic disease, aortic pathologies, aortic surgery, and aortic grafting [17]. Damage to the spinal cord in ISCI is potentiated by ischemic/reperfusion (I/R) injury, which can occur during open surgical repair of thoracoabdominal aortic aneurysms (TAAA). In open surgery of TAAA, a cross-clamp is employed across the damaged aorta while the graft is implanted. Transient use of the cross-clamp induces ischemia of the spinal cord followed by blood flow reperfusion [18]. I/R of the spinal cord exacerbates damage as free radicals are generated and hyperemia contributes to spinal cord edema which subsequently induce neuronal death and LP [19]; concurrently, an inflammatory response in ISCI also contributes to damage through inflammatory cytokine secretion [20, 21]. Studies of I/R injury in rats indicate that targeting components of the inflammatory cascade attenuated I/R injury and supported neurological improvement [22,23]. In addition, deletion of the pro-inflammatory microRNA *miR-155* in mice reduced the incidence of paralysis after aortic cross-clamping in mice, further suggesting an inflammatory component to ISCI damage and paralysis after open aortic repair [21].

In the United States, the prevalence of SCI is reported to be 906 per million [24], and 90% of SCI cases have a traumatic etiology [4]. The impact of SCI upon patients and their families is tremendous: the damage caused by SCI can cause loss of function at and/or below the level of the neurological injury, patients who sustained the injury between the age of 25 and 34 years have a life expectancy of 38 years post-injury [25], and per individual economic burden can reach as high as \$3.0 million [26]. As of 2013, the only approved pharmaceutical therapy for SCI is methylprednisolone. Methylprednisolone possesses anti-inflammatory characteristics and attenuates LP yet it demonstrates varying efficacy in patients [27]. Accordingly, it is necessary to develop novel therapeutics aimed at attenuating neurological injury, promoting functional recovery, and bolstering endogenous regenerative efforts.

B- Long noncoding RNAs

Long non-coding RNAs (Lnc-RNAs), as the name implies, are RNA transcripts longer than 200 nucleotides that are for the most part not translated [28]. While there are also some Lnc-RNAs that have been shown to encode very short peptides [29], the research in this field is scarce [30]. Lnc-RNAs can be generated from the transcription of intergenic sequences (large intergenic non-coding RNA ie. Linc-RNA), from the antisense strand of recognized transcription units, from transcribed pseudogenes, from spliced-out introns, or from extraneous transcripts produced at transcription start sites [28]. Lnc-RNAs exert biologically relevant functions through a variety of mechanisms including as a scaffold for epigenetic regulators and as molecular sponges through RNA-RNA interactions [28]. The biological functions of Lnc-RNAs involve modulation of gene expression during development, the pathogenesis of cancer, and senescence [28,30]. The rest of this review will center on examining the role and potential therapeutic applicability of Lnc-RNAs in SCI.

Lnc-RNAs in SCI

As noted earlier, one mechanism by which Lnc-RNAs can exert their effects is through serving as a decoy for regulatory factors (sponging). Binding of a particular Lnc-RNA to a microRNA through complementary base recognition impairs the microRNA from binding to its targets; thus, the microRNA is unable to reduce the expression of its protein-coding target transcripts, ultimately changing cellular homeostatic conditions. Lnc-RNA-microRNA interactions are the most extensively studied due to the possibility of predicting (*in silico*) Lnc-RNA-microRNA pairs.

In a contusion model of rat SCI, Lnc-RNA *MALAT1*, which was studied based on its roles in other diseases such as non-small cell lung carcinoma, was suggested to propagate inflammatory processes by interacting with *miR-199b* [31], a known regulator of the NF- κ B inflammation pathway [32]. In fact, the study indicated that *in vitro* Lnc-RNA *MALAT1* knockdown (KD) reduced tumor necrosis factor-alpha (TNF- α) and interleukin 1 Beta (IL-1 β); these effects were reversed for the Lnc-RNA *MALAT1* KD + *miR-199b* inhibition condition. Furthermore, Lnc-RNA *MALAT1* (increased in SCI rats) is inversely correlated with *miR-199b* (decreased in SCI rats) expression and *in vivo* Lnc-RNA *MALAT1* inhibition with lentiviral (LV)-siRNA-*MALAT1* reduced inflammatory cytokine production and improved motor scores; these effects were reversed with *antago-miR-199b* treatment [31]. On the other hand, Qiao *et al.* proposed that Lnc-RNA *MALAT1* has a beneficial effect after I/R SCI in rats by noting that Lnc-RNA *MALAT1* overexpression in oxygen-glucose deprived neurocytes reduced *miR-204*, increased anti-apoptotic Bcl-2 and overall reduced apoptosis. These results translated to *in vivo* studies and I/R rats subjected to Lnc-RNA *MALAT1* overexpression exhibited lower motor deficit indices while *miR-204* overexpression reversed the anti-apoptotic effects of Lnc-RNA *MALAT1* overexpression [33]. We speculate that the contrasting effects of Lnc-RNA *MALAT1* in these two studies could be due to the utilization of different SCI models, and the fact that Zhang *et al.* studied Lnc-RNA *MALAT1* in microglial cell culture while the study conducted by Qiao *et al.* examined expression in neurocytes. These differential results raise a key point: it is important to acknowledge the cellular components involved in SCI and the cellular origin of genes/proteins, Lnc-RNAs, or microRNAs that are changed after SCI. In addition, considering the fact that microRNAs target different transcripts at different concentrations [34,35], depending on the level of expression of microRNAs and their interacting sponging Lnc-RNA, differential functional outcomes are expected. Another Lnc-RNA transcript involved in SCI is *XIST*. Studies have indicated that Lnc-RNA *XIST* has pro-apoptotic and pro-inflammatory role in SCI. Specifically, Zhao *et al.* indicates that in *in vitro* and *in vivo* models of SCI, Lnc-RNA *XIST* is upregulated and exerts deleterious effects through targeting the *miR-27a*/Smurf1 axis which was confirmed with a dual-luciferase assay and anti-*miR-27a* treatment in microglial cell culture; furthermore, in a contusion SCI rat model, Lnc-RNA *XIST* silencing using LV-sh-*XIST* infection decreased TNF- α and IL-6 secretion, and Bax and cleaved-Caspase-3 expression, two

genes involved in apoptosis [36]. Gu *et al.* suggested that Lnc-RNA *XIST* may sponge *miR-494*, an oncomiR in hepatocellular carcinoma, which was confirmed using a luciferase assay; LV-sh-Lnc-RNA *XIST* administration in a contusion SCI rat model increased *miR-494* expression, activated the PI3K/Akt pathway, and improved functional recovery post-injury. The beneficial effects of LV-sh-Lnc-RNA *XIST* administration were reversed when *antago-miR-494* was also administered supporting the interaction between Lnc-RNA *XIST* and *miR-494* [37]. It is interesting that this study found that reduction of expression of a Lnc-RNA using shRNA against *XIST* caused increased expression of its target microRNA. Our current understanding is that Lnc-RNAs bind and block the activity of a microRNA without necessarily changing the level of expression of this microRNA. Blocking the function of a microRNA does not necessarily translate to decreased expression. Therefore, we caution that much more work should be done to better characterize and understand the outcomes of Lnc-RNA-microRNA interactions.

In an *in vitro* model of SCI, pc12 cells (neuronal cell culture) were more susceptible to H₂O₂-induced apoptosis and displayed higher protein levels of Bax, cleaved-Caspase-3 and 9, and lower Bcl-2 when Lnc-RNA *H19* was inhibited; Lnc-RNA *H19* was studied because of seminal work demonstrating its putative roles in various cancers. The effect of Lnc-RNA *H19* inhibition was attributed to higher *miR-155* expression which targets *FOXO1*; *miR-155* was demonstrated to be bound by Lnc-RNA *H19*. This experiment suggested a Lnc-RNA *H19*/*miR-155*/*FOXO1* axis by which Lnc-RNA *H19* exerts neuroprotective effects; this paradigm is supported by the fact that the Lnc-RNA *H19* inhibition + antisense-*miR-155* condition reduced H₂O₂-induced injury [38]. In pc12 cells exposed to H₂O₂, Lnc-RNA *Sox2ot* is upregulated and Lnc-RNA *Sox2ot* inhibition attenuated injury induced by H₂O₂, which was attributed to the inverse correlation between LNC-RNA *Sox2ot* and *miR-211* expression; *miR-211* inhibitor treatment reversed the protective effects of Lnc-RNA *Sox2ot* inhibition. MCL-1 isoform 2 (*MCL-1-i2*) was identified as a direct target of *miR-211*, and *miR-211*-mediated silencing of *MCL-1-i2* was determined to be responsible for the Akt/mTOR/p70S6k pathway activation [39]. Of note, the Akt/mTOR/p70S6k pathway is very well known for pro-survival signals, while the *Mcl1* gene is part of proapoptotic machinery. In another *in vitro* model, pc12 cells exposed to LPS to mimic inflammatory conditions (LPS is a component of gram-negative bacterial cell wall) demonstrated attenuated NF-κB and p38 pathway activation and TNF-α and IL-6 secretion when Lnc-RNA *Mirt2*, which was found to be upregulated in serum samples from SCI patients, was overexpressed. These results were attributed to Lnc-RNA *Mirt2*-mediated downregulation of *miR-429* [40]. Downregulation of *PRDM5*, which has numerous biological functions, by LNC-RNA *DGCR5* or *miR-130b-5p* (which is sponged by LNC-RNA *BDNF-AS*) reduces neuronal apoptosis *in vitro* and *in vivo* [41,42]; in hypoxia-treated AGE1.HN (neural cell line [43]) and pc12 cell culture, Lnc-RNA *DGCR5* overexpression reduced apoptosis while *PRDM5* overexpression reversed these effects [41]. In hypoxia-treated AGE1.HN and pc12 cells, Lnc-RNA *BDNF-AS* KD reduced apoptosis

– an effect that was reversed with *miR-130b-5p* inhibition [42]. Following contusion SCI to rats, pcDNA-Lnc-RNA *DGCR5* treatment improved motor scores [41]. Similarly, contusion SCI rats treated with LV-siRNA-Lnc-RNA *BDNF-AS* demonstrated increased *miR-130b-5p* expression, and less *PRDM5* and cleaved-Caspase3 expression, and fewer TUNEL positive cells [42]. In SY-SH-5Y cells (cell line derived from human hippocampal neurons) under oxygen-glucose deprivation conditions, autophagy was induced by Lnc-RNA *TCTN2* overexpression. Lnc-RNA *TCTN2*, which was downregulated after SCI in rats, was found to attenuate apoptosis and *miR-216b*-mediated LC3II and Beclin-1 (both autophagy proteins) silencing; these effects were reversed with 3-methyladenine (an inhibitor of autophagy) or *miR-216b* mimic treatment. In a contusion model of rat SCI, overexpression of *TCTN2* using pcDNA-Lnc-RNA *TCTN2* resulted in better motor scores for contusion SCI rats thus demonstrating a beneficial role of autophagy after SCI [44].

Endogenous regenerative and repair efforts are also impacted by the ability of LNC-RNAs to serve as miR sponges. Neuronal proliferation supported by fibroblast growth factor 1 (FGF1) is impaired by *miR-199a* which was shown to target *FGF1*; Lnc-RNA *MAP2K4* – *miR-199a* binding interaction, first identified by the authors through bioinformatic software, promotes proliferation and survival. The observed effects of Lnc-RNA *MAP2K4* were reduced when *miR-199a* mimics were utilized or when *miR-199a* binding sites on Lnc-RNA *MAP2K4* were mutated [45]. LNC-RNA *PTENP1*, described as a tumor suppressor, was demonstrated by luciferase activity to regulate *miR-21* and *miR-19b* which targets phosphatase and tensin homolog (PTEN) [46], a phosphatase that antagonizes Akt activation [47]. Wang *et al.* further reported that *PTENP1* inhibition (using exosome-Lnc-RNA *PTENP1* shRNA) may promote recovery after SCI as *miR-21* and *miR-19b*-mediated *PTEN* targeting reduced neuronal apoptosis and improved recovery in contusion SCI rats [46].

LNC-RNAs exerting biological functions through sense-antisense interactions are also relevant in the context of SCI. In a study concerning neuropathic pain, following induction of nerve injury via spinal nerve ligation in rats, Lnc-RNA *Kcna2-AS* was upregulated in the dorsal root ganglion [48]. Moreover, when Lnc-RNA *Kcna2-AS* was introduced in the spinal cord using AAV5-Lnc-RNA *KCNA2-AS*, it was demonstrated that this antisense transcript targets *Kcna2* mRNA which resulted in increased dorsal root ganglion neuronal excitability and accordingly neuropathic pain symptoms. Finally, treatment with *Kcna2* sense in spinal nerve ligation rats alleviated thermal, cold, and mechanical hypersensitivity [48].

Evidence indicates that several LNC-RNAs are implicated in the pathophysiology of SCI and its corresponding symptoms through complex mechanisms though the mechanisms that underly the functions of these Lnc-RNAs have not been completely elucidated. Bupivacaine-induced neurotoxicity in an *in vitro* explant model upregulated Lnc-RNA *BDNF-AS*, and Lnc-RNA *BDNF-AS* inhibition increased neurite outgrowth, reduced apoptosis, and increased Akt and TrkB phosphorylation [49]. The authors suggested that it

is unlikely that Lnc-RNA *BDNF-AS* exerts its deleterious effects by targeting *BDNF*, as the expression of *BDNF* and Lnc-RNA *BDNF-AS* are not consistently negatively correlated [49]. Lnc-RNA *IGF2-AS* inhibition in a dorsal root ganglion explant model also demonstrates neuroprotective effects following anesthetic treatment: Lnc-RNA *IGF2-AS* inhibition promoted neurite outgrowth, attenuated apoptosis, and upregulated neurotrophins and growth factors following lidocaine treatment [50]. Astrogliosis following SCI is potentially linked to LNC-RNA *SCIR1* based on a study conducted by Wang *et al.* LNC-RNA *SCIR1* was found to be downregulated post contusion SCI in rats and knockdown of LNC-RNA *SCIR1* in astrocyte culture prompted astrogliosis while *Adm* and *Bmp7* mRNAs were upregulated and *Wnt* and *SCNA* mRNAs were downregulated. While bioinformatics predicted interactions between LNC-RNA *SCIR1* and *Adm*, *Bmp7*, *Wnt* and *SCNA* mRNAs, the exact mechanism of LNC-RNA *SCIR1*-mediated regulation is yet to be delineated [51]. LNC-RNA *SNHG16* was shown to be downregulated following H₂O₂ treatment; LNC-RNA *SNHG16* overexpression ameliorated H₂O₂-induced injury in pc12 cells via upregulation of *miR-423-5p* which results in increased p-AMPK levels and decreased p-ERK1/2 levels; apoptosis and decreases in cell viability were reinstated with *miR-423-5p* inhibition [52]. Finally, in contusion SCI mice, Lnc-RNA *ZNF667-AS-1*, studied for its role in cervical cancer, was overexpressed with LV-Lnc-RNA *ZNF667-AS-1* which reduced JAK2, STAT3, and inducible nitric oxide synthase expression, thus displaying anti-inflammatory effects [53].

Expression profiles of Lnc-RNAs in animal models of SCI

Lnc-RNA expression profiling in SCI models is useful in identifying candidate Lnc-RNAs that may be involved in the pathophysiology of SCI. In a study conducted by Zhou *et al.*, microarray analysis was used to identify differentially expressed (DE) Lnc-RNAs in naïve rats compared to contusion SCI female Sprague-Dawley rats 2h after injury [54]. In this study, 772 Lnc-RNAs were DE of which 528 Lnc-RNAs were upregulated and 244 Lnc-RNAs were down-regulated compared to naïve rats [54]. Utilizing a near identical protocol, Shi *et al.* examined DE Lnc-RNAs 2 days post-injury; 3,193 DE Lnc-RNAs were identified of which 1,332 Lnc-RNAs were upregulated and 1,861 Lnc-RNAs were downregulated compared to naïve rats [55]. There was no convergence between the top 10 upregulated Lnc-RNAs reported by Zhou *et al.* and the top 10 upregulated Lnc-RNAs reported by Shi *et al.*; there was no convergence between the top 10 downregulated Lnc-RNAs reported by Zhou *et al.* and the top 10 downregulated Lnc-RNAs reported by Shi *et al.* [54,55]. These differences are likely due to the different sampling times used in each experiment. In a study conducted by Cuevas-Diaz *et al.*, female Sprague-Dawley rats were subjected to contusion SCI and DE (contusion SCI vs. sham operation) Lnc-RNAs and protein-coding mRNAs were identified 1 month, 3 months, and 6 months post-injury using RNA-Seq [56]. The results indicated that 137 DE Lnc-RNAs were detected (120 upregulated, 17 downregulated compared to the sham group) 1 month post-injury, 239 DE Lnc-RNAs were detected (162 upregulated, 77 downregulated compared to the sham group) 3 months post-

injury, and 179 DE Lnc-RNAs were detected (125 upregulated, 54 downregulated compared to the sham group) 6 months post-injury [56]. Hierarchical clustering indicated 5 clusters of DE Lnc-RNAs: the expression 79 Lnc-RNAs along with 790 protein-coding genes related to neuronal function gradually decreased as a function of time; the expression of 30 Lnc-RNAs along with 540 protein-coding genes enriched in cellular motility function genes gradually increased as a function of time; the expression of 46 Lnc-RNAs along with 880 protein-coding genes enriched in various focal adhesion genes increased rapidly at 3 months post-injury and increased until 6 months post-injury; the expression of 60 Lnc-RNAs and 1,420 protein-coding genes enriched in epigenetic regulation genes peaked at 1 month post-injury; the expression of 62 Lnc-RNAs along with 1,003 protein-coding genes enriched in inflammation-associated genes sharply increased at 1 month post-injury and retained high levels of expression over time [56]. Similarly, Ding *et al.* conducted a temporal analysis via microarray to study DE Lnc-RNAs and protein-coding mRNAs in contusion SCI mice compared with sham-operated mice [57]. The results indicated that 345 DE Lnc-RNAs were detected (164 upregulated, 181 downregulated compared to the sham group) 1 day post-injury, 502 DE Lnc-RNAs were detected (212 upregulated, 290 downregulated compared to the sham group) 3 days post-injury, 891 DE Lnc-RNAs were detected (326 upregulated, 565 downregulated compared to the sham group) 7 days post-injury and 181 DE Lnc-RNAs were detected (141 upregulated, 40 downregulated compared to the sham group) 21 days post-injury [57]. By examining correlations between DE protein-coding genes and Lnc-RNAs, Ding *et al.* were able to construct a dynamic Lnc-RNA-mRNA network with offers insight into Lnc-RNA function in SCI; this approach allowed identification of murine Lnc-RNAs that are mathematically associated with genes involved in the pathophysiology of SCI such as *FGF1* and *THBS1*, which is reportedly involved AMPA receptor excitability, neuronal adhesion, and neurite outgrowth [57]. Both Cuevas-Diaz *et al.* and Ding *et al.* utilize Lnc-RNA – mRNA profiles to speculate the function of DE Lnc-RNA yet both articles also caution against drawing conclusions without further evidence [56,57]. Rather, the results of expression profiling studies serve as the foundation for more rigorous *in vivo* and *in vitro* studies designed to probe the function and mechanism of Lnc-RNAs in SCI. The latter two experiments raise two important points in Lnc-RNA expression following SCI: (1) Lnc-RNA signatures are highly variable and are functions of time and likely other experimental factors such as SCI model and must thus be understood in the context of experimental conditions, and (2) developing hypotheses regarding the functions of Lnc-RNA in SCI can be accomplished by computational and mathematical analysis of Lnc-RNA and protein-coding gene expression profiles.

Conclusion

Lnc-RNAs are RNA transcripts that could potentially exert many biologically relevant effects in numerous physiological and pathological processes including SCI. Recent studies indicate that modulating specific Lnc-RNAs in SCI models alters biochemical,

histological, and neurological outcomes post-injury. We must emphasize however that the current knowledge regarding the roles of Lnc-RNAs in SCI is fragmented and must be consolidated and supplemented to develop future therapeutic applicability. One technical reason that has diminished our ability to rigorously study Lnc-RNAs is the lack of well-developed *in situ* hybridization techniques which is important in detecting the cellular localization of Lnc-RNAs. Moreover, Lnc-RNAs are poorly conserved across species rendering it difficult to identify their putative functions [58]. To improve our understanding of Lnc-RNAs in SCI, future studies may identify candidate Lnc-RNAs through RNA expression signatures. Such experiments may offer insight into novel mechanisms of Lnc-RNA activity in SCI. For instance, although chromatin remodeling is implicated in SCI pathophysiology [59] and evidence indicates that Lnc-RNAs participate in the process of chromatin remodeling [58], Lnc-RNA-mediated chromatin remodeling has not been studied in SCI to our knowledge. Because there is a paucity of effective pharmacotherapies for SCI, it is important to study the roles of Lnc-RNAs, their differential expression in response to cellular insult, and their cellular and subcellular localizations. In conclusion, Lnc-RNAs hold potentials to be used for future therapeutics in SCI but much work remains to be done.

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Conflict of Interest

No conflict of interest.

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