The emerging role of long non-coding RNA in spinal cord injury

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Introduction

Spinal cord injury (SCI) is a severe trauma often caused by car accidents or falls, and it is characteristic of high incidence, high morbidity and huge cost [1]. SCI is an overwhelming neurological disorder and have devastating physiological consequences, and it affects approximately 180,000 new patients each year [2, 3]. SCI comprises primary and secondary phases [4]. After the initial trauma in spinal cord caused by a bone fracture or compression, SCI can lead to many complex pathological changes including inflammatory responses, hypoxia and neuronal cell death [5, 6]. Because of the inhabitation microenvironment after SCI, the regenerative capacity of the adult spinal cord is poor, and it can result in severe sensory and motor deficits [2]. Therefore, understanding the pathophysiological and biological processes involved in SCI is essential to promote functional recovery in patients with SCI.

Long non-coding RNAs (lncRNAs) are defined as thousands of RNA transcripts longer than 200 nucleotides in length with no protein-coding potential, and lncRNAs have attracted great attention from the researchers all over the world [7, 8]. LncRNAs can be grouped into five main categories: long intergenic non-coding RNAs (lincRNAs), intronic lncRNAs, antisense lncRNAs, divergent lncRNAs and enhancer-derived lncRNAs [9–11]. LncRNAs can be detected in the nucleus, cytoplasm or both; however, they are was mainly located in cell nucleus [12, 13]. It has been shown that lncRNAs could regulate the downstream genes expression via mediating chromatin, transcriptional and post-transcriptional modification, and lncRNAs have been regarded as a new frontier in the study of many human diseases [14–16]. The roles of lncRNAs in cell physiology include chromatin remodelling, transcriptional and epigenetic regulatory factors, RNA

Keywords: spinal cord injury – long non-coding RNA – neuron – astrocyte – oligodendrocyte – microglia – inflammation – angiogenesis

Abstract

Spinal cord injury (SCI) is a significant health burden worldwide which causes permanent neurological deficits, and there are approximately 17,000 new cases each year. However, there are no effective and current treatments that lead to functional recovery because of the limited understanding of the pathogenic mechanism of SCI. In recent years, the biological roles of long non-coding RNAs (lncRNAs) in SCI have attracted great attention from the researchers all over the world, and an increasing number of studies have investigated the regulatory roles of lncRNAs in SCI. In this review, we summarized the biogenesis, classification and function of lncRNAs and focused on the investigations on the roles of lncRNAs involved in the pathogenic processes of SCI, including neuronal loss, astrocyte proliferation and activation, demyelination, microglia activation, inflammatory reaction and angiogenesis. This review will help understand the molecular mechanisms of SCI and facilitate the potential use of lncRNAs as diagnostic markers and therapeutic targets for SCI treatment.
conformational dynamics, modification of specific protein targets and control of protein complex formation and localization [17]. However, for the vast majority of IncRNAs, their action and physiological function in spinal cord injury remain to be uncovered.

In this review, we overviewed the recent studies on the molecular functions of IncRNAs involving in spinal cord injury, and further discussed their potential roles of diagnosis and prognostic biomarkers and therapeutic targets, and this review aimed to help deepen the current understanding of IncRNAs in spinal cord injury.

The biogenesis, classification and function of IncRNAs

Non-coding RNAs (ncRNAs) cover more than 98% of the human genome [18]. LncRNAs are a subgroup of non-coding RNA transcripts longer than 200 nucleotides, most of IncRNAs are transcribed by RNA polymerase II and are capped at the 5’ end, spliced and polyadenylated [19–21]. LncRNAs were initially thought to be ‘transcriptional noise’ of the transcriptome [22]. In recent years, the research of IncRNAs developed rapidly, and IncRNAs were being increasingly recognized as key regulators of many cellular processes, especially gene expression [23–25]. Compared to mRNAs, IncRNAs are generally regarded to be exquisitely regulated and are restricted to specific cell types [26].

According to their location in the genome, IncRNAs can be classified into five categories: (i) sense IncRNAs, IncRNAs overlap with one or more exons from another transcript in the same strand; (ii) antisense IncRNAs, IncRNAs overlap with one or more exons from another transcript in the opposite strand; (iii) bidirectional IncRNAs, IncRNAs that share their promoter with another gene in the opposite strand and are initiated <1000 base pairs away in close genomic proximity; (iv) intronic IncRNAs, IncRNAs initiated completely within an intron of a protein-coding gene without overlapping exons; and (v) intergenic IncRNAs (also termed large intervening non-coding RNAs or lincRNAs), those that are independent transcripts located between two genes [27–29].

The main functions of IncRNAs are as follows: (i) scaffold molecules for providing stabilization in chromatin modification complexes; (ii) providing molecular guides for localization of their binding targets; (iii) as signals, regulated the expression of target genes by recognizing the transcription factors; (iv) as decoys, binding to molecules and block their role on their target genes; (v) acting as miRNA ‘sponges’ to regulate mRNA activity by sharing common miRNA-binding sites with mRNAs; and (vi) acting as enhancer RNAs or even encoding short peptides with regulating function [24, 26, 27, 30–32]. However, there is still biological significance of a large number of IncRNAs remaining unclear and needing to further illuminated.

Alterations and regulation in IncRNAs expression following SCI

After SCI, a series of pathophysiological events occur at molecular and cellular levels. To understand the changes in the expression levels and the corresponding regulatory functions of IncRNAs following SCI, previous studies have performed microarray method and RNA sequencing and found that a large number of IncRNAs are found in the spinal cord and changed following SCI [33–35]. Wang et al. performed a large-scale screening of expression changes of IncRNAs in a rat contusion SCI model at 1, 4 and 7 days following SCI, and the transcripts with a false discovery rate (FDR) ≤0.001 and a fold change ≥2 were considered as differentially expressed [35]. Wang et al. demonstrated that seven IncRNAs that were detected in the adult rat spinal cord showed significant expression changes, and among the seven IncRNAs, two (LOC100910973, H19) were up-regulated, one (RGD1559747) was down-regulated, four (Rn28s, Rn45s, RT1-CE6, Rmrp) were up-regulated at 1 day post-SCI, and then subsequently down-regulated at 4 and 7 days post-SCI [35]. Ding et al. used a microarray method in a contusion SCI mouse model at 1 day, 3 days, 1 weeks and 7 weeks following SCI, and the results showed that few changes were found at 1 day following SCI and the changes peaked 1 week following SCI and subsequently decreased compared with sham operation group [33]. Another study investigates alterations of the IncRNAs expression of in the subchronic and chronic stages of SCI (1 month, 3 months and 6 months post-SCI) using RNA sequencing, and the analyses of the SCI transcriptome identified 277 differentially expressed IncRNAs [34]. LncRNAs microarray and RNA sequencing studies involving SCI are summarized in Table 1. These researches on IncRNAs provided new molecular information and have shown that the changes of IncRNAs expression have effects on many key processes of SCI physiopathology. Thus, these researches may provide novel insights into the molecular mechanisms of SCI.

The regulative roles of IncRNAs in neural cells behaviour

Neuron

After SCI, permanent neuronal loss is a major obstacle and will result in functional disfigurement, so enhancing the survival of neurons is critical for recovery in patients with SCI [36]. It is really difficult to avoid the neuronal loss happened; however, during the secondary injury after SCI, genes expression can be regulated to promote post-traumatic spinal neuron survival, and regulation of IncRNAs is an important way [37, 38]. LncRNAs have been found to function in the central nervous system (CNS) development and neurogenesis [39, 40]. Many exploratory studies characterizing IncRNA expression involving neuron behaviour. In one study, the researchers demonstrate that IncRNA-Map2k4 can promote neuron proliferation and inhibit neuron apoptosis through a miR-199a/FGF1 pathway [41]. LncRNA IGF2AS was first identified as a cancer regulator in Wilm's tumours, a recent study showed that inhibiting endogenous lncRNA IGF2AS can promote neuronal growth and protect local anaesthetic-induced neurotoxicity in DRG neurons [42]. Pnky is a neural-specific IncRNA that regulates neurogenesis, and a previous study showed...
that knockdown of Pnky may promote neuronal differentiation [40], and this result is beneficial to improve the results of neural stem cells transplantation in patients with SCI. Together, these studies have provided a good start for understanding the roles of lncRNAs in neuron behaviour, and in-depth analysis in this field is very necessary.

**Astrocyte**

In the central nervous system, astrocytes are the most abundant glial cell type [43, 44]. Astrocytes have been a primary focus of researchers in both neuropathology and neurophysiology, and they play an essential role in provision of energy metabolites to neurons and maintenance of the extracellular balance of ions [45, 46]. As a typical feature following SCI, astrocyte proliferation and reactive gliosis can contribute to the formation of glial scar and lead to a physical and biochemical barrier to plasticity and regeneration, and inhibit functional recovery finally [47, 48]. However, reactive astrocytes also serve as beneficial factors for SCI including endogenous neuroprotection and secreting growth-promoting neurotrophic factors [43]. Therefore, reactive astrocytes can be beneficial or detrimental for SCI, so how to make full use of its positive aspect and inhibit its detrimental aspects will be the future directions of research. More recent studies have begun to examine the effects of lncRNAs on astrocyte proliferation and reactive gliosis. In a previous study, the researchers knocked down IncSCIR1 expression in cultured astrocytes and found that down-regulation of IncSCIR1 may promote astrocyte proliferation and migration in vitro and might play a detrimental role in the pathophysiology of SCI [35]. Another study showed that IncRNA Gm4419 could promote trauma-induced astrocyte apoptosis via up-regulating the expression of inflammatory cytokine tumour necrosis factor α (TNF-α), and the up-regulation of TNF-α was possible via competitively binding miR-4661 [49]. Therefore, identifying the crucial lncRNAs to regulate the astrocyte proliferation and activation has become the main concern in SCI treatment.

**Oligodendrocyte**

Myelin sheath, the insulating layer surrounding the axon, is necessary for maintaining structural and functional integrity of neural circuits in vertebrate spinal cords [50, 51]. Apoptosis of myelin-forming oligodendrocytes (OLs) and demyelination of surviving axons is a vital part of the cascading secondary events in spinal cord injury (SCI), and then it leads to conduction failure [52, 53]. Furthermore, the post-injury microenvironment can limit the endogenous oligodendrogenesis and remyelination processes via increased remyelination-inhibitory molecules [54]. Therefore, enhance remyelination is one of the important factors in promoting functional recovery in SCI. In recent years, more and more researchers found that IncRNAs may be promising therapeutic targets for spinal cord repair, so it is necessary to know the roles of IncRNAs in remyelination. He et al. established dynamic expression profiles of IncRNAs at different development stages of oligodendrocyte, and they found that overexpression of IncOL1 promotes the differentiation of precocious oligodendrocyte in the developing brain and inactivation of IncOL1 could cause the defects in CNS myelination and remyelination after injury [55]. Furthermore, IncOL1 could promote oligodendrocyte maturation via interaction with Suz12 [56]. In another study, the researchers identified IncRNAs that are regulated during Oligodendrocyte Precursor Cell (OPC) differentiation from Neural Stem Cells (NSCs), and they found that Inc-OPC was the top candidate and showed highly specific expression in OPCs [56]. This study elucidated the roles of IncRNAs in the development of astrocytes and in the promotion of their functions in SCI. Further researches involving the effect of IncRNAs on remyelination are needed to provide useful clues for the treatment of SCI.

![Table 1 Summary of studies about the changes of lncRNAs expression following spinal cord injury](image-url)
Microglia

Inflammation is a crucial biological process in response to injury, infection and trauma suffered by cells or tissues, and it involves the cells present within the central nervous system (CNS), including the neurons, macroglia and microglia [57]. Microglia are known as the resident macrophages of CNS, which play a key role in active immune defence mechanism in the CNS, and they are also a type of glial cell lesser in number than astrocytes [58, 59]. Activated microglia can release many pro-inflammatory molecules, such as interleukin-1beta (IL-1β), TNF-α, reactive oxygen species and nitric oxide [60]. After SCI, microglia undergo significant cellular, molecular and functional changes, and microglial activation is often used to represent neuronal inflammation during secondary phases of SCI [61, 62]. A recent study demonstrated that lncRNA fantom3_F730004F19 may be associated with microglia-induced inflammation via the Toll-like receptor signalling pathway in early brain injury (EBI) following subarachnoid haemorrhage (SAH) [63]. Qi et al. demonstrated that lncRNA SNHG14 could increase the expression of PLA2G4A by inhibition of miR-145-5p, which resulted in the activation of microglia [64]. Activated microglia can be divided into two functional types: M1/classic and M2/alternative polarization [65]. M1 polarized microglia have generally been considered to promote neuronal apoptosis and inhibit OPCs differentiation into mature OLs, whereas M2 polarized microglia are known to promote neuronal survival, neurite outgrowth and OPCs differentiation [66-68]. In a recent study, the researchers identified the lncRNA GAS5 as an epigenetic regulator of microglial polarization and suggested that GAS5 may be a promising target for the treatment of demyelinating diseases [69]. Furthermore, the function of lncRNAs in activation of microglia following SCI also requires further study.

LncRNAs involved in inflammation after SCI

After SCI, the inflammatory response involves the activation of microglia and the infiltration of neutrophils, monocytes and lymphocytes [70]. As mentioned above, microglia are capable of regulating activation and polarization of microglia, so what are the roles of lncRNAs in infiltration of neutrophils, monocytes and lymphocytes? As a type of inflammatory cell, neutrophils are the main cells and enter the injury site first [71]. It has been shown that many lncRNAs are present in neutrophils and the levels of lncRNA expression are associated with development, differentiation and activation of neutrophils [72, 73]. Furthermore, previous studies have identified lncRNAs expressed in B lymphocytes and T lymphocytes development and activation [74, 75]. Panzeri et al. suggested that long intergenic non-coding RNAs could be novel drivers of human lymphocyte differentiation [76]. Moreover, previous researches performed RNA sequencing of monocytes from four individuals and combined their data with eleven other publicly available datasets and provided a landscape of lncRNAs in monocytes [77]. LncRNA LINC00341 has been shown to suppress vascular cell adhesion molecule 1 (VCAM1) expression and inhibit monocyte adhesion, and it also has the anti-inflammatory effect [78]. A recent research demonstrated that lncRNA LINC00305 could promote monocyte inflammation via activating the AHRR-NF-κB pathway [79].

Fig. 1 Involvement of lncRNAs in spinal cord injury.
Although various publications report lncRNAs to regulate inflammation after SCI, most of the related mechanism of lncRNAs is not fully understood. Therefore, further experiments are needed to confirm lncRNAs to be essential in the inflammation process.

LncRNAs involved in angiogenesis after SCI

After SCI, injury to vessels may lead to haemorrhage [80]. An important cause of cell and tissue damage in the injured spinal cord is the ischaemic conditions brought about by injury to blood vessels following SCI [81, 82]. Therefore, it is a problem that how to promote angiogenesis and provide the transport of oxygen, growth factors and other nutrients to the injured spinal cord [83]. Accumulating evidence showed that lncRNAs could directly regulate the process of angiogenesis by targeting related signalling molecules [84–87]. A recent study showed that lncRNA HIF1A-AS2 could promote the angiogenesis in human umbilical vein endothelial cells (HUVECs) in hypoxia via facilitating the up-regulation of HIF-1α by sponging to miR-153-3p [88]. LncRNA MEG3 is known as an important tumour suppressor in some human cancers, and overexpression of MEG3 suppressed the angiogenesis in vascular endothelial cells (VECs) significantly [99]. Furthermore, MEG3 was significantly decreased after ischaemic stroke, and overexpression of MEG3 could decrease the capillary density after ischaemic stroke via inhibition of notch signalling [90]. Thus, MEG3 may play an important role in the control of angiogenesis following SCI. Moreover, previous studies demonstrated that two intergenic lncRNAs called linc00323-003 and MIR503HG are induced by hypoxia in endothelial cells, which would help promote angiogenesis [91]. Overall, more and more evidence indicates that lncRNA plays an important role in angiogenesis; however, the role of these lncRNAs in angiogenesis following SCI need to be examined in future research.

Conclusion and perspective

SCI is a complex process integrating multiple related targets and signalling pathways in the nervous, immune and vascular systems, accompanied by many cellular and molecular mechanisms; however, the molecular mechanisms of SCI are not yet completely understood. Furthermore, no effective therapy is currently available to control the secondary injury following SCI [2, 92]. Recent studies have found that the expression of lncRNAs changed after SCI and lncRNAs may play key roles in the pathological process of SCI. Utilization of lncRNAs provides an attractive proposition for the development of spinal cord repair. Furthermore, in contrast to miRNAs that are frequently expressed from various tissues and likely to target multiple mRNAs, however, lncRNAs display the characteristics of specificity [93]. In the current review, we summarized the recent studies about lncRNAs in SCI, and we believed that this review will contribute to a global understanding of the molecular mechanisms of SCI and promote the development of clinical applications of lncRNAs (Fig. 1).

Moreover, several issues will be the research focus for further studies. First, the majority of the studies on the effect of lncRNAs on SCI are preclinical animal studies, and further investigations applying to humans will be needed in order to improve the transition to the clinic. Second, an appropriate delivery system is required for implementation of lncRNA therapy, so how to choose an appropriate vector which ensures the successful delivery of the lncRNAs to the desired targets is the future research direction. Furthermore, most of molecular mechanisms of lncRNAs in SCI are still unclear, so further investigations a deeper understanding of the causes and consequences of the dysregulation of lncRNAs in SCI and choosing the most promising lncRNAs will push the future development of lncRNAs for therapeutic applications, including the treatment of SCI.

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Conflict of interest

The authors have no conflict of interests to disclose.

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