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A Review of The Potential of Neural Stem Cells in Spinal Cord Injury Repair and Neural Tissue Regeneration

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Abstract. *Cedera tulang belakang (Spinal Cord Injury/SCI) merupakan kondisi neurologis serius yang menyebabkan gangguan fungsional jangka panjang dan penurunan kualitas hidup secara signifikan. Keterbatasan mekanisme regeneratif dalam sistem saraf pusat (CNS) menjadikan pemulihan SCI sebagai tantangan besar dalam dunia medis. Neural Stem Cells (NSCs) muncul sebagai terapi potensial karena kemampuannya berdiferensiasi menjadi berbagai jenis sel saraf dan berintegrasi dengan jaringan yang rusak. Studi ini bertujuan untuk memetakan lanskap riset terkini terkait penggunaan NSCs dalam regenerasi jaringan saraf akibat SCI melalui metode scoping review. Kajian ini dilakukan berdasarkan pedoman PRISMA-ScR, dengan pencarian literatur dari tahun 2015 hingga 2025 melalui database PubMed dan Google Scholar menggunakan kata kunci terkait "Neural Stem Cells" dan "Spinal Cord Injury". Sebanyak 145 studi memenuhi kriteria inklusi, terdiri dari 88% studi praklinis dan 12% uji klinis. Mayoritas penelitian menyoroti keberhasilan transplantasi NSCs pada model hewan SCI, dengan 60% di antaranya melaporkan peningkatan signifikan dalam fungsi motorik dan sensorik. NSCs terbukti dapat berdiferensiasi menjadi neuron, oligodendrosit, dan astrosit, serta memperbaiki jaringan yang rusak. Meskipun hasil praklinis menunjukkan harapan tinggi, penerapan klinis masih menghadapi hambatan seperti rendahnya tingkat kelangsungan hidup sel, metode transplantasi yang belum optimal, dan isu etik. Oleh karena itu, penelitian lebih lanjut diperlukan untuk mengatasi tantangan tersebut, termasuk perluasan uji klinis dengan populasi lebih besar guna mengevaluasi efektivitas dan keamanan terapi NSC dalam pengobatan SCI.*

Keywords: *Neural Stem Cells, Spinal Cord Injuries, Nerve Regeneration*

1. INTRODUCTION:

Spinal Cord Injury (SCI) refers to any damage to the spinal cord, typically caused by trauma such as vehicular accidents, falls, or violence, although it can also result from diseases or congenital conditions (van Den Hauwe et al., 2020). SCI can lead to partial or complete loss of sensory, motor, and autonomic functions, depending on the level and severity of the injury. The spinal cord is a crucial part of the central nervous system, serving as the communication pathway between the brain and the body. The causes of SCI can be classified into traumatic and non-traumatic types (Alito et al., 2021). Traumatic SCI is the most common and includes Physical Trauma, Penetrating Injuries, Compression Injuries. Non-traumatic causes of SCI include conditions like spinal tumors , infections (such as tuberculosis or meningitis), vascular issues (such as hemorrhagic strokes), and degenerative diseases like multiple sclerosis and amyotrophic lateral sclerosis (ALS) . The consequences of SCI are not limited to the physical damage at the injury site but can also involve secondary effects, such as inflammation, oxidative stress, and further neuronal damage that worsens the patient's clinical condition (Ahuja et al., 2017). The consequences of SCI are profound, leading to life-long disabilities, such as paralysis, loss of sensation, and autonomic dysfunction. The severity of these outcomes

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depends on the location of the injury along the spinal cord (eg, cervical, thoracic, or lumbar). The higher the level of injury, the more severe the loss of function, with cervical injuries typically leading to tetraplegia, whereas thoracic and lumbar injuries may result in paraplegia (Ahuja et al., 2017).

Neural stem cells (NSCs) are multipotent progenitor cells capable of differentiating into various types of neural cells, including neurons, astrocytes, and oligodendrocytes (Homem, Repic, & Knoblich, 2015). NSCs are found in specific areas of the adult brain and spinal cord, notably in the subventricular zone and subgranular zone , but their potential to regenerate tissue in the central nervous system (CNS) is severely limited by the inhibitory environment in injured spinal tissues (Shoemaker & Kornblum, 2016). NSCs possess several key properties that make them of interest for treating neurological disorders, particularly SCI Self-Renewal, Multipotency, Plasticity.

The therapeutic potential of NSCs in SCI is being extensively explored in both preclinical and clinical studies. NSCs offer several promising benefits, the transplantation of NSCs into SCI sites aims to promote tissue repair by replacing lost neurons, providing structural support, and stimulating endogenous repair mechanisms. NSCs have the potential to improve functional recovery by restoring lost motor and sensory functions (Nagappan, Chen, & Wang, 2020). Transplanted NSCs can integrate into the host tissue, form new neural connections, and promote remyelination, which is crucial for restoring proper nerve function. In addition to regeneration, NSCs can secrete trophic factors that protect surviving neurons from further damage and promote healing in the surrounding spinal cord tissue. Despite the promising therapeutic potential, there are significant challenges in translating NSC-based therapies into clinical practice. These include difficulties in achieving sufficient survival of transplanted cells, ensuring proper integration with the host tissue, and addressing safety concerns related to the potential for tumor formation or immune rejection (Gao et al., 2022).

Several clinical trials and preclinical studies are investigating the use of NSCs for SCI repair. Current approaches focus on optimizing the source of NSCs (eg, using induced pluripotent stem cells, embryonic stem cells, or adult-derived NSCs) and improving the methods for delivering NSCs to the injury site (eg, via direct injection, scaffolds, or biomaterial carriers).

The research landscape for NSCs in SCI is advancing, but challenges remain in overcoming barriers such as limited cell survival, the need for safe and efficient delivery systems, and regulatory issues regarding the use of stem cell-based therapies. Moving forward, it will be crucial to conduct large-scale, randomized clinical trials to fully evaluate the efficacy

and safety of NSC-based treatments for SCI and to identify the best strategies for integrating these therapies into clinical practice (Narouiepour et al., 2022).

Pathophysiology of Spinal Cord Injury (SCI)

Spinal Cord Injury (SCI) is a serious medical condition that occurs due to trauma to the spinal cord, often leading to permanent neurological deficits such as loss of movement and sensation below the level of injury. The pathophysiology of SCI involves both primary and secondary injury mechanisms, each playing a critical role in the extent of damage and functional loss (Hachem & Fehlings, 2021).

Primary Spinal Cord Injury Mechanisms

Primary injury is the direct result of mechanical trauma to the spinal cord at the moment of impact. This initial injury typically causes axonal damage, where the long nerve fibers (axons) that transmit signals between neurons are disrupted (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). The disruption can occur through stretching, tearing, or severing of axons, leading to an immediate loss of communication between the brain and the body. Another significant aspect of the primary injury is vascular disruption, which includes hemorrhage and rupture of blood vessels (Hachem & Fehlings, 2021). This leads to ischemia, or a lack of blood supply, which worsens the damage to neurons by depriving them of oxygen and nutrients. Additionally, cell membrane damage occurs, resulting in the influx of calcium ions (Ca^{2+}), which activates enzymes that further degrade cell structures, exacerbating the injury (Venkatesh et al., 2019).

Secondary Spinal Cord Injury Mechanisms

Secondary injury occurs after the primary insult and significantly contributes to the progression of SCI. One of the most prominent mechanisms is excitotoxicity, where excessive release of the neurotransmitter glutamate leads to overactivation of NMDA (N-Methyl-D-Aspartate) receptors on neurons. This overactivation causes an influx of calcium ions into the cells, triggering a cascade of harmful events, including mitochondrial dysfunction, oxidative stress, and cell death. Inflammation is another key secondary mechanism; microglia and astrocytes become activated at the injury site and release pro-inflammatory cytokines like TNF-α and IL-1β, which recruit more immune cells to the area and perpetuate the cycle of damage. Alongside inflammation, oxidative stress plays a crucial role, where the overproduction of reactive oxygen species (ROS) further damages cellular components such as lipids, proteins, and DNA, contributing to the breakdown of tissue and impairing repair mechanisms (Shultz & Zhong, 2017).

Apoptosis, or programmed cell death, is a critical process that is triggered by secondary injury. This occurs primarily in neurons, oligodendrocytes (which are responsible for myelin production), and astrocytes, leading to a significant loss of spinal cord cells. Demyelination also occurs as a result of SCI, where the loss of oligodendrocytes leads to the degradation of myelin sheaths, impairing the conduction of electrical signals along the affected axons. This further contributes to the sensory and motor deficits observed in patients (Hu et al., 2023).

Glial Scar Formation and Ischemia

Following the Spinal Cord Injury, glial cells, particularly astrocytes, proliferate at the site of the injury, forming a glial scar. While initially protective by sealing off the injury site, the glial scar creates a barrier that hinders the regeneration of axons and limits recovery. Furthermore, the injury triggers ischemia and hypoxia, which worsen the situation by reducing blood flow and oxygen to the damaged tissue, aggravating the loss of function and delaying recovery processes.

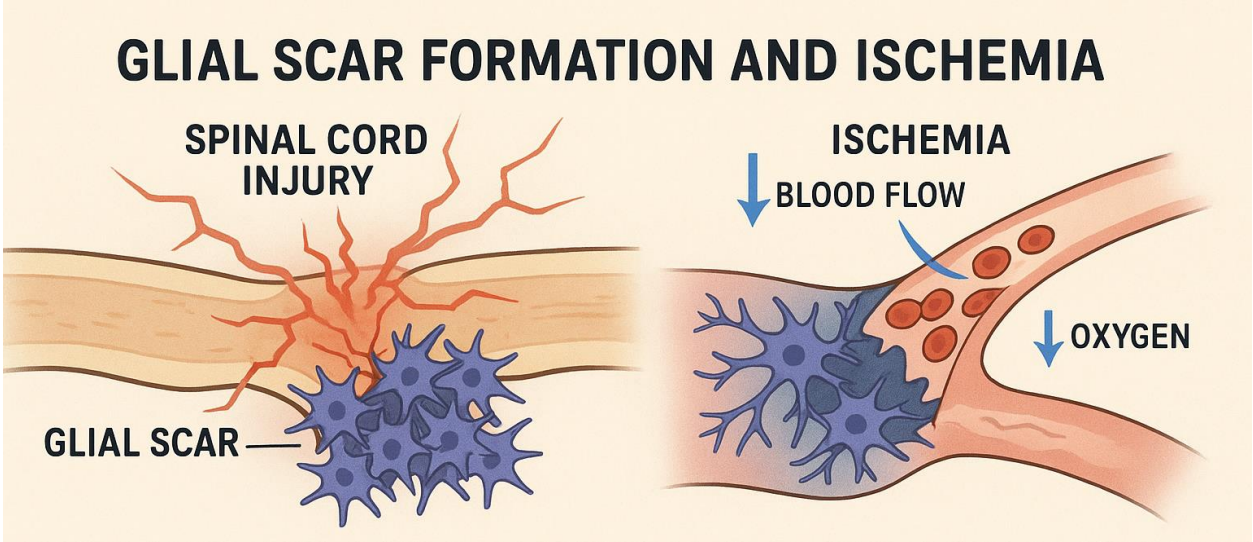

Figure 01: Following spinal cord injury, reactive astrocytes form a dense glial scar, creating a barrier to axonal regeneration. This scar contributes to local ischemia by compressing nearby vasculature and reducing blood flow. The resulting oxygen deprivation exacerbates neuronal damage and impairs recovery.

The pathological processes of SCI result in various clinical consequences, depending on the level and severity of the injury. Motor dysfunction is common, with individuals losing the ability to voluntarily move parts of their body below the level of injury. Sensory loss, including the inability to feel touch, pain, or temperature, also occurs. Autonomic dysfunction, such as blood pressure instability and impaired bladder and bowel control, can significantly impact the

quality of life. In severe cases, particularly with high cervical injuries, respiratory function may also be compromised, requiring ventilatory support (Sweis & Biller, 2017).

The pathophysiology of spinal cord injury involves a complex interplay of primary mechanical damage and secondary molecular and cellular events. While the primary injury leads to immediate disruption of spinal cord function, it is the secondary injury mechanisms, including excitotoxicity, inflammation, oxidative stress, apoptosis, and demyelination, that cause ongoing damage and limit recovery. Understanding these processes is essential for developing therapeutic strategies aimed at minimizing injury and promoting recovery in SCI patients. However, despite advances in research, overcoming the challenges posed by secondary injury mechanisms remains a significant hurdle in achieving successful outcomes in SCI treatment (Ahuja et al., 2017).

Neural Stem Cells (NSCs) and Their Characteristics

Neural Stem Cells (NSCs) are a unique class of stem cells found in the nervous system that possess the ability to self-renew and differentiate into various types of neural cells, such as neurons, astrocytes, and oligodendrocytes. These cells play a critical role in the development, repair, and maintenance of the nervous system. NSCs are considered a promising tool for regenerative medicine, especially for conditions like Spinal Cord Injury (SCI), where the natural regenerative ability of the central nervous system (CNS) is limited (Kaminska et al., 2022). NSCs are found in both embryonic and adult stages of life, with distinct properties and locations based on their developmental stage.

Types of NSCs

1. **Embryonic Neural Stem Cells (eNSCs)**

   Embryonic neural stem cells are derived from the **neuroectoderm** during early development. They have the highest differentiation potential and can give rise to all neural lineages, including neurons, astrocytes, and oligodendrocytes. These cells are considered the most versatile and are widely used in research exploring regenerative therapies for CNS damage. However, their use in clinical applications is controversial due to ethical concerns associated with the source of these cells, as they are harvested from embryos (McCann & Thapar, 2018).

2. **Adult Neural Stem Cells (aNSCs)**

   Adult neural stem cells are found in the adult brain, particularly in the **subventricular zone** (SVZ) of the lateral ventricles and the **dentate gyrus** of the hippocampus. These cells retain a more limited capacity for differentiation compared to embryonic NSCs but still possess the ability to generate neurons, astrocytes, and oligodendrocytes under

certain conditions. Adult NSCs play a role in neurogenesis (the creation of new neurons) throughout life, particularly in areas associated with learning, memory, and response to injury (Chaker, Codega, & Doetsch, 2016).

3. **Induced Pluripotent Stem Cells (iPSCs)**

   Induced pluripotent stem cells are a type of stem cell that can be generated from **adult somatic cells**, such as skin or blood cells, through the introduction of specific genes that reprogram the cells into a pluripotent state. iPSCs are similar to embryonic stem cells in their ability to differentiate into any type of cell, including neural cells. This makes them an attractive option for research and therapeutic applications, as they bypass the ethical issues associated with using embryonic cells. iPSCs have shown great promise in the development of personalized treatments for SCI, as they can be derived from the patient's own cells, reducing the risk of immune rejection (Cerneckis, Cai, & Shi, 2024).

In the context of **Spinal Cord Injury (SCI)**, the use of NSCs has been extensively researched for their potential to regenerate neural tissue and repair damaged spinal cord structures. SCI results in the loss of motor and sensory functions due to damage to the spinal cord neurons and their supporting cells. Unlike peripheral nerves, the central nervous system (CNS), which includes the spinal cord, has a very limited ability to regenerate after injury. However, NSCs offer potential as a therapeutic strategy for promoting spinal cord repair and functional recovery.

Mechanisms of Neural Tissue Regeneration

Neural tissue regeneration is a complex process that involves the repair and restoration of functional neural circuits in the central nervous system (CNS). This process is especially critical in conditions like Spinal Cord Injury (SCI), where the loss of neurons, oligodendrocytes, and astrocytes disrupts motor and sensory functions. Neural stem cells (NSCs) are central to this regenerative process, and their ability to differentiate into various neural cell types—neurons, oligodendrocytes, and astrocytes—offers significant potential for SCI repair. However, the integration of NSCs into the injured spinal cord and their interactions with the local tissue environment remain areas of intense research.

Role of NSCs in Neurogenesis

Neurogenesis refers to the process by which new neurons are generated from neural progenitor cells, including NSCs. In the context of SCI, neurogenesis plays a pivotal role in replacing lost neurons and restoring lost functions. The role of NSCs in neurogenesis can be

understood through their ability to differentiate into neurons, oligodendrocytes, and astrocytes, each of which is crucial for repairing the damage caused by SCI.

NSCs possess the ability to differentiate into neurons, the primary functional cells of the nervous system that are responsible for transmitting electrical signals. Following SCI, the loss of neurons disrupts the transmission of motor and sensory signals from the brain to the body. The differentiation of NSCs into neurons offers the potential to replace damaged or lost neurons in the spinal cord. However, this process is challenging because the newly differentiated neurons must integrate into existing neural networks and form functional synapses to restore proper signaling. Recent studies have shown that transplanted NSCs can generate functional neurons in animal models of SCI, although the full integration of these neurons into complex spinal cord circuits remains a challenge (Jin, 2016).

Another important aspect of NSCs in SCI repair is their ability to differentiate into oligodendrocytes, the cells responsible for producing myelin in the CNS. Myelin is a fatty substance that forms a sheath around axons, enabling rapid conduction of electrical signals. In SCI, oligodendrocytes are often damaged, leading to demyelination, which impairs neural signaling. By differentiating into oligodendrocytes, NSCs can potentially restore myelin to the injured areas, promoting remyelination and improving the conduction of nerve signals. Successful remyelination is critical for individuals with incomplete SCI, where some motor and sensory functions may still be preserved despite the loss of myelin.

In addition to neurons and oligodendrocytes, NSCs can differentiate into astrocytes, which are critical for maintaining the homeostasis and structural integrity of the spinal cord. Astrocytes provide support to neurons, maintain the blood-brain barrier, and help modulate the local environment in response to injury. Following SCI, astrocytes can also become reactive and contribute to glial scarring, a barrier that inhibits axonal regeneration. While reactive astrocytes can be beneficial in sealing off the injury site and protecting surrounding tissue, their overproduction can impede the regeneration of nerve fibers. NSCs can potentially provide beneficial astrocytes that promote tissue repair without contributing excessively to glial scarring (Bagheri-Mohammadi, 2022).

Integration of NSCs into the Injured Spinal Cord

The successful integration of transplanted NSCs into the injured spinal cord is a key challenge for SCI therapy. For NSCs to promote meaningful tissue regeneration, they must not only survive after transplantation but also integrate into the damaged tissue and interact with the local cellular and extracellular environment. The process of integration is complex and involves several steps:

Following transplantation, NSCs must first survive in the hostile environment of the injured spinal cord. This environment is characterized by inflammation, oxidative stress, and the presence of inhibitory molecules that can impair cell survival. To improve survival, researchers have been exploring pre-conditioning strategies, such as genetic modification or the use of neurotrophic factors, which support cell viability and function. Once they survive, NSCs must migrate to the site of injury, where they can differentiate and participate in tissue repair (Kumamaru et al., 2018).

After migrating to the injury site, NSCs must interact with the local cellular environment. This includes forming connections with existing neurons and other cell types such as astrocytes and oligodendrocytes. The integration of transplanted neurons into the local network is essential for restoring functionality. However, the formation of functional synapses is a significant hurdle, as the injured spinal cord does not provide the same supportive environment for synaptic growth as an intact nervous system. Researchers are exploring methods to enhance synapse formation, such as by using scaffolds or matrix proteins that promote cellular adhesion and network formation.

The extracellular matrix (ECM) plays a crucial role in the integration of NSCs. The ECM provides structural support for cells and is involved in signaling pathways that regulate cell behavior. Following SCI, the ECM is often disrupted, which can impede the migration, differentiation, and integration of NSCs. NSCs interact with ECM components like laminin, fibronectin, and collagen to facilitate their movement and differentiation. Strategies to modify the ECM or use biomaterials to mimic the natural matrix are being explored to improve the integration of transplanted NSCs into the damaged spinal cord (Liu & Chen, 2019).

One of the main barriers to NSC integration is the presence of inhibitory molecules in the injured spinal cord, including chondroitin sulfate proteoglycans (CSPGs) and myelin-associated inhibitors such as Nogo-A. These molecules are produced as part of the glial scar and can block axonal growth and cell migration. Researchers are investigating ways to neutralize or bypass these inhibitory factors, such as by using enzyme treatment to degrade CSPGs or by engineering NSCs to resist inhibitory signals. Overcoming these barriers is critical for promoting long-term integration and functional recovery.

Table 1: Challenges in Translating NSC Therapies to Clinical Application

Author, Year	Gender/ Species/ Weight	Cell source/Donor/Graft/Dose/Type/Intervention time (day)	Immunosuppressive/ Antibiotic/Blinding	Follow-up (week)
Nishimura et al., 2013 https://doi.org/10.1186/1756-6606-6-3	Female/ Mice/18–22	Brain/Fetus/Mice/IS/5 × 10^5/Xenogeneic/9 or 42	No/No/Yes	6
Nori et al., 2011 https://doi.org/10.1073/pnas.1108077108	Female/ Mice/20–22	Skin fibroblast/Adult/Human/IS/5 × 10^5/Xenogeneic/9	Yes/Yes/Yes	9
Nutt et al., 2013 https://doi.org/10.1016/j.expneurol.2013.07.010	Female/Rat/180–230	Lung/Adult/Human/IS/2 × 10^5/Xenogeneic/28	Yes/Yes/Yes	8
Ormond et al., 2014 https://doi.org/10.1371/journal.pone.0088916	Female/Rat/200–250	Brain/Adult/Rat/IS/1 × 10^6/Allogeneic/7	No/No/Yes	5
Piltti et al., 2013a https://doi.org/10.5966/sctm.2012-0110	Female/Rat/180–200	Brain/Fetus/Human/IS/2 × 10^5/Xenogeneic/9	Yes/Yes/Yes	13
Piltti et al., 2013b https://doi.org/10.5966/sctm.2013-0064	Female/Rat/180–200	Brain/Fetus/Human/IS/2 × 10^5/Xenogeneic/9	Yes/Yes/Yes	13
Pomeshchik et al., 2015 https://doi.org/10.3727/096368914X684079	Female/ Mice/18–23	Skin/Adult/Human/IS/4 × 10^5/Xenogeneic/9	Yes/No/Yes	5
Romanyuk et al., 2015 https://doi.org/10.3727/096368914X684042	Male/Rat /270–300	Lung/Fetus/Human/IS/5 × 10^5/Xenogeneic/7	Yes/Yes/Yes	8

Despite the promising potential of neural stem cell (NSC) therapies for Spinal Cord Injury (SCI), translating these therapies from preclinical studies to clinical applications presents numerous challenges. These challenges include issues related to the survival, integration, immune rejection, and long-term efficacy of transplanted NSCs. Each of these challenges must be addressed to ensure that NSC-based therapies can effectively regenerate neural tissue and restore function in SCI patients. One of the most significant challenges in the clinical application of NSCs for SCI is ensuring the survival, differentiation, and proper integration of transplanted cells within the injured spinal cord. After transplantation, NSCs must not only survive in the hostile microenvironment of the injury site but also effectively differentiate into the appropriate neural cell types (e.g., neurons, oligodendrocytes, astrocytes) and integrate into the local tissue.Another significant challenge in the clinical application of

NSC therapies is the immune response to transplanted cells. The immune system may recognize transplanted NSCs as foreign entities, leading to immune rejection and the destruction of the cells. Immune rejection can significantly hinder the therapeutic potential of NSC transplants, particularly when allogeneic (donor-derived) NSCs are used. However, using autologous (patient-derived) stem cells—such as induced pluripotent stem cells (iPSCs) or adult NSCs derived from the patient's own tissue—can reduce the risk of immune rejection.

2. CONCLUSION:

The potential of neural stem cells (NSCs) in SCI repair is immense, offering the possibility of functional recovery and neural regeneration where no effective treatments currently exist. However, to realize this potential fully, significant challenges must be addressed, including optimizing cell survival, promoting integration into the injured tissue, and overcoming immune barriers. Despite these hurdles, the progress made so far demonstrates the viability of NSC-based therapies in addressing SCI-related disabilities.

The future of SCI repair may involve personalized NSC therapies, leveraging autologous NSCs or iPSCs to reduce immune-related complications, while ongoing advancements in tissue engineering and biomaterial development will help facilitate more effective cell integration. The continued exploration of NSC therapies in clinical trials will be essential to determine the long-term outcomes and sustainability of these therapies.

Ultimately, the path toward successful NSC-based treatments for SCI will require continued collaboration across disciplines, including stem cell biology, neurobiology, immunology, and regenerative medicine. With ongoing research, innovation, and clinical validation, NSC therapies have the potential to significantly improve the quality of life for individuals with SCI, offering hope for functional recovery and better clinical outcomes in the future.

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