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REVIEW ARTICLE

Advances in understanding the mechanism and treatment strategies of radiation myelopathy

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Abstract

Radiation myelopathy (RM) is a severe, late-onset complication of radiotherapy, involving complex pathological processes, such as vascular endothelial cell damage, disruption of the blood-spinal cord barrier, inflammation, demyelination, hypoxia, and tissue necrosis. Traditional treatments, including corticosteroids and immunoglobulins, can effectively alleviate acute symptoms, but their long-term use may cause side effects and offer limited efficacy, especially in advanced stages of the disease where significant neurological recovery remains challenging. In recent years, emerging therapeutic strategies for RM – such as neuromodulation technologies, stem cell transplantation, tissue engineering, and gene therapy – have gained increasing attention. These approaches promote spinal cord repair and functional recovery through mechanisms, such as neuroprotection, myelin regeneration, axonal regeneration, and immune modulation. In addition, the use of biomaterials, such as hydrogels and nanodelivery systems has enhanced the delivery efficiency and therapeutic efficacy of both drugs and cells. Future research should focus on optimizing intervention timing and developing combination treatment strategies – such as incorporating antifibrotic drugs, anti-inflammatory therapies, and hyperbaric oxygen therapy – to improve the microenvironment of injury and enhance therapeutic outcomes. This review evaluates the pathological mechanisms of RM, explores emerging therapeutic strategies, and highlights future research directions to improve clinical efficacy.

Keywords: Pathological mechanisms; Radiation myelopathy; Review; Treatment strategies

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1. Introduction

Radiotherapy is an essential treatment for both primary and metastatic tumors. However, its dosage is limited by late and irreversible damage to surrounding normal tissues and organs, known as late effects. Radiation myelopathy (RM) is a serious late complication of radiotherapy that requires special attention when treating spinal, spinal cord, and paraspinal tumors, as well as head, neck, and lung cancers. In clinical practice, radiotherapy is typically administered in small fractionated doses over several weeks. The cellular response to this fractionated approach is influenced by four key biological factors: Radiosensitivity, the ability to repair sublethal damage, cell cycle redistribution and reoxygenation, and the ability to repopulate after radiation.

Fractionated radiotherapy optimizes treatment efficacy by taking advantage of the differential responses of normal tissues and tumors. Based on extensive clinical experience, it is widely accepted that when the radiation dose to the spinal cord is controlled at 1.8 – 2.0 Gy per day, and the total dose remains within 45 – 50 Gy, the risk of permanent injury is low – estimated at 0.03 – 0.2%.[1] Stereotactic body radiation therapy (SBRT) has been widely used in the treatment of spine, spinal cord, and paraspinal tumors due to its precise and efficient dose delivery. However, the high-dose fractionation mode used in SBRT presents new challenges for the prevention and treatment of RM. A study analyzing data from patients with spinal metastases treated with SBRT identified new dosimetric constraints aimed at reducing RM risk, but further research is required to validate the efficacy and safety of these measures.[2] There is no evidence indicating that RM caused by SBRT differs significantly from that caused by standard fractionated radiotherapy in terms of pathobiological mechanisms. While permanent myelopathy is extremely rare with conventional fractionated radiotherapy, the incidence of RM has increased with the rise in spinal SBRT and re-irradiation treatments.[3]

The pathophysiological mechanisms of RM involve several complex processes, including vascular endothelial cell injury, blood-spinal cord barrier (BSCB) disruption, inflammation, demyelination, hypoxia, and angiogenesis.[4] Present treatments for RM primarily include steroids, anticoagulants, anti-inflammatory therapies, and physical rehabilitation. Although these treatments are effective in alleviating acute symptoms and slowing disease progression, their long-term use may lead to side effects, such as opportunistic infections, endocrine abnormalities, and weight gain. In addition, their overall efficacy is limited, particularly in advanced stages of the disease, where significant neurological recovery is difficult to achieve. Furthermore, these treatments generally lack the specificity required to reverse spinal cord injury or promote regeneration. Emerging therapies, such as stem cell transplantation and gene therapy, have shown promising results in animal studies but face challenges including low transplantation efficiency, ethical concerns, and long-term safety in clinical applications. Therefore, exploring more precise and efficient therapeutic strategies – particularly those based on nerve repair and tissue regeneration – has become a key focus in RM research. This review aims to evaluate the pathological mechanisms and emerging treatment strategies for RM, with a focus on the potential of neuromodulation, stem cell transplantation, tissue engineering, and gene therapy, while also highlighting future research directions to improve clinical treatment effects.

2. Pathophysiologic mechanisms of RM

2.1. Vascular endothelial cell injury and BSCB disruption

The BSCB is a specialized structure that separates the blood and spinal cord tissues and plays a crucial role in maintaining spinal cord homeostasis. Radiation induces apoptosis in spinal cord vascular endothelial cells through the lipid second messenger ceramide, activating the acid sphingomyelinase-mediated apoptotic signaling pathway. The death of these endothelial cells disrupts BSCB integrity, impairing its function and allowing blood components to infiltrate the spinal cord parenchyma. This infiltration triggers an inflammatory response, exacerbating tissue damage,[5] and represents an early critical stage in RM progression.[6] Interestingly, radiation therapy does not significantly increase blood-brain barrier permeability following a total dose of 20 Gy delivered in two fractions,[7] suggesting that vascular endothelial cell injury in the spinal cord is closely associated with cumulative radiation dose and regional susceptibility. While spinal cord vascular endothelial cell injury contributes significantly to late-stage damage in RM,[8] it does not appear to be directly linked to long-term neuroinhibition.[9]

2.2. Demyelination

Demyelination is a key hallmark of advanced radiation injury in the spinal cord, indicating that oligodendrocytes (OLs) – the cells responsible for myelin formation – have been damaged by radiation. Animal model studies have demonstrated that OLs in the spinal cord of mice exhibit significant apoptosis, decreased density, and impaired function within hours of radiation exposure.[10] This process is primarily driven by the activation of the p53 signaling pathway in response to radiation-induced DNA damage. In addition, oligodendrocyte progenitor cells (OPCs) undergo early apoptosis following radiation, leading to a reduced cell population. These progenitor cells begin to proliferate approximately 2 weeks post-radiation and typically recover to baseline density by approximately 6 weeks.[11] Both the rate of apoptosis in OL and the recovery of OPCs after 6 weeks are dose-dependent. The early reduction of OPCs following radiation may impair OL turnover, potentially leading to demyelination and neurological dysfunction. The ability of OPCs to proliferate and recover is crucial for preventing or mitigating these long-term injuries.[12] Neural stem cells (NSCs) – which can differentiate into neurons, astrocytes, and OLs – may support OL turnover when administered early post-radiation, offering a promising therapeutic strategy for RM.

2.3. Hypoxia and angiogenesis

Vascular endothelial cell injury and disruption of the BSCB can lead to localized hypoxia in the spinal cord.

Animal studies have shown that hypoxia stimulates the upregulation of hypoxia-inducible factor-1α (HIF-1α) and the expression of the vascular endothelial growth factor (*VEGF*) gene, with a positive correlation to radiation dose.[13,14] *VEGF*, a transcriptional target gene of HIF-1α, is upregulated under hypoxic conditions and plays crucial roles in angiogenesis and neurogenesis in RM. In RM models, hypoxia-induced VEGF has been shown to exacerbate secondary injury by increasing vascular permeability and disrupting the BSCB. This effect may be mediated either directly by VEGF's action on vascular endothelial cells or indirectly through other mediators, such as matrix metalloproteinase-9.[15]

VEGF has been shown to play multiple roles in RM (Table 1). VEGF increases BSCB permeability, leading to edema and contributing to secondary injury in RM.[16,17] Conversely, VEGF may also exert neuroprotective effects by enhancing vascular density, restoring blood supply, and promoting neuronal survival, axon regeneration, and functional recovery.[10,18-22] The diverse roles and underlying mechanisms of VEGF in RM warrant further investigation.

2.4. Tissue necrosis and neurodegeneration

The persistent progression of hypoxia, inflammation, and demyelination eventually leads to necrosis of the spinal cord white matter. Neurons within necrotic regions lack regenerative capacity, leading to permanent neurological deficits. In addition to direct tissue necrosis, radiation can also cause neuronal degeneration, potentially due to the increased sensitivity of neurons to hypoxic and inflammatory conditions, along with the impaired axonal transport mechanisms.

2.5. Oxidative stress and inflammation

Radiation therapy can induce oxidative stress – including the generation of reactive oxygen species and reactive nitrogen species – by damaging neuronal membranes, mitochondria, and DNA. Oxidative stress not only directly harms neurons, impedes axonal regeneration, and hinders functional recovery, but also exacerbates vascular endothelial cell injury and disrupts the blood-brain barrier. In addition, it activates inflammatory signaling pathways (e.g., the nuclear factor kappa B pathway), leading to the release of inflammatory cytokines (e.g., tumor necrosis factor α, interleukin [IL]-1β, and IL-6), which further aggravate tissue damage.

3. Present status of RM treatment

3.1. Traditional treatments

3.1.1. Glucocorticosteroid

Glucocorticoids play a crucial role in the treatment of RM by suppressing inflammatory responses, modulating immune activity, and reducing spinal cord edema, thereby effectively alleviating the neurological dysfunction caused by radiation injury. In the acute phase (within 8 h of trauma), high-dose shock therapy is typically administered during the first 24 h. This involves an initial loading dose of methylprednisolone at 30 mg/kg infused over 15 min, followed by a maintenance dose of 5.4 mg/kg/h infused for 45 min. After the loading dose, the same infusion rate is maintained for 23 h. This treatment is effective as an early intervention, helping to reduce pain and improve sensory as well as motor function. However, the dosage used far exceeds standard shock doses, increasing the risk of adverse effects such as infections.[24] In chronic or advanced RM patients, glucocorticoids show limited efficacy and are primarily used to control secondary inflammation and relieve residual symptoms. Moreover, long-term use of glucocorticoids can lead to side effects such as hyperglycemia, increased infection risk, and osteoporosis. Therefore, the risks and benefits of treatment must be carefully evaluated and tailored to each patient's specific condition. Overall, glucocorticoids are essential

Table 1. Summary of literature on the mechanisms of vascular endothelial growth factor in radiation myelopathy

Source of VEGF	Impact of VEGF	Summary mechanism	References
Endogenous	-	Arteriosclerosis.	16
Exogenous	-	Increased permeability of BSCB.	17
Endogenous	+	Relief of spinal cord infarction and apoptosis inhibition.	20
Endogenous	+	Improvement of ischemia and hypoxia.	22
Endogenous	+	Inhibit apoptosis.	23
Endogenous	+	Promotes angiogenesis in response to hypoxic environments.	19
Exogenous	+	Protects or repairs blood vessels and reduces apoptosis.	18
Exogenous	+	Promotes angiogenesis and contributes to neural support.	21

Note: "-" indicates negative impact of VEGF, while "+" indicates positive impact of VEGF.
Abbreviations: BSCB: Blood-spinal cord barrier; VEGF: Vascular endothelial growth factor.

in the treatment of RM and hold significant clinical value, especially during the acute phase.

Studies have shown that intravenous immunoglobulin (IVIG) is highly effective in treating hormone-resistant RM.[25] In cases of delayed RM, even when neurological symptoms fully resolve after adequate glucocorticoid shock therapy, imaging often reveals that the lesion persists, presenting a potential risk for delayed injury. However, combining IVIG with glucocorticoid therapy led to complete resolution of the lesion on imaging after 6 months, suggesting that IVIG may provide a therapeutic advantage in stabilizing delayed RM.[26] For RM induced by immunotherapy combined with radiotherapy, conventional treatments (such as glucocorticoids alone) have limited efficacy, with more than 80% of patients left with neurological deficits.[27-29] However, a regimen combining high-dose glucocorticoids with IVIG has demonstrated better efficacy in treating immune-related RM. For patients with poor response or disease recurrence, further treatments – such as plasma exchange or mycophenolate mofetil – may be considered.[30]

3.1.2. Adjunctive treatment

Adjunctive therapies for RM include antioxidant treatments, therapies that enhance the blood supply, and rehabilitative therapies. These are typically used as supplementary treatments alongside primary therapies – such as glucocorticoids – to alleviate symptoms, improve the spinal cord microenvironment, and promote functional recovery.

Antioxidant therapy can mitigate the pathological changes associated with RM, promote functional recovery, and improve patients' quality of life by scavenging free radicals, reducing oxidative stress and inflammation, and protecting neuronal and vascular function. Examples of antioxidant agents include oxygen radical scavengers, such as edaravone[31]; minerals such as magnesium, copper, and manganese; antioxidant vitamins such as vitamin E and vitamin C; polyphenol-rich botanicals, such as grape seed and raspberry seed; and saponin-rich botanical extracts from plants, such as *Panax ginseng*, Rhizoma Ligustici Chuanxiong, Heptaphyllum seed, alfalfa, and spinach. These agents primarily function by maintaining antioxidant enzyme activity, scavenging free radicals, and inhibiting inflammatory responses.[32-37] For example, *Panax notoginseng* and Chuanqiong are well-known traditional Chinese medicinal herbs. *Panax notoginseng* is particularly recognized for its ability to promote blood circulation. Its saponins exhibit calcium antagonist properties, preventing calcium ions (Ca^{2+}) influx by blocking exogenous Ca^{2+} entry and inhibiting intracellular $Ca2^{+}$ release. This mechanism contributes to immune regulation and enhances the activity of antioxidant enzymes such as superoxide dismutase and reduced lipid peroxide. The early application of *Panax notoginseng* saponins has significant antioxidant effects, increases spinal cord blood flow, improves gray matter necrosis after injury, and creates favorable conditions for white matter survival.

Chuanqiong inhibits the expression of nitric oxide synthase following spinal cord injury, thereby preventing cell damage or apoptosis caused by excessive nitric oxide. It also inhibits the expression of c-fos, Bax, and caspase-3 proteins, which are involved in secondary pathological changes after spinal cord injury. In addition, Chuanqiong enhances the mitochondria's ability to scavenge free radicals, reduces lipid peroxidation, and prevents the reduction in calcium-magnesium adenosine triphosphatase activity. This helps reduce mitochondrial membrane structure and function damage caused by oxygen-free radicals, maintain mitochondrial integrity, inhibit neuronal apoptosis at the subcellular level, and protect the injured spinal cord. Furthermore, amphotericin may provide protective effects by stabilizing cell membranes.[38] However, the specific mechanisms and clinical value of antioxidant therapy in RM still require further research and validation.

The occurrence of RM is closely associated with local vascular injury and ischemia. Improving blood supply can enhance the delivery of oxygen and nutrients, promote tissue repair, and support nerve regeneration, thereby contributing to functional recovery. Common medications used to improve blood supply include angiotensin-converting enzyme inhibitors such as ramipril[39]; anticoagulants, such as heparin and warfarin[40]; antiplatelet agents such as disulfiram[41]; anti-VEGF receptor agents[42]; and valproic acid.[43] These drugs exert their effects through mechanisms, such as reducing inflammatory cell infiltration, decreasing *VEGF* expression, protecting vascular endothelial cells, repairing the BSCB, and promoting myelin regeneration. For example, Bevacizumab, an anti-VEGF agent, has been explored based on the hypothesis that radiation-induced endothelial damage and subsequent vascular permeability contribute to spinal cord edema and necrosis. By inhibiting VEGF, bevacizumab may reduce vascular permeability and alleviate edema.

Rehabilitation for RM includes various approaches – such as physiotherapy, occupational therapy, psychological rehabilitation, spinal cord electrical stimulation, traditional Chinese medicine rehabilitation, and hyperbaric oxygen therapy (HBOT). Studies have shown that exoskeleton gait training significantly improves walking ability in patients with spinal cord injuries,[44] while robot-assisted gait training offers systematic rehabilitation. The Lokomat

robot has been proven effective in enhancing daily living abilities and muscle strength, wearable robots improve walking ability, and end-effector robots are particularly effective in balance enhancement.[45] In recent years, virtual reality (VR) technology combined with physical therapy (e.g., VR gait training) has emerged as a research focus, demonstrating promising potential for promoting motor function recovery.[46] In addition, occupational therapy primarily utilizes wearables and smart aids (e.g., robotic gloves) to improve hand function and mobility in daily life.[47] Remote occupational therapy – which integrates intelligent devices and VR technology – improves treatment accessibility and effectiveness, reduces healthcare costs, and facilitates personalized care and psychological support. This approach holds promising application potential.[48] Psychological interventions aim to address depression and anxiety in RM patients, enhancing both mental health and rehabilitation outcomes.[49]

Interventions based on positive thinking are gaining increasing attention, with studies demonstrating their effectiveness in improving sleep quality and reducing perceived stress.[50] Electrical spinal cord stimulation aids motor function recovery by activating spinal cord neural networks, increasing spinal cord excitability, and promoting neuroplasticity.[51] Individualized neurostimulation programs, when combined with rehabilitation training, have been shown to significantly improve both motor and autonomic functions in patients.[52,53] Traditional Chinese medicine rehabilitation includes acupuncture, tuina, and Chinese herbal medicine, which help improve blood circulation, regulate nerve function, and alleviate pain. Acupuncture promotes functional recovery by modulating central nervous system plasticity through stimulation of specific acupuncture points.[54] Modern acupuncture techniques, such as electroacupuncture, have shown greater efficacy in pain relief.[55] HBOT is believed to exert therapeutic effects by improving oxygen delivery to hypoxic tissues, stimulating angiogenesis, and promoting wound healing. In the context of RM, HBOT may help counteract radiation-induced vascular endothelial cell injury by promoting capillary regeneration and reducing tissue hypoxia. Furthermore, enhanced oxygenation may facilitate remyelination and repair of radiation-damaged spinal cord tissue, though further research is needed to fully understand its efficacy. Therefore, HBOT has the potential to target both major pathophysiological mechanisms, which are vascular compromise and demyelination.[56] Recent studies suggest that HBOT is effective in early-stage RM patients and may be combined with glucocorticoids and bevacizumab to enhance efficacy, although this remains to be validated in clinical trials.[57,58]

3.2. Emerging treatments

3.2.1. Neuromodulation and brain-spinal cord interface (BSCI) technology

The brain-machine-spinal cord interface is a technology that connects the brain to the spinal cord, aiming to decode brain signals and transmit them in real-time to an external device. This enables control of muscle movements using a neuromuscular electrical stimulation system, thereby improving motor function and enhancing patients' quality of life.[59] Recent studies have demonstrated that real-time control of muscle activation through cortical signaling can facilitate motor function recovery in patients with mechanical spinal cord injury.[60] However, the brain-machine-spinal cord interface system primarily targets functional rehabilitation, and research on its application in neurorehabilitation remains limited.

Recently, a new system called the BSCI has been proposed. This technique establishes a digital bridge directly between the brain and the spinal cord, aiming to restore the natural walking ability of patients paralyzed due to mechanical spinal cord injury. Studies have shown that with the BSCI, patients can regain neurological function and walk independently, even after the system is turned off.[61] The BSCI technique holds promise for restoring ambulation in a broader group of spinal cord injury patients and is expected to have expanded applications in the treatment of RM and other neurological disorders.

3.2.2. Stem cell transplantation and tissue engineering therapy

Stem cell transplantation therapy for RM aims to promote neural repair and functional recovery by introducing stem cells into the damaged spinal cord region. The underlying mechanisms may involve various processes, including neuroprotection, immunomodulation, axon regeneration, synapse formation, myelin sheath formation, and angiogenesis, all of which contribute to spinal cord tissue repair and functional recovery. The primary cell types used in stem cell transplantation for spinal cord injury include Schwann cells, neural stem and progenitor cells, OPCs, olfactory ensheathing cells (OECs), and mesenchymal stem cells (MSCs). Schwann cells – which are myelin-forming glial cells of the peripheral nervous system – guide axon regeneration and support both axonal and myelin repair after transplantation. Neural stem and progenitor cells are pluripotent stem cells that can differentiate at the site of spinal cord injury into various cell types – including neurons, astrocytes, OLs, and OPCs – thereby promoting axon regeneration, myelin formation, and the restoration of neural connections. OPCs, also known as OL precursor cells, facilitate myelin

regeneration at the injury site, thereby restoring nerve conduction. OECs are glial cells that support the growth of olfactory receptor axons into the olfactory bulb. When transplanted into the injured spinal cord, OECs promote axonal regeneration and help reduce glial scar formation. MSCs are pluripotent progenitor cells found in various tissues and capable of self-renewal and differentiation into multiple cell types. After transplantation, MSCs may promote spinal cord injury repair, reduce inflammation, and mitigate scar formation by secreting neurotrophic and anti-inflammatory factors. Transplantable cells can be derived from adult or embryonic pluripotent stem cells through induced differentiation,[62] or generated using direct transformation techniques.[63] Furthermore, their mechanisms of action may vary depending on the origin of allogeneic transplanted cells (Table 2).

The primary objectives of stem cell therapy for RM are to restore vascular function, inhibit fibrosis and chronic inflammation, and promote nerve regeneration. Vascular regeneration typically involves MSCs or endothelial progenitor cells, which possess vascular regenerative capabilities, as well as stem cells (e.g., NSCs or genetically modified stem cells) that secrete neurotrophic factors, such as brain-derived neurotrophic factor and VEGF. MSCs are the preferred choice for RM treatment due to their crucial roles in angiogenesis and antifibrosis.[94,95] MSCs can secrete factors that regulate the gene expression in endothelial cells, thereby promoting vascular integrity recovery and repairing the BSCB. The interaction between endothelial cells and pericytes is essential for the structural and functional maintenance of the BSCB following spinal cord injury. When pericytes separate from endothelial cells, it leads to BSCB destruction. MSCs transplantation has been shown to enhance pericyte coverage to endothelial cells, which helps promote BSCB repair by secreting bioactive molecules that stimulate pericyte recruitment and proliferation.[96] In contrast, NSCs, OPCs, OECs, and Schwann cells are more suitable for treating mechanical spinal cord injuries, as their primary therapeutic mechanism involves reducing secondary damage and promoting nerve regeneration. These cells are widely used in mechanical spinal cord injury and are expected to be applied to RM as well.

Fang *et al.*[97] developed a modified MSC therapy known as MSC-MM@LPHN, aimed at restoring the vascular microenvironment in a pulmonary fibrosis model. The therapy utilizes the inherent homing ability of MSCs to target lung tissue, promoting the dedifferentiation of myofibroblasts. This process reduces cytokine secretion responsible for endothelial cell damage, prevents endothelial cell transformation into a fibrotic phenotype, and ultimately restores vascular endothelial cell function. This approach is expected to be applicable in treating radiation-induced spinal cord fibrosis. Yusoff *et al.*[98] demonstrated that hypoxic pre-conditioning of MSCs enhances their proliferation and activity while increasing the expression of VEGF, CD31, HIF-1α, and other factors. This process effectively promotes angiogenesis, as well as

Table 2. Possible mechanisms of action of transplanted cells from different origins and relevant references

Cell types	Origins	Possible mechanisms of action	References
Schwann cells	Skin pre-cursor cells	Neuroprotection, myelin formation, and axonal regeneration.	64,65
	Sciatic nerve	Neuroprotection, myelin formation, and axonal regeneration.	66,67
Neural stem and progenitor cells	Spinal cord	Neuroprotection, myelin formation, and axonal regeneration. Immunomodulation and synapse formation.	68-71
	Brain	Neuroprotection, myelin formation, and axonal regeneration.	72-75
Oligodendrocyte progenitor cells	Stem cells	Neuroprotection, myelin formation, and axonal regeneration. Immunomodulation and synapse formation.	76,77
	Peripheral blood mononuclear cells	Neuroprotection and myelin formation.	78
Olfactory ensheathing cells	Olfactory bulb	Neuroprotection, myelin formation, and axonal regeneration. Reduced inflammation and angiogenesis.	79-83
	Lamina propria of spinal cord	Axonal regeneration.	84
	Lamina propria of olfactory mucosa	Axonal regeneration.	85
Mesenchymal stem cells	Tibial/femoral bone marrow	Neuroprotection, myelin formation, and axonal regeneration.	86-89
	Pelvic bone marrow	Neuroprotection and immunomodulation.	90,91
	Wharton's jelly of the umbilical cord	Angiogenesis and immunomodulation.	92,93

Note: The mechanisms discussed in this review are limited to the main mechanisms proposed by most of the present studies, including: Neuroprotection, immunomodulation, axonal regeneration, synapse formation, myelin formation, attenuation of inflammation, and vascular regeneration.

improves blood flow and blood perfusion. The engineering of MSCs and other cell types to enhance their specific capabilities shows significant potential and warrants further investigation.

Regarding transplantation timing and methods, early intervention is crucial for inhibiting progressive fibrosis and preventing chronic damage. Intravenous or intrathecal injections are commonly used to ensure widespread coverage of the affected area. In terms of microenvironment regulation, stem cell transplantation for radiation injury often requires the use of antifibrotic drugs (e.g., pirfenidone)[99] or antioxidants (e.g., edaravone)[100] to improve stem cell survival. In addition, targeted inhibition of pro-fibrotic and inflammatory pathways, such as transforming growth factor β and nuclear factor κB, is also crucial. For RM, the main objective of stem cell therapy is to slow disease progression and improve function; however, achieving full recovery remains challenging. Since radiation injury is a chronic and progressive condition, therapeutic effects tend to be gradual.

Tissue engineering therapy for spinal cord injury integrates stem cells, biomaterials, and bioactive factors to promote nerve regeneration, repair myelin, exert anti-inflammatory effects, and enhance the microenvironment. A key component of this approach is the use of scaffolds that provide structural support, facilitate stem cell differentiation into neurons and glial cells, and regulate the release of neurotrophic factors to restore the neural network. Despite challenges, such as low cell survival, poor biocompatibility, and difficulty in clinical translation, technological advancements show promising potential for functional recovery. Present research is focusing on controlled-release systems for biomaterials and bioactive factors, which are increasingly being applied in the treatment of mechanical spinal cord injuries. Chen *et al.*[101] developed an injectable hydrogel that responds to early reactive oxygen species and late matrix metalloproteinases, enabling precise, on-demand drug delivery to the injury site. The accumulation of matrix metalloproteinases in the late stage of spinal cord injury can promote angiogenesis and NSC differentiation by triggering the release of VEGF, which can effectively resist the adverse effects caused by vascular endothelial cell injury.

For example, in the field of biomaterials, hydrogels[102] and decellularized spinal cord scaffolds have been developed with mechanical properties that closely mimic those of damaged spinal cord tissue. These materials support neural regeneration and functional recovery by providing mechanical stability and fostering a neuroregenerative microenvironment following mechanical spinal cord injury.[103] In terms of controlled release systems for bioactive factors, some studies have developed gamma-aminobutyric acid-ergic neuron nanomedicine, which has been shown to effectively regulate neuronal excitability, protect residual neural tissues, and promote functional recovery after spinal cord injury. This approach has emerged as an innovative method for enhancing functional recovery.[104] In addition, a highly drug-loaded microsphere technology has been developed using a nano-microsphere structure. This method significantly enhances drug loading capacity and therapeutic efficiency, reduces the frequency of administration and excipient usage, and consequently minimizes side effects.[105] Nanodelivery systems with controlled release characteristics play a crucial role in targeting spinal cord tissues and addressing the limitations of conventional drug delivery methods through strategic design and modification. However, tissue engineering therapy is currently primarily applied to mechanical spinal cord injuries, and its application and efficacy in RM still require further exploration.

3.2.3. Other emerging treatments

The treatment of RM is transitioning from single-modality interventions to multimodal integrated approaches, with numerous emerging treatments that still require further research and validation. Gene therapy aims to restore function by precisely regulating gene expression. For instance, viral vectors can be used to deliver neurotrophic factor genes (e.g., brain-derived neurotrophic factor and *NT-3*) to the injury site, thereby activating neuronal regeneration pathways and inhibiting apoptosis. Recent studies have demonstrated that gene editing techniques, such as clustered regularly interspaced short palindromic repeats-associated protein 9 (commonly known as CRISPR-Cas9), have successfully repaired spinal cord injury-related gene mutations in animal models; however, their clinical applicability still requires further validation.[106]

Anti-inflammatory and immunomodulatory therapies aim to break the vicious cycle of chronic inflammation. New anti-inflammatory agents, such as monoclonal antibodies targeting IL-6 and small-molecule Janus kinase inhibitors, are currently undergoing clinical trials to attenuate secondary injury by blocking pro-inflammatory cytokine signaling pathways. Kong[107] reported that the use of poly lactic-co-glycolic acid scaffolds loaded with immunomodulators (e.g., fingolimod) and NSCs was effective in restoring locomotor ability and promoting the formation of new neurons in spinal cord-injured rats.

Metabolic intervention strategies aim to remodel microenvironmental homeostasis at the energy supply level. A study by Minhas *et al.*[108] revealed that indoleamine 2,3-dioxygenase 1 inhibitors (e.g., Epacadostat) restore

astrocyte glucose metabolism and reverse neuronal energy crises, showing significant effects in Alzheimer's disease models. These potential mechanisms could be extended to RM therapy. The development of targeted drugs is based on molecular mechanisms to enable personalized treatment. For example, inhibition of the transforming growth factor β signaling pathway reduces fibrotic scar formation,[109] and drugs targeting the glial cell water channel protein aquaporin-4 (e.g., TGN-020) alleviate radiation-induced edema.[110,111]

While these advances are still in pre-clinical or early clinical stages, they have demonstrated promising synergistic potential. However, their safety and translational value require further validation through interdisciplinary studies in the future. Most of the emerging therapies discussed in this section are still under investigation in pre-clinical models, with limited data available on their optimal dosing or dose–response relationships.

4. Conclusion and outlook

RM, a severe late complication of radiotherapy, presents a significant challenge to present treatment strategies due to its complex pathological mechanisms and the progressive nature of injury. Traditional treatments – such as glucocorticoids and immunoglobulins – are effective in alleviating acute symptoms and controlling secondary inflammation, but they are insufficient for achieving substantial recovery of neurological function in the advanced stages of the disease. In recent years, emerging therapeutic approaches, including neuromodulation techniques, stem cell transplantation, tissue engineering, biomaterials, and gene therapy, have made notable advancements, offering new directions for RM treatment. These strategies have demonstrated promising potential through multiple mechanisms – including neuroprotection, myelin regeneration, axonal repair, immunomodulation, antifibrosis, and angiogenesis – that work synergistically.

However, several challenges remain in the treatment of RM, including low stem cell survival rates, the biocompatibility of tissue-engineered materials, treatment safety, and long-term efficacy. In addition, the optimization of multimodal combination therapies requires further investigation, and the development of personalized treatment strategies must be supported by more robust clinical data. Future research should focus on several key areas, including: (i) conducting in-depth analyses of the pathological mechanisms of RM to identify key therapeutic targets; (ii) optimizing the application of stem cell transplantation, nanodelivery systems, and gene editing technologies to enhance therapeutic efficacy; (iii) advancing neuromodulation technologies and tissue engineering scaffolds to promote nerve regeneration and functional recovery; and (iv) validating the safety and efficacy of emerging therapies through large-scale clinical trials.

In conclusion, with ongoing advancements in basic research and clinical technology, the treatment of RM is shifting from single-modality interventions to multimodal integrated approaches. Across interdisciplinary collaboration, the integration of precision medicine, and the application of advanced technologies, significant recovery of neurological function in RM patients may become achievable – ultimately offering practical solutions to enhance patients' quality of life.

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Conflict of interest

The authors declare they have no competing interests.

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