Press Release

Keio University

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Keio University School of Medicine
Keio University Regenerative Medicine Research Center

A New Indicator for Predicting Recovery After Spinal Cord Injury

miR-9-3p in cerebrospinal fluid extracellular vesicles shows neuroprotective effects, highlighting its potential as a novel biomarker

A research team at Keio University has identified that miR-9-3p (1) contained in cerebrospinal fluid (CSF) extracellular vesicles (EVs) (2) can serve as a novel biomarker (3) capable of predicting spontaneous functional recovery and exhibits neuroprotective responses after spinal cord injury (SCI). The team was led by Dr. Narihito Nagoshi, Assistant Professor at the Department of Orthopaedic Surgery, Keio University School of Medicine; Hideyuki Okano, Director of the Keio University Regenerative Medicine Research Center; Dr. Tomoharu Tanaka, Assistant Professor; and Satoru Morimoto, Associate Professor/Vice Director.

Although biomarker development for SCI has been actively pursued worldwide, no biomarker has yet been established that can predict the potential for spontaneous recovery during the early phase after injury. To address this gap, the research team performed a comprehensive analysis of CSF-derived EVs. In rat SCI models, they identified a marked increase in miR-9-3p levels in CSF-derived EVs following injury. Furthermore, in human CSF samples, miR-9-3p levels were significantly higher in the non-recovery group (4) than in the spontaneous recovery group (5), demonstrating its usefulness as a prognostic biomarker.

In addition, in an acute SCI rat model, miR-9-3p expression decreased at the spinal lesion site but increased in the brain, where it was found to be highly expressed in astrocytes (6). These findings suggest that miR-9-3p may be actively secreted from astrocytes in the brain as a compensatory response to spinal cord injury. Analysis using human-derived motor neurons further revealed that miR-9-3p regulates genes associated with suppression of energy metabolism (7), synaptic plasticity (8), and stress responses, suggesting its involvement in adaptive neuroprotective responses.

These findings provide new insights into intercellular communication within the central nervous system (9) during the acute phase (10) of SCI and suggest that CSF EV-derived miR-9-3p may serve as both a novel biomarker for predicting spontaneous recovery and a therapeutic target.

The findings were published online in *Communications Biology* on October 27, 2025, at 18:00 JST.

1. Research Background

Spinal cord injury (SCI) causes paralysis and sensory impairment, profoundly reducing quality of life. Despite advances in acute-phase treatments such as stem-cell transplantation and anti-inflammatory therapies, clinical efficacy remains limited, partly because SCI pathophysiology—especially at the molecular level—has not been fully elucidated.

EVs are key mediators of intercellular communication that carry regulatory cargos, including miRNAs. EV-derived miRNAs are implicated in diverse diseases, from cancer to neurodegeneration. However, their roles in SCI remain underexplored, and analyses of CSF-derived EVs—which directly reflect local pathology within the neuraxis—have been particularly scarce.

Here, we established a robust method for CSF collection in a rat SCI model and performed comprehensive miRNA profiling of EVs from CSF and plasma. We then evaluated clinical relevance using CSF from patients with SCI to test whether EV-miRNA signatures could predict spontaneous recovery. Finally, we investigated the biological functions of the most altered miRNAs using gene-expression analyses.

2. Research Significance and Future Development

Comprehensive miRNA profiling of EVs isolated from rat CSF revealed that CSF EV–derived miR-9-3p was selectively and markedly increased in the acute phase after SCI (Fig. 1a). In Fig. 1a, red circles indicate miRNAs that were upregulated after SCI, whereas blue circles represent miRNAs that were downregulated. Figure 1b plots miRNAs in human CSF EVs that showed differential expression between patients with non-recovery and those with spontaneous recovery. Among these, only miR-9-3p was elevated in the non-recovery group compared with the spontaneous recovery group. Furthermore, receiver operating characteristic (ROC) analysis demonstrated that CSF miR-9-3p effectively predicted recovery outcomes, with an area under the curve (AUC) of 0.80. At a cutoff value of 2,097.92 CPM, the sensitivity and specificity for distinguishing recovery status were 80% and 89%, respectively, indicating that CSF EV–derived miR-9-3p could serve as a predictive biomarker for spontaneous recovery in the early phase after SCI (Fig. 1c).

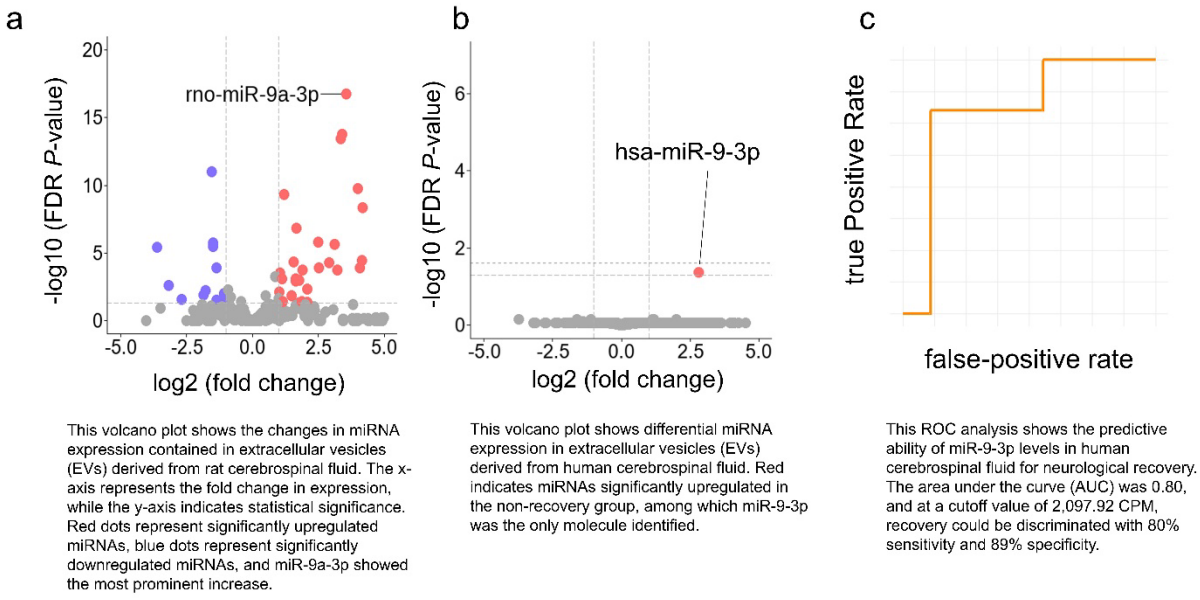


Figure 1. Dynamics of CSF EV-derived miR-9-3p and its predictive accuracy for spontaneous recovery.

Additionally, analysis of rat spinal cord and brain tissue showed that miR-9a-3p expression decreased at the spinal cord lesion site (T10), whereas it was increased in the brain. This indicates that the brain and spinal cord exhibit opposite responses, suggesting that the brain may sense and respond to spinal cord injury (Fig. 2a). In Fig. 2a, representative spinal levels including C1, T9, T10, and T11 are shown. We further examined the localization of miR-9a-3p in the brain and spinal cord and found it was predominantly localized in astrocytes in both regions (Fig. 2b). These findings suggest that, following spinal cord injury, astrocytes in the brain may release EVs enriched in miR-9a-3p into the CSF.

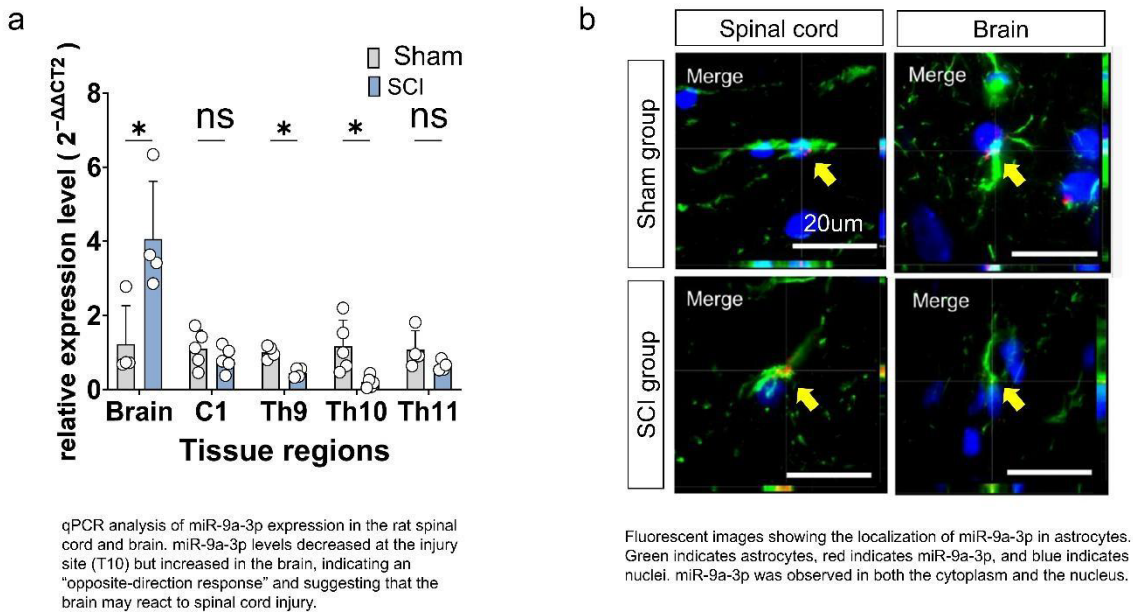
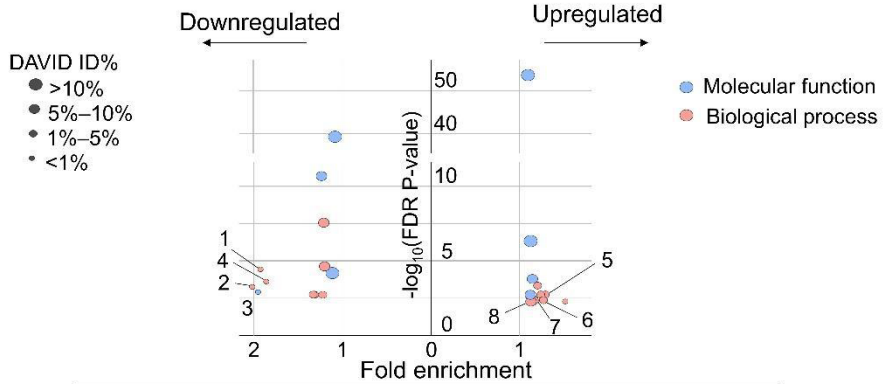


Figure 2. miR-9-3p is highly expressed in brain astrocytes, which may suggest its secretion into CSF via EVs following injury.

When miR-9-3p was overexpressed in human motor neurons, most of the downregulated genes were involved in cellular energy metabolism, including ATP synthesis, aerobic respiration, and the electron transport chain. In contrast, the upregulated genes were enriched for those related to neuronal development and synaptic function. These findings suggest an adaptive protective response after spinal cord injury, in which cells suppress metabolic activity to minimize unnecessary energy consumption while activating mechanisms required for the maintenance and regeneration of neural functions (Fig. 3).



Number	Downregulation (suppression of energy metabolism)	Function
1	mitochondrial ATP synthesis	Cellular energy production
2	Mitochondrial electron transport (NADH→ubiquinone)	ATP synthesis by the electron transport chain
3	NADH dehydrogenase activity	Oxidative phosphorylation
4	Aerobic respiration	Overall reduction in energy metabolism

Number	Upregulation (neuronal development and neuroprotective response)	Function
5	Nervous system development	Promotion of neural circuit reconstruction
6	Intracellular signal transduction	Activation of neural responses
7	Signal transduction	Intercellular communication
8	Regulation of transcription by RNA polymerase II	Promotion of neural gene expression

miR-9-3p suppressed genes involved in energy metabolism (ATP synthesis, aerobic respiration) while activating those related to neuronal development and synaptic function, suggesting an adaptive energy-saving response supporting neural maintenance and regeneration after spinal cord injury.

Figure 3. miR-9-3p may exert neuroprotective effects while downregulating energy metabolism

3. Notes

This study was supported by a designated donation to the Department of Orthopaedic Surgery, Keio University School of Medicine. Animal experiments were conducted with the approval of the ethics

committees of Keio University and the Central Institute for Experimental Animals (approval number 13020). Human cerebrospinal fluid samples were obtained under ethical approval and written informed consent, based on the clinical study for acute spinal cord injury (ClinicalTrials.gov: NCT02193334) and through the provision of the National Center of Neurology and Psychiatry Biobank (NCBN) (approval numbers 20231158 and NCNPBB-0132).

4. Research Paper

Title: *Cerebrospinal fluid extracellular vesicle-derived miR-9-3p in spinal cord injury with neuroprotective implications and biomarker development*

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5. Glossary

(1) MicroRNAs (miRNAs): Short (~20 nucleotides) non-coding RNAs that bind to messenger RNAs (mRNAs) to regulate gene expression by inducing mRNA degradation or inhibiting translation. They are involved in various physiological and pathological processes such as cancer, neurological diseases, and immune responses, and are attracting attention as potential diagnostic, prognostic, and therapeutic targets.

(2) Extracellular vesicles (EVs): Tiny membrane-bound structures (50–200 nm in diameter) secreted from cells, containing proteins, lipids, and miRNAs. They mediate intercellular communication and are found in body fluids such as blood and CSF. EVs are known to be involved in many pathological conditions, including cancer and neurological disorders.

(3) Biomarker: An indicator that can be used for disease diagnosis, evaluation of treatment response, or prognosis. In addition to imaging and blood tests, molecular-level measurements such as EVs and miRNAs have recently drawn attention.

(4) Non-recovery group: A group of SCI patients who show no or minimal neurological improvement over time without treatment. Patients who fail to achieve meaningful functional recovery in the chronic phase are classified in this group.

(5) Spontaneous recovery group: A group of SCI patients whose neurological function improves over time without specific therapeutic intervention. Some degree of spontaneous recovery can be observed from the acute to chronic phase in certain cases of SCI.

(6) Astrocytes: A type of glial cell in the central nervous system that supports neurons by regulating metabolism and maintaining synaptic function. Upon injury, astrocytes become activated and participate in inflammatory responses and tissue repair.

(7) Suppression of energy metabolism: A cellular phenomenon in which metabolic activities such as ATP production are intentionally reduced. By limiting excessive energy consumption, cells adapt to stress conditions and avoid cell death.

(8) Synaptic plasticity: The ability of neuronal connections (synapses) to change their strength in response to activity. It underlies learning and memory and also contributes to functional recovery after injury.

(9) Intercellular communication within the central nervous system: The mechanisms by which neurons and glial cells in the brain and spinal cord exchange information through cytokines, neurotransmitters, and extracellular vesicles.

(10) Acute phase: The period within approximately two weeks after injury. It includes the primary mechanical damage and the secondary injury processes caused by ischemia, edema, and inflammatory cell infiltration, leading to cell death. Suppressing secondary injury and limiting tissue damage may improve functional outcomes.

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