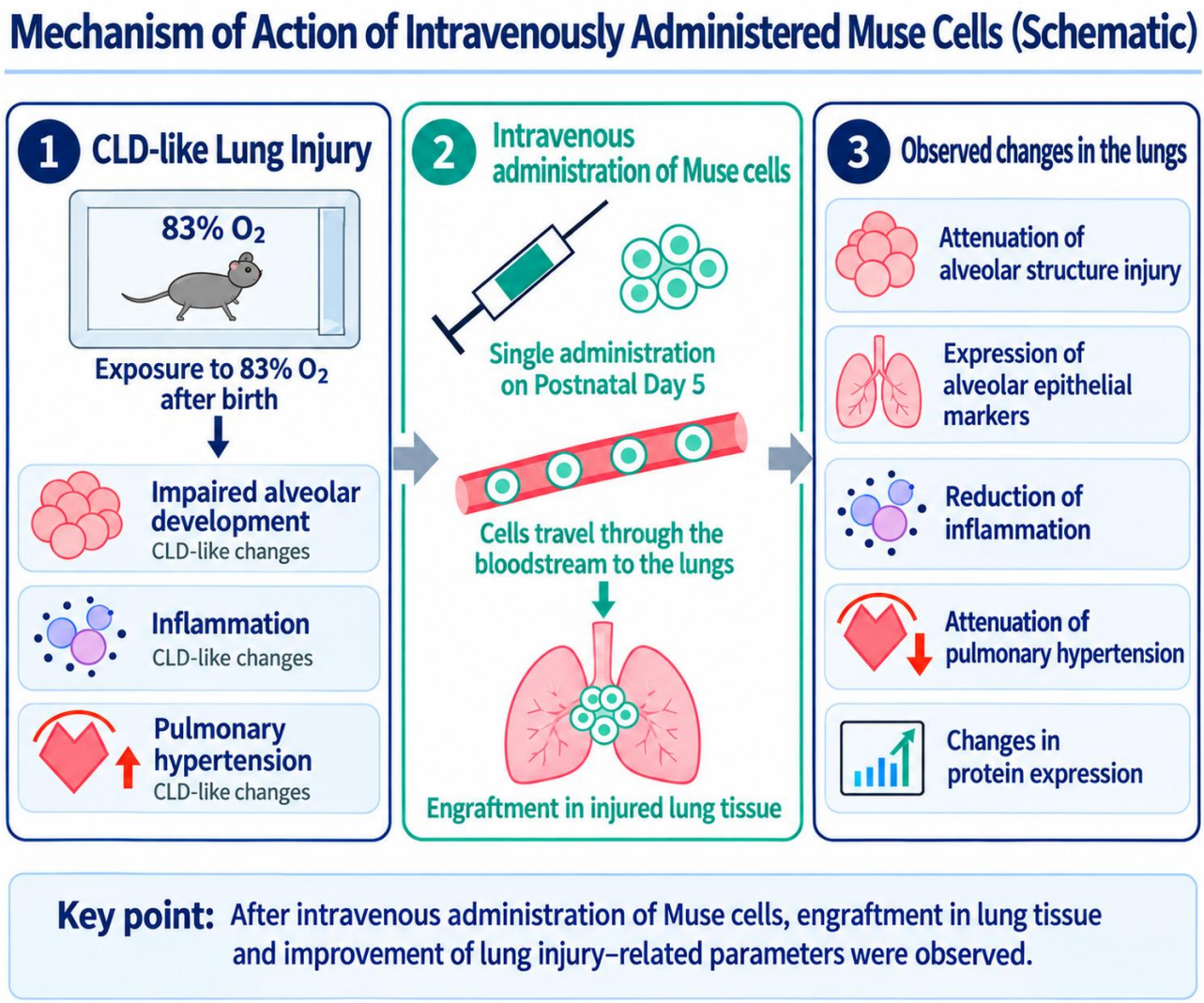
News Release

Therapeutic Potential of Intravenously Administered Multilineage-Differentiating Stress-Enduring (Muse) Cells for Bronchopulmonary Dysplasia Demonstrated in a Rat Model

— Muse cells alleviate lung tissue injury, inflammation, and pulmonary hypertension in a hyperoxia-induced lung injury rat model with features of bronchopulmonary dysplasia —

Key Points

- In a hyperoxia-induced neonatal rat model of lung injury with features of severe bronchopulmonary dysplasia (BPD), a condition commonly seen in preterm infants, intravenous administration of multilineage-differentiating stress-enduring (Muse) cells, a subpopulation of mesenchymal stromal cells (MSCs), showed the potential to alleviate lung injury.
- Compared with non-Muse cells (MSCs depleted of Muse cells), Muse cells more effectively attenuated lung tissue injury, pulmonary inflammation, and pulmonary hypertension.
- The administered Muse cells engrafted in the lung tissue, and some expressed markers associated with alveolar epithelial cells.
- Proteomic analysis showed that subsets of cell adhesion- and coagulation/fibrinolysis-related proteins altered in BPD-like lung injury were also modulated following Muse cell administration.
- This study is a preclinical investigation using a rat model, and further studies are required to evaluate the safety and efficacy of Muse cells before their potential application in human neonates.



Summary

A research group led by Ryosuke Miura, Designated Assistant Professor; Atsuto Onoda, Researcher; and Yoshiaki Sato, Director of the Center and Clinical Professor of Pediatrics, Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital; and Yoshiyuki Takahashi, Professor, Department of Pediatrics, Nagoya University Graduate School of Medicine, investigated the therapeutic effects of intravenous administration of multilineage-differentiating stress-enduring (Muse) cells using a hyperoxia-induced rat model of lung injury with features of bronchopulmonary dysplasia (BPD).

BPD is a lung disease that commonly affects preterm infants and is characterized by impaired alveolar development, inflammation, and pulmonary hypertension. Respiratory problems may persist long after hospital discharge, and affected infants may also experience developmental impairments. As no definitive treatment for BPD has yet been established, there is a need to develop new therapeutic approaches.

In this study, neonatal rats were exposed to hyperoxia to establish a model of BPD-like lung injury and were administered either Muse cells or non-Muse cells. The intravenously administered Muse cells engrafted in the lung tissue, and some expressed markers associated with alveolar epithelial cells. In addition, Muse cell administration attenuated lung tissue injury, inflammation, and pulmonary hypertension.

Proteomic analysis further revealed that groups of proteins involved in cell adhesion and coagulation/fibrinolysis-related pathways were altered in association with BPD-like lung injury and Muse cell administration.

The researchers also compared intravenous and intratracheal administration of Muse cells. No substantial differences between the two routes were observed in their effects on respiratory function, lung histology, or inflammation; however, intratracheal administration was associated with poorer body weight gain and survival.

These findings provide preclinical evidence supporting the potential of Muse cell therapy for BPD and may contribute to the future development of novel therapeutic strategies for this condition.

The findings were published in the international journal Stem Cell Research & Therapy on September 4, 2026.

Research Background

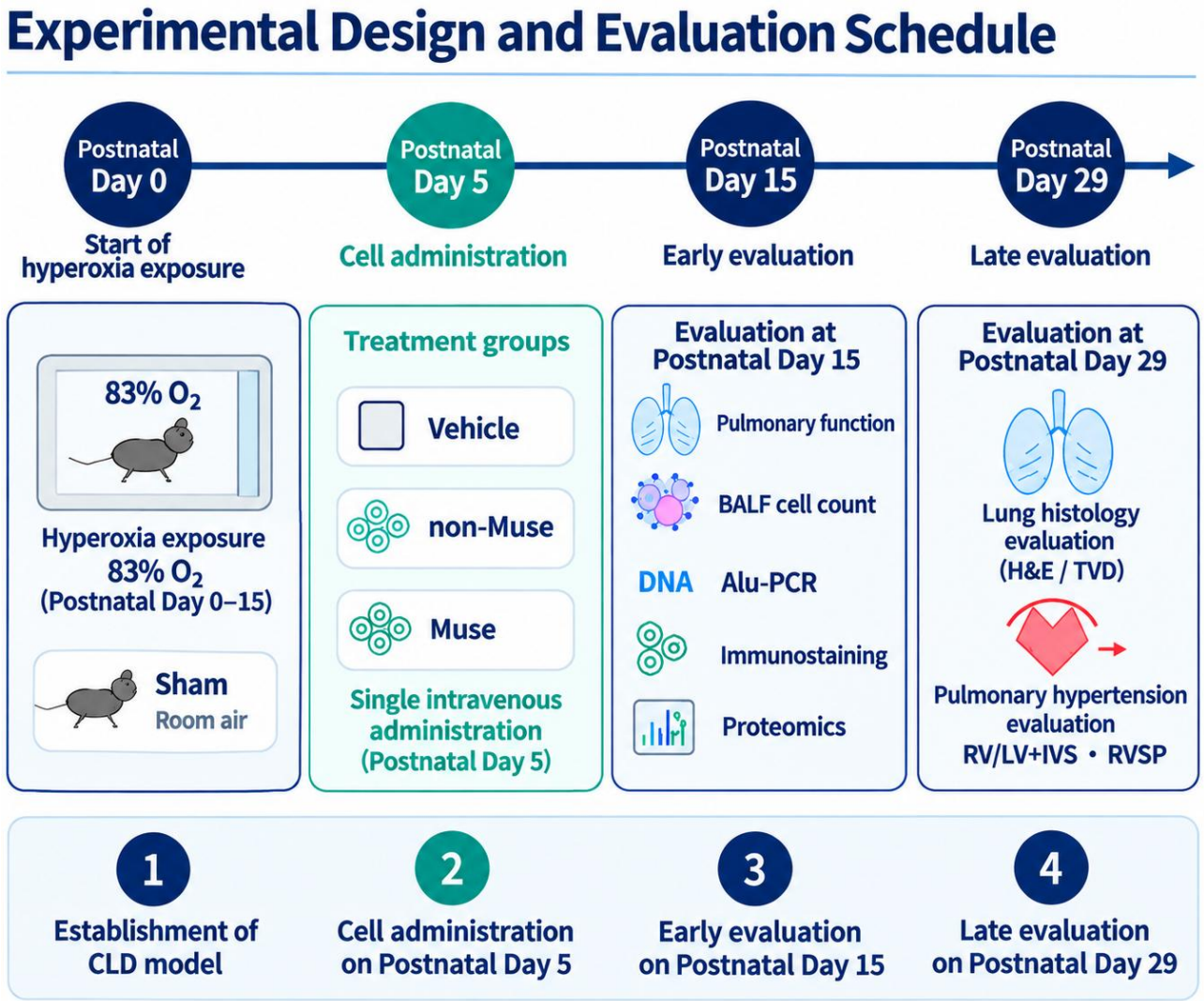
BPD is a lung disease that commonly affects preterm infants, particularly those born at earlier gestational ages and with lower birth weights. Advances in neonatal care have improved survival rates among preterm infants; however, BPD remains a major complication and is associated with impaired alveolar development, chronic inflammation, pulmonary vascular abnormalities, and pulmonary hypertension. In severe cases, prolonged mechanical ventilation or home oxygen therapy may be required. Even after hospital discharge, affected infants may experience respiratory problems, including hospitalization due to respiratory infections and impaired pulmonary function, as well as neurodevelopmental problems.

Current management of BPD includes respiratory support and corticosteroid therapy; however, no definitive treatment has yet been established. In recent years, cell-based therapies using mesenchymal stromal cells (MSCs) have attracted considerable attention. However, improving therapeutic efficacy and optimizing the route of administration remain important challenges for clinical

application.

Multilineage-differentiating stress-enduring (Muse) cells are a pluripotent cell population present within MSC populations. Muse cells have been reported to preferentially home to sites of tissue injury and may contribute to tissue repair. Clinical studies and trials using Muse cells have already been conducted in several disease areas, raising expectations for their potential application to neonatal diseases.

In this study, using a rat model, we investigated whether Muse cells are effective against BPD-like lung injury and compared intravenous and intratracheal administration to determine which route may be more suitable.



Research Results

2-1. Intravenous administration may be advantageous over intratracheal administration in terms of body weight gain and survival

The research group first compared intravenous and intratracheal administration of Muse cells. No substantial differences were observed between the two routes in their effects on respiratory function, lung histology,

or inflammation. However, intratracheal administration was associated with poorer body weight gain and survival. These findings suggest that intravenous administration may represent a less invasive and more practical route for the development of Muse cell-based therapies.

2-2. Muse cells attenuate lung injury, inflammation, and pulmonary hypertension more effectively than non-Muse cells

The research group next focused on intravenous administration and compared the effects of Muse cells with those of non-Muse cells. The BPD-like lung injury model exhibited impaired alveolar development, inflammation in the airways and alveoli, and pulmonary hypertension. Compared with animals receiving vehicle alone or non-Muse cells, those treated with Muse cells showed attenuation of impaired lung tissue development. Muse cell administration also reduced the number of inflammatory cells in bronchoalveolar lavage fluid and decreased inflammatory cytokine levels. In addition, increases in right ventricular pressure and right ventricular hypertrophy, both indicators of pulmonary hypertension, were attenuated. Together, these findings suggest that Muse cells have the potential to comprehensively ameliorate lung tissue injury, inflammation, and pulmonary hypertension associated with BPD-like lung injury.

2-3. Administered Muse cells engraft in lung tissue and express alveolar epithelial cell-associated markers

Analysis of the distribution of administered cells revealed that Muse cells were detected abundantly in lung tissue. Immunofluorescence staining confirmed the engraftment of Muse cells within the lung tissue, with Muse cells detected at higher levels than non-Muse cells. Furthermore, some Muse cells expressed podoplanin, a human type I alveolar epithelial cell marker, and hPE10, a human type II alveolar epithelial cell marker. These findings suggest that Muse cells may acquire characteristics associated with alveolar epithelial cells within injured lung tissue. However, marker expression alone does not establish complete functional differentiation, and further detailed investigation is required.

2-4. Proteomic analysis reveals alterations in cell adhesion- and coagulation/fibrinolysis-related pathways

To investigate the mechanisms underlying the effects of Muse cells, the research group performed comprehensive proteomic analysis of lung tissue. The results showed that BPD-like lung injury was associated with changes in the expression of groups of proteins involved in cell adhesion, energy metabolism, inflammation, and coagulation/fibrinolysis-related pathways. In

particular, among the proteins altered in BPD-like lung injury, those that were also modulated following Muse cell administration included proteins associated with cell adhesion- and coagulation/fibrinolysis-related pathways. In contrast, these pathways were not identified as major enriched clusters among the proteins that responded to non-Muse cell administration. These findings suggest that Muse cells may influence molecular networks related to cell adhesion and vascular and inflammatory processes in the injured lung.

The researchers also considered the possibility that changes in coagulation/fibrinolysis-related proteins could be influenced by residual blood components in the lung tissue. They therefore analyzed protein markers derived from erythrocytes and platelets. The results indicated that the observed changes in coagulation-related proteins were unlikely to be explained solely by differences in the amount of residual blood among samples. However, because the present study did not include functional assays of coagulation or fibrinolysis, further investigation is required to clarify the functional significance of these findings.

Research Summary and Future Perspective

This study provides preclinical evidence that intravenous administration of Muse cells may attenuate lung tissue injury, inflammation, and pulmonary hypertension in a rat model of BPD-like lung injury. Following intravenous administration, Muse cells engrafted in the lung tissue, and some expressed markers associated with alveolar epithelial cells, suggesting that Muse cells may contribute to the repair of injured lung tissue.

However, this study was conducted using a rat model, and it remains unknown whether similar effects can be achieved in human neonates. Further studies are needed to determine the optimal dose and timing of administration and to evaluate safety, long-term effects, and the detailed mechanisms of action.

In addition, the alterations in cell adhesion- and coagulation/fibrinolysis-related pathways identified by proteomic analysis warrant further investigation to clarify their cell type-specific localization and functional significance.

These findings are expected to provide a foundation for the development of novel cell-based therapeutic strategies for severe neonatal lung diseases.

Publication

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Intravenously delivered multilineage-differentiating stress-enduring cells

dampen hyperoxia-induced lung injury in a rat model with features of bronchopulmonary dysplasia

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