Therapeutic Benefits of MSC-NTF (NurOwn®) Exosomes in Acute Lung Injury Models

Revital Aricha, Haggai Kaspi, Natalie Abramov, Chen Dekel, Stacy Lindborg, Chaim Lebovits, Ralph Kern

Brainstorm Cell Therapeutics, Ltd., 1325 Avenue of Americas, New York City, NY, 10019, USA

Background

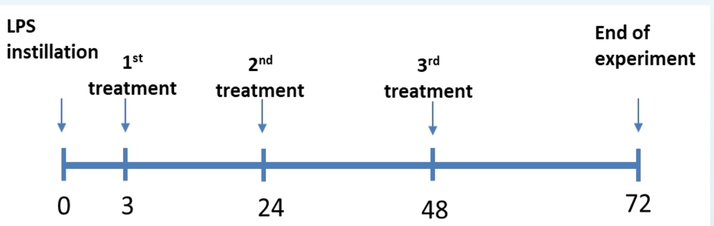
Lung diseases are one of the leading global causes of acute and chronic morbidity and mortality across all ages and need innovative solutions. Mesenchymal stem cells (MSCs) and MSC-derived small extracellular vesicles (sEVs) have been suggested as a potential treatment for inflammation and fibrosis, common pathologies of lung diseases, due to their significant immunomodulatory and regenerative properties. While MSCs and their sEVs share functional properties, sEVs have the added advantages of increased safety and improved tissue penetration.

Design/Methods

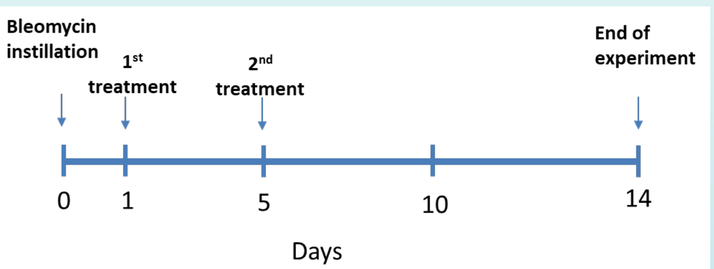
Using two different acute lung injury models, lipopolysaccharide (LPS) and Bleomycin (BLEO), we compared the effect of two types of sEVs: sEVs isolated from naïve MSC (Exo MSC) or sEVs isolated from MSCs which were induced to secrete increased levels of regenerative and immunoregulatory factors (Exo MSC-NTF). Exo MSC or Exo MSC-NTF were administered intratracheally to mice following induction of lung injury by intratracheal administration of LPS or BLEO.

Study Schematic

LPS model



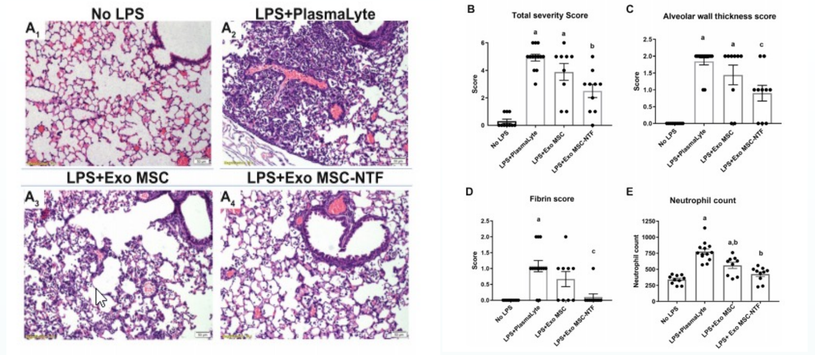
Bleomycin model



Results

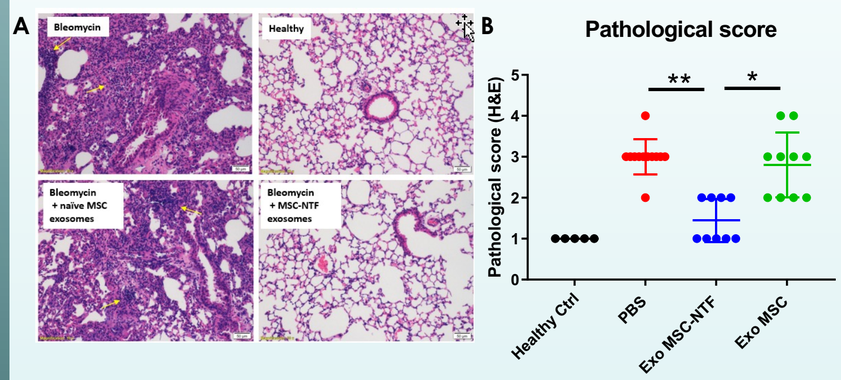
Exo MSC-NTF mitigates pathological lung effects in both models

LPS model

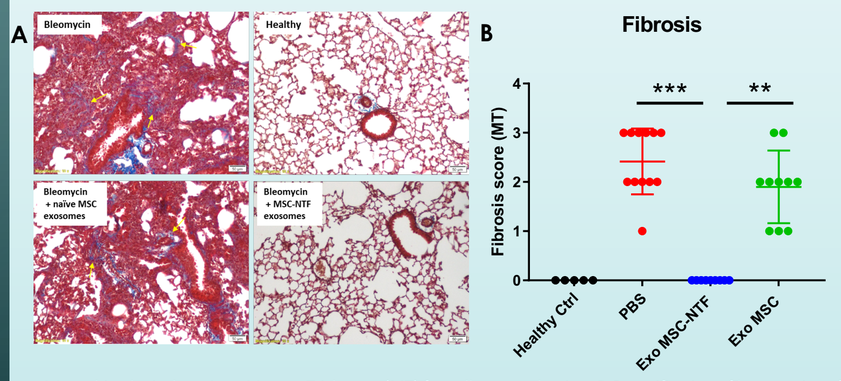


A. Lung histological sections. Quantification of lung damage according to American Thoracic Society documents: B severity score, C alveolar wall thickness, and D fibrin accumulation. E Neutrophil count in lung tissue. Mean ± SEM, n = 9–13. ap < 0.05 vs. no LPS control; bp < 0.05 vs. LPS + PlasmaLyte; cp ≤ 0.01 vs. LPS + PlasmaLyte. Kruskal–Wallis followed by Dunn's post hoc (4b-d) and one-way ANOVA followed by Tukey's post hoc (e)

Bleomycin model

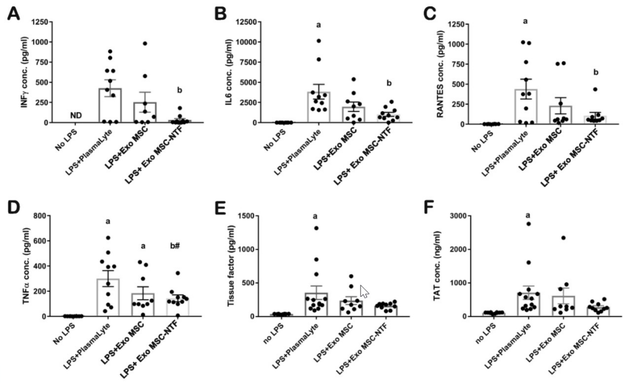


A Lung histological sections (H&E staining for general histopathology) . B Quantification of lung damage according to American Thoracic Society documents. *<0.05, **<0.01 Bars represent SD



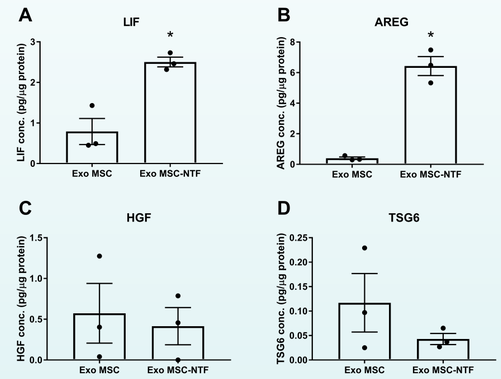
A Lung histological sections-Masson Trichrome (MT) for collagen evaluation. B Quantification of lung sections for the presence of fibrosis. **<0.01, ***<0.001 Bars represent SD

Exo MSC-NTF repress several LPS-induced immune effects in the bronchoalveolar lavage fluid (BALF) of LPS-treated mice



Quantification of the immune response in the BALF of treated mice. Measurements of a IFN-γ, b IL-6, c RANTES, and d TNF-α using ProcartaPlex platform. A measure of coagulation by e tissue factor and f thrombin–antithrombin complex (TAT) using ELISA. Mean ± SEM, n = 9–10 (ProcartaPlex) or 9–13 (ELISA). ap < 0.05 vs. no LPS control, bp < 0.05 vs. LPS + PlasmaLyte, b#p = 0.058 vs. LPS + PlasmaLyte. One-way ANOVA followed by Tukey's post hoc

Differences in protein cargo between Exo MSC-NTF and Exo MSC



ELISA of Exo MSC and Exo MSC-NTF lysates from three independent donors displayed higher abundance of LIF (A) and AREG (B) in Exo MSC-NTF. HGF (C) and (D) TSG-6 were detected in both Exo MSC and Exo MSC-NTF but without significant differences. Mean ± SEM, n = 3, *p < 0.05 paired t test

Conclusions

- Intratracheal (IT) MSC-NTF exosomes are and innovative biological solution for ARDS and acute lung injury.
- MSC-NTF - exosomes improve lung histology and function, reduce cellular infiltration, inflammatory cytokines, fibrin deposition, and decrease coagulopathy biomarkers in addition to reduction of lung fibrosis in Bleomycin model.
- MSC-NTF exosomes produce superior results in the respective acute lung injury models compared to naïve-MSC exosomes

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