SOHO ANNUAL MEETING

Role and Mechanism of Mesenchymal Stem Cells in Regulating the Sirt1-hnRNPA3-P53 Signaling Pathway to Improve Immune Function in Aging

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INTRODUCTION

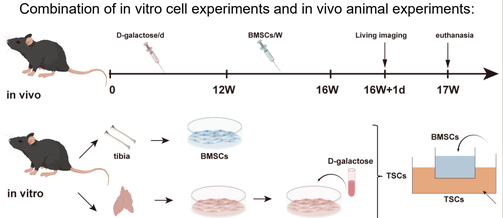
- Mesenchymal stem cells (MSCs) are highly proliferative stem cells with self-renewal capacity and multidirectional differentiation potential, which play a crucial role in the regulation of inflammation and immune functions[1].
- MSCs can migrate and home to aging or injured tissues, improving their structure and function[2].
- In the elderly, a compromised thymic stromal microenvironment hinders lymphocyte development. Thymic stromal cells (TSCs), especially thymic epithelial cells (TECs), are potential targets for thymic rejuvenation[3].
- Mesenchymal stem cell therapy shows promise in improving immune system dysfunction caused by thymic involution.

OBJECTIVE

- This study aims to evaluate the potential of bone marrow mesenchymal stem cells (BMSCs) in enhancing the aging thymic stromal microenvironment, specifically by targeting thymic stromal cells (TSCs).
- Additionally, this study seeks to investigate whether BMSCs provide thymic immune protection through the Sirt1-hnrnpa3-P53 signaling pathway.

METHOD

Combination of in vitro cell experiments and in vivo animal experiments:



in vivo:Subcutaneous injection of D-galactose at 1000mg/kg/day to establish an aging model in C57/BL6 mice

in vitro:D-galactose treatment (48 hours, 32mg/ml) to induce an aging TSCs mode

REFERENCES

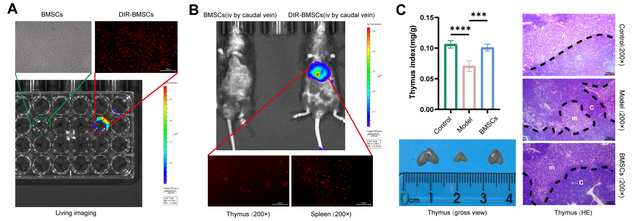
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RESULTS

Figure1: Allogeneic transplanted BMSCs can be homed into the thymus and spleen of immune organs in aging mice



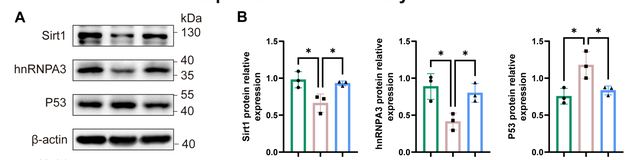
(A)The light microscopy as well as living imaging of BMSCs and DIR-BMSCs. (B)Small animal living imaging as well as frozen sections of the thymus and spleen observed that tail vein-injected BMSCs could homing migrate to the thymus and spleen, the immune organs of aging mice. (C)Tail vein transplantation treatment with BMSCs improves thymic index and thymic structure in aging mice.

Table1: Allogeneic transplanted BMSCs affected CD4/CD8 and TH1/TH2 balance in mouse spleen

Group	CD4(%)	CD8(%)	CC4/CD8	TH1(%)	TH2(%)	TH1/TH2
Control	10.72±0.11	7.12±0.23	1.51±0.06	4.56±0.80	10.79±1.67	0.43±0.06
Model	6.39±0.92[a]	5.10±0.33[a]	1.25±0.12[a]	13.69±2.80[a]	18.95±5.11[a]	0.73±0.06[a]
BMSCs	10.51±0.41[b]	6.98±0.04[b]	1.51±0.05[b]	5.52±0.25[b]	11.89±0.59	0.46±0.02[b]

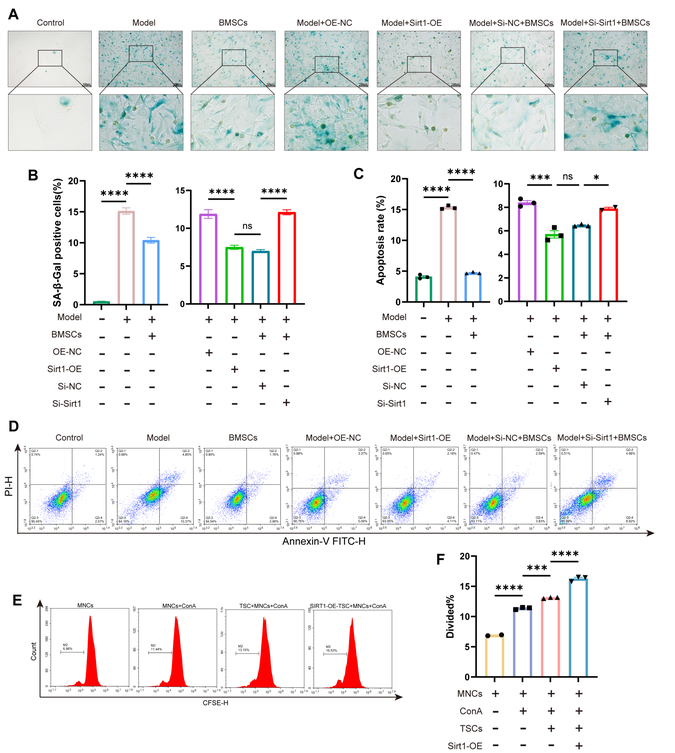
BMSCs transplantation treatment group had an elevated CD4/CD8 ratio and a tilted TH1/TH2 balance toward anti-inflammatory TH2 compared to the aging model group.Data represent the mean ± SD, a: P < 0.05 vs Control, b: P < 0.05 vs Model.

Figure2: Allogeneic transplanted BMSCs affected Sirt1/hnRNPA3/P53 expression in mouse thymus



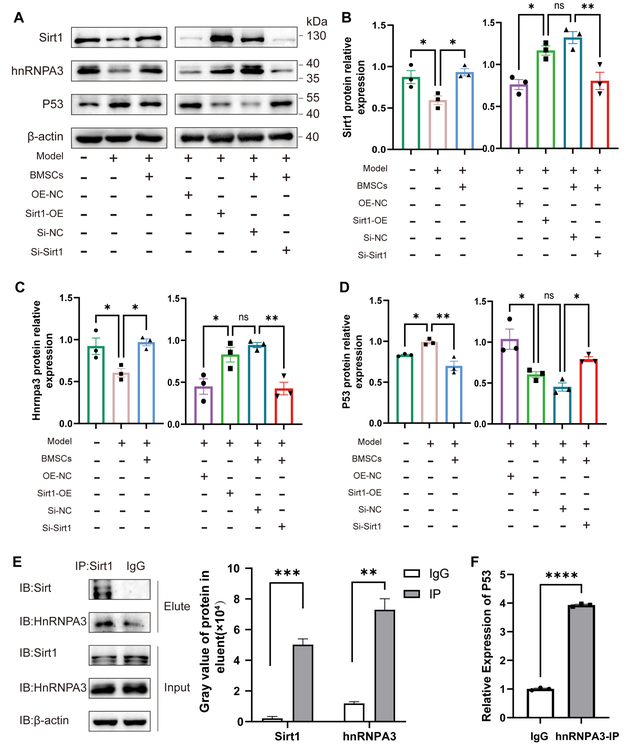
(A)Western Blot bands of Sirt1, hnRNPA3, P53 and β-actin in each group.(B)Sirt1, hnRNPA3, P53 protein relative expression.Data represent the mean ± SD, *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****: P < 0.0001.

Figure3: The Sirt1 signaling pathway played a key role in BMSCs regulated the microenvironment of the aging thymus represented by senescent TSCs



(A)Results of β-galactosidase staining of TSCs (200×). (B)Semi-quantitative analysis of the results of β-galactosidase staining of TSCs. (CD)Detection of apoptosis in TSCs by flow cytometry. (EF)TSCs with overexpression of Sirt1 promote the proliferation of MNCs.Data represent the mean ± SEM, *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****: P < 0.0001.

Figure4: BMSCs in Regulating the Sirt1/hnRNPA3/P53 Pathway to Improve functions of senescent TSCs



(A)Western Blot bands of Sirt1, hnRNPA3, P53 and β-actin in each group.(B-D)Sirt1, hnRNPA3, P53 protein relative expression. (E)Co-IP experiments revealed the interaction between Sirt1 and hnRNPA3. (F)RIP experiments demonstrated the binding of hnRNPA3 to the P53 mRNA. Data represent the mean ± SEM, *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****: P < 0.0001.

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CONCLUSION

The improvement of thymic immune function by BMSCs relies on the activation of the Sirt1/hnRNPA3/P53 signaling pathway.