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# UMBILICAL CORD MESENCHYMAL STROMAL CELLS AMELIORATE MYELOFIBROSIS IN VIVO

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## INTRODUCTION

Myelofibrosis is a rare and chronic bone marrow disorder characterized by the abnormal production of blood cells. In myelofibrosis, the bone marrow is replaced by fibrous tissue, leading to ineffective blood cell production. This condition is part of a group of disorders known as myeloproliferative neoplasms, which also include polycythemia vera and essential thrombocythemia. Currently, allogeneic hematopoietic stem cell transplant is the only way to get cured. For those who are not able to receive transplant, JAK inhibitor such as ruxolitinib is currently the only drug approved by FDA for symptom relief and spleen size decrement, but with little effects on suppression of fibrosis progression.

Umbilical cord mesenchymal stromal cells (UCMSCs) are a type of stroma cell derived from the umbilical cord blood and have been shown promise in various preclinical and clinical studies for a range of therapeutic applications including tissue repair, immune modulation and anti-fibrosis. UCMSCs exert the function by secreting extracellular vesicles (EV). Many studies have shown that EV of UCMSCs could decelerate fibrosis of lung, kidney and liver through anti-inflammation and immune modulation. However, studies of the effects on myelofibrosis remain scarce

## AIM

We aimed to evaluate the effects of UCMSCs on myelofibrosis alone and in combination with ruxolitinib by preclinical models.

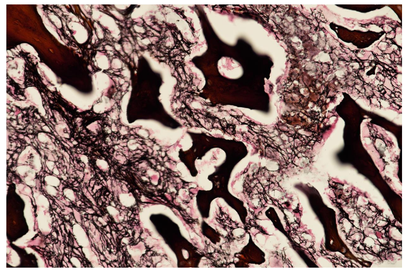
## METHOD

UCMSCs were isolated from human umbilical cord tissues, which were ground and cultured in dishes until the fibroblast-like adherent stroma cells reached 80% to 90% confluence, and were collected for new passages within 10 to 14 days after plating. The number of re-plating for expansion was four to six. Next, we transplanted mice bone marrow cells overexpressed with thrombopoietin (TPO) construct through virus to develop the myelofibrosis model for further experiments. UCMSCs were given intravenously weekly at the amount of 10^6 cells each time, for 4 times and ruxolitinib was given 90mg/kg twice daily orally for those receiving each of the treatment.

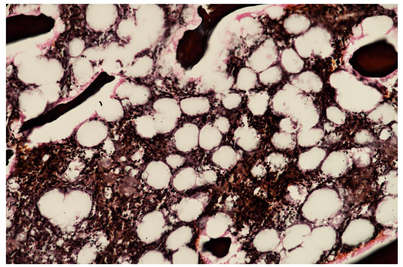
## RESULTS

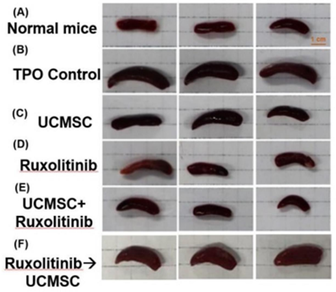
The mice were divided into 6 groups: group A was normal wild type mice, group B was TPO-induced myelofibrosis mice receiving no medication, group C was TPO mice receiving UCMSCs, group D was TPO mice receiving ruxolitinib, group E was TPO mice receiving UCMSCs in combination with ruxolitinib, group F was TPO mice receiving ruxolitinib for 4 weeks, then discontinued and followed by UCMSCs treatment bi-weekly for 4 times. After 3 months, the mice were sacrificed for further evaluation. Compared to group A, TPO mice (group B) developed anemia, myelofibrosis and splenomegaly. Ruxolitinib only group (group D) improved splenomegaly, but had little effects on hemogram and myelofibrosis, while those receiving UCMSCs (group C, E, F) had significant improvement in not only spleen size, but also hemoglobin levels and myelofibrosis degree (Figure). Combination use of both ruxolitinib and UCMSCs (group E) had the best response in ameliorating myelofibrosis compared to other groups.

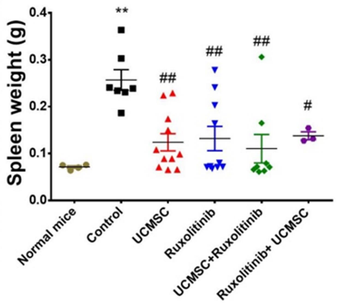
TPO mice with myelofibrosis

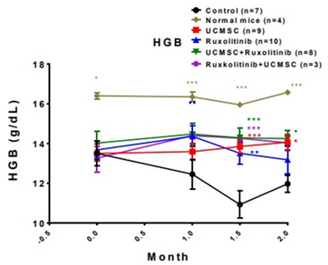


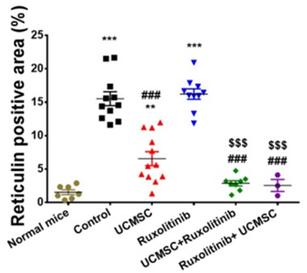
TPO mice receiving UCMSC treatment






## CONCLUSIONS

To our knowledge, this is the first time we showed that UCMSCs are beneficial for myelofibrosis by improving anemia, reducing spleen size and even had the potential to reverse myelofibrosis, while traditional JAK inhibitors could not. Further first in human trial may be launched for further safety and efficacy evaluation.

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