

Specific comments to authors: Some more detailed explanation for the differences in species may be added in Introduction and Discussion.

Response: More explanations for “differences in species” were added to “Introduction and Discussion” as yellow highlighted on pages 6, 7, 20, and 21.

Page 6: Premature ovarian failure (POF) disease has similar characteristics such as hypoestrogenism, elevated gonadotropin levels, and infertility in animal models and in human. Some women also have symptoms such as hot flushes, night sweats, vaginal dryness, chronic anxiety, sadness and depression^[1].

Page 6-7: Moreover, obtaining MSCs from bone marrow requires suitable donors and invasive procedures and number of bone marrow-derived mesenchymal stem cells (BM-MSCs) is very limited, which greatly restrict use of BM-MSCs for clinical application^[21]. The immunomodulating feature of MSCs seems to be different between species^[22]. Human MSCs decrease the secretion of interferon gamma (IFN- γ), interleukin 12 (IL-12) and tumour necrosis factor alpha (TNF alpha), while increase interleukin 10 (IL-10) secretion^[23-25]. Moreover, human MSCs-mediated inhibition of T-cell response could not be reverse by nitric oxide synthase inhibitor compared with mice MSCs^[26]. Integrin β 1 expression is important for mice MSCs migration, while C-X-C chemokine receptor type 4 (CXCR-4) expression is involved for human MSCs migration to sites of tissue injury^[27, 28]. It has been demonstrated that 92% of MSCs proteins expression is similar in human and mice^[29]. MSCs represent only a small proportion of the cells in bone marrow, their proliferation and differentiation capacity correlates inversely with age^[23].

Page 20: Understanding the pathogenesis of POF plays an important role in the development of effective therapeutic options for this disease. Therefore, elucidation of the mechanism for POF development is critical for the clinical treatment of POF disease^[58]. The estrous cycle of female mice is similar to that of humans, although the estrous cycle of mice is shorter than that of humans^[59].

Page 21: Previous studies demonstrated that chemotherapeutic drugs can cause POF in various species such as mouse, rat, rabbit and human^[62-66]. Our results was consistent with

previous reports as we showed an decrease in number of follicles, decreased serum E2 levels, increased serum FSH levels and infertility

Not only MSCs features depend on the tissue source from which they were obtained but also on species. Previous studies indicated that MSCs obtained from various species and sources differ in their biological characteristics such as surface marker expression, proliferative capacity, multi-lineage differentiation potential and immunomodulation feature^[67,68]. In this study, we investigated biological properties of ES-MSCs and BM-MSCs. We have found that ES-MSCs and BM-MSCs both expressed CD44, CD73, CD90 and CD105 but they showed no expression of CD34, CD45 and CD 11b which is consistent with previous study^[34]. We indicated that ES-MSCs showed enhanced proliferation capacity compared to the BM-MSCs. On the fourth and fifth passages, there were significant difference between ES-MSCs and BM-MSCs. Previous studies have similarly reported that ES-MSCs are more proliferative compared to BM-MSCs^[34, 36].

In addition, we demonstrated that multilineage differentiation potential of BM-MSCs was greater than ES-MSCs. This finding was consistent with previous studies^[34, 36]. MSCs from different species and sources produce different cytokines. Our results were consistent with previous studies that cytokines secreted from MSCs could influence on cell proliferation, differentiation, survival and tissue repair^[69,70]. We observed no significant difference between ES-MSCs and BM-MSCs secreted cytokines in culture medium.

We have transplanted human ES-MSCs to mice animal model and showed their capability in restoring ovarian function in POF mice model. In support of transplantation of human derived MSCs to another species, previous studies have demonstrated that the transplantation of MSCs derived from various human tissues including menstrual blood, umbilical cord and amniotic fluid into animal models of POF restore ovarian function^[71].