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In vitro differentiation process of human Wharton's jelly mesenchymal stem cells to male germ cells in the presence of gonadal and non-gonadal conditioned media with retinoic acid

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Human umbilical Wharton's jelly-derived mesenchymal stem cells (HWJMSCs) are the best candidate to get plentiful stem cells and differentiate them to germ cells under appropriate conditions to treat infertility. We sought to determine under which conditions HWJMSCs could form male germ cells *in vitro*. So, HWJMSCs were differentiated to male germ cells under a mixture of bone morphogenetic protein-4 (BMP-4) and testicular and placental culture condition (TCC and PCC) medium followed by retinoic acid for 21 days. In the present study, the HWJMSCs were obtained from Wharton's jelly of umbilical cords of male neonates delivered by cesarean section. At the third passage, mesenchymal stem cell markers and differentiation to osteocytes and adipocytes were investigated. Then, HWJMSCs were induced to differentiate into male germ cells in the presence of BMP-4, all-trans retinoic acid, PCC, and TCC for 21 days. The profile of *c-Kit*, *DDX4*, *Piwil2*, and *Dazl* gene expression was evaluated by qPCR and ICC. Data was analyzed by ANOVA test. After 3 weeks of treatment with different reagents, the morphology of these spindle-like cells changed to shiny clusters and germ cell-specific markers in mRNA were up-regulated in both TCC+retinoic acid (RA) and BMP-4+RA. Induction of HWJMSCs with TCC in the presence of RA resulted in significant up-regulation ($P \leq 0.05$) of all germ cell-specific genes (*c-Kit* 2.6795±0.75, DDX4 4.3188±1.18, *Piwil2* 4.9962±1.55 and *Dazl* 6.1199±0.78) compared to control and PCC+RA. Our results indicated that TCC and RA are involved in human germ cell development. Moreover, BMP signaling also induced differentiation. Our findings provide a novel effective approach for generation of germ cells *in vitro* and studying the interaction of germ cells with their niche. Our work represents an essential step toward gaining knowledge of the molecular properties of HWJMSCs in the field of cell therapy. We demonstrated that under a suitable situation, HWJMSCs have the ability to differentiate into germ cells and this provides an excellent pattern to study infertility cause and cure.

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