Placenta derived mesenchymal stem cells (PDMSCs) modulate HIF-1a, VEGF and JunB genes in ovarian cancer cells.

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Ovarian cancer (OC) has the highest mortality rate of all gynecological cancers. We previously demonstrated that PDMSCs produce soluble factors able to inhibit OC cell cycle and growth through a pathway that still remains to be determined. Hypoxia Inducible Factor-1 alpha (HIF-1a), main player in cellular response to hypoxia, promotes the expression of VEGF, responsible for neo-angiogenesis. HIF-1a over-expression has been described in most human malignancies and it is linked to bad cancer prognosis. Activating Protein-1 (AP-1) molecules are pivotal regulators of OC cell cycle progression and metastatization. Herein, we investigated HIF-1a, VEGF and JunB expression in OC ES-2 and SKOV-3 cells treated by PDMSCs conditioned medium (CM) in order to verify our hypothesis that PDMSCs could act through the modulation of HIF-1a and anti-proliferative AP-1 molecules.

Methods: PDMSCs were isolated from physiological human term placentae (n=12). CM will be produced by incubating PDMSCs for 24-48 hours in DMEM medium. CM will be harvested and filtered to remove cellular debris. ES-2 and SKOV-3 cells were treated by 24/48h CMs for 24h or 48h and mRNA was isolated. Expression of HIF-1a, VEGF and JunB was assessed by Real Time PCR.

Results: HIF-1a mRNA levels were significantly decreased in both ES-2 and SKOV-3 cells treated by 24/48h PDMSCs-CMs for 24/48h. HIF-1a decrease was accompanied by VEGF down-regulation at 48h in ES-2 and at 24h in SKOV-3 cells. Interestingly, CM promoted anti-proliferative JunB mRNA accumulation in ES-2 at 24h/48h, while it induced JunB down-regulation in SKOV-3 at both time points.

Conclusions: We demonstrated, for the first time to our knowledge, that healthy PDMSCs-CM treatment exerts its anti-tumoral activity through HIF-1α pathway down-regulation and anti-proliferative JunB accumulation in malignant ES-2 OC cells. JunB down-regulation in moderately differentiated/less aggressive SKOV-3 PDMSCs-treated cells requires further investigation.

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