Impact of obesity on human endometrial stromal cell decidualization and endometrial control of trophoblast invasion: implication of endometrial extracellular vesicles

Laurent Galio, L Bernet, Yoann Rodriguez, Marie-Noëlle Dieudonne, H Pinatel, V Sérazin, K Fathallah, François Vialard, Esther dos Santos

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L. Galio [1], L. Bernet [2], Y. Rodriguez [2], M.N. Dieudonne [2], H. Pinatel [2], V. Sérazin [3], K. Fathallah [3], F. Vialard [2], E. Dos Santos [2]

[1]Université Paris-Saclay, UVSQ, INRAE, BREED - Jouy-En-Josas (France), [2]Université Paris-Saclay, UVSQ, INRAE, BREED - Saint Quentin En Yvelines (France), [3]Centre Hospitalier de Poissy-Saint Germain - Poissy (France)

Background

Human infertility incidence is increasing in obese women (Ob) causing it to become an emerging global health challenge requiring improved treatment. Different data clearly evidence that obesity causes female reproductive dysfunction by detrimentally altering uterine receptivity. However, the underlying molecular and cellular mechanisms remain to be fully elucidated. Extracellular vesicles (EVs) are important emerging players in reproductive biology and, more specifically, in conceptus-endometrial interactions during peri implantation periods.
The aim of this study was i) to determine whether obesity impacts human decidualization and endometrial control of trophoblast invasion and ii) to investigate about the possible implication of endometrial EVs on such physiological regulations in women.

Material & Methods

In vitro decidualization test on human primary cell culture of endometrial stromal cells (ESCs): prolactin and IGFBP1 expressions.
Invasion test: HTR-8/SVneo trophoblastic cell line's invasive ability measured by zymography assays: gelatinase activities of MMP-2 and MMP-9 and expression of TIMP-1, TIMP-2 and TIMP-3 mRNAs (RT-qPCR).
EVs purification from supernatants of uterine biopsies of Ob women by SEC (qEVs, IZON).
EVs QC: Electronic Microscopy; Nanoparticle Tracking Analysis (NTA).
Mass spectrometry-based quantitative proteomics on EVs preparations.
Functional experiments: endometrial EVs added in the culture medium of ESCs in the decidualization test and in to the medium of HTR-8/SVneo cells in the invasion test.

Results

1) using human primary cell culture, obesity clearly reduces in vitro decidualization of ESCs as reflected by the significant decrease of prolactin and IGFBP1 expressions, 2 biomarkers of decidualized cells. 2) the HTR-8/SVneo trophoblastic cell line's invasive ability was elevated in the presence of conditioned media from ESCs isolated from Ob. This pro-invasive action was associated with a specifically decrease in TIMP-2 mRNA expression. 3) no significant difference between EVs from

Ob and non obese (NOb) women was observed by using NTA. 4) using mass spectrometry-based quantitative proteomics, EVs isolated from uterine supernatants of Ob, compared to NOb women, present a molecular signature since they are laden and/or devoid with different proteins more specifically implicated in cell remodeling and angiogenesis. 5) functional experiments using endometrial EVs from NOb, added in the culture medium of ESCs from Ob, showed that the supplementation with EVs from NOb can repair, at least in part, the injured in vitro decidualization of Ob. 6) The addition of EVs from Ob significantly increased invasive abilities of HTR-8/SVneo cells compared to EVs from NOb women.

Conclusion

These results suggest that EVs from endometrium could participate in the control of physiological processes, e.g. decidualization and trophoblast invasion. This study provides novel insights into endometrial EVs pivotal role with poor uterine receptivity described in Ob women.