Prion: a novel regulator of spiral artery remodelling at the maternal-fetal interface

Index No.: 22/19/Life Sc./26

Abstract: Uterine spiral artery remodelling (uSAR) is a hallmark of haemochorial placentation, as compromised uSAR leads to adverse pregnancy outcome like IUGR and pre-eclampsia. In our study, we showed that cellular prion (PRNP) is expressed in the rat metrial gland, the entry point of spiral arteries with highest expression on E16.5, the day at which trophoblast invasion peaks. Co-localization studies demonstrates, VSMCs which are adherent to the linings of the spiral arteries, express both PRNP and a smooth muscle marker caldesmon, whereas, the actively migrating VSMCs exclusively express PRNP. RNA interference of *Prnp* transcript functionally restricted migration and invasion in cultured rat VSMCs. PRNP interacts with two migration promoting factors, focal adhesion kinase (FAK) and platelet-derived growth factor receptor-β (PDGFR-β) forming a ter-molecular complex in both metrial gland and A7r5 cells. Ectopic over-expression of the transcription factor OSR1 increased and knockdown of OSR1 decreased expression of PRNP in VSMCs, thus revealing its regulation on Prnp gene expression. Culturing rat VSMCs with rat primary trophoblast cells decreased levels of PRNP as well as OSR1. This observation led to the hypothesis that trophoblast cell-derived factors regulate PRNP expression and/or function via Osr1. Interestingly, PRNP knockdown led to apoptotic death in VSMCs and activated extrinsic apoptotic pathway. PRNP interacts with TRAIL-receptor DR4 and protects VSMCs from TRAIL-mediated apoptosis. Sequencing of total RNA from control and Prnp knock down cells have identified different biochemical pathways that might be regulated by Prnp. Using bioinformatics tool, we have shortlisted 51 differentially expressed genes which were further validated using qRT-PCR technique. Downregulation of PRNP led to increased proliferation rate of VSMCs, as determined by BrdU incorporation assay and confirmed by Ki67 staining assay. Taken together, our research work indicates towards migration-promoting role of cellular prion protein in a sub-population of VSMCs, allowing them to avert trophoblast-induced apoptosis, and untimely proliferation.

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