Impaired decidualisation in obese mice is associated with epigenetically mediated changes in leptin signalling

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Obesity is a major burden for our health systems, and infertility is one of the associated comorbidities. Indeed, obese mothers present decreased pregnancy rate, largely associated with impaired decidualisation. Equally important is the evidence of nutritional programming during pregnancy and the increased predisposition of offspring from obese mothers to disease and obesity. Despite its notorious relevance, little is known about the molecular mechanisms compromising decidualisation in obese mothers. We presently hypothesise that maternal obesity in mice affects local endometrial leptin signalling, which is associated with epigenetic changes and consequently impaired decidualisation. After feeding mice with chow diet (CD) or high fat diet (HFD) for 16 weeks, we confirmed by immunofluorescence the decreased in Ki67 staining in stromal cells of uteri from 3.5 days post coitum (dpc) HFD mice. Subsequently, we found both mRNA and protein levels of leptin signalling inhibitors: Suppressor of cytokine signalling 3 (SOCS3) and Protein Tyrosine Phosphatase Non-Receptor Type 2 (PTPN2) upregulated in whole uterus ($p<0.05$), as well as in mouse endometrial stromal cells (MESC) from HFD mice ($p<0.05$). Furthermore, the mRNA analysis of the decidualisation markers Decidual/trophoblast PRL-related protein (Dtprp), Bone Morphogenetic Protein 2 (Bmp2), Heart And Neural Crest Derivatives Expressed 2 (Hand2) and Homeobox A10 (Hoxa10) showed their downregulation in MESC from HFD mice ($p<0.05$). Finally, bisulphate sequencing analysis of MESC revealed no changes globally, but identified 536 differently methylated regions (DMRs) with at least 10% absolute difference in methylation which tended to be hypomethylated in HFD ($p<0.05$). Importantly, one of the hypomethylated DMRs overlapped Socs3 promotor gene ($p<0.05$). Generally, decreased proliferation in uteri from HFD treated mice was drastic changes in leptin signalling components, particularly the upregulation of the inhibitors SOCS3 and PTPN2. Finally, increased expression of SOCS3 seems to be epigenetically regulated and associated with hypomethylation of its gene promoter.

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