Aged endometrium displays perturbations of inflammation-related molecular pathways compared with fertile endometrium in the bovine species

Olivier Sandra, Maud Pez, Audrey Lesage-Padilla, Pierrette Reinaud, Luc Jouneau, Sophie Mockly, Anais Vitorino Carvalho, Christophe Richard, Valerie Gelin, Corinne Giraud-Delville, et al.

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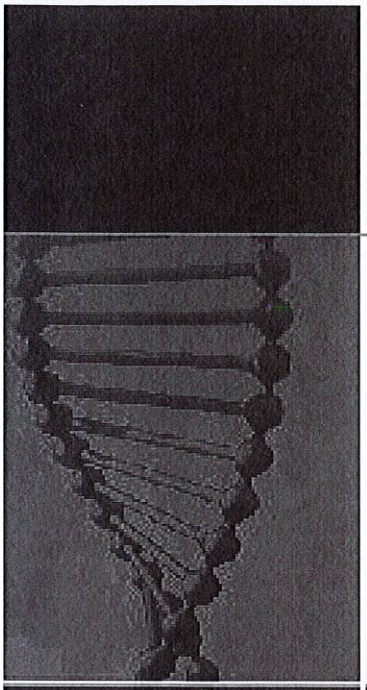

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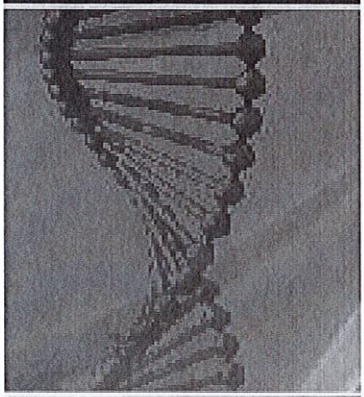

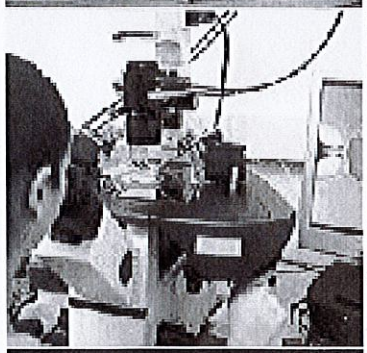

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ABSTRACT BOOK

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Endometrial biopsy, or 'scratch', is a well-tolerated procedure offered as part of routine clinical investigation and treatment for implantation failure and miscarriage. Further to reported benefits of the procedure itself, probably due to the induction of local inflammatory and wound-healing responses driving tissue stem cell recruitment and regeneration, the collected endometrial tissue may be used for investigations such as natural killer (uNK) cell testing and analysis of endometrial receptivity.

The rapid turnaround of next generation sequencing (NGS) projects, combined with ever-reducing per-sample costs, makes NGS screening an attractive prospect for in-cycle analyses. However, the contribution of the different cellular compartments of the endometrium to the transcriptome of the whole tissue is fundamentally unknown, complicating the interpretation of whole tissue sequencing results. Furthermore, identifying endometrial transcriptomic signatures predictive of success in future pregnancies is of interest to IVF practitioners and recurrent miscarriage clinics, as well as the patients themselves.

We isolated cells from the stromal, epithelial and immune compartments and subjected them to RNA sequencing. These signatures were then used to deconvolve the expression profile of whole tissue bioinformatically, identifying proportional contributions of each lineage to whole tissue expression profiles. Single cell RNA sequencing (Drop-Seq) reveals that endometrial stromal cells decidualized for either 2 or 8 days *in vitro* are transcriptionally distinct both from each other and from undecidualized cells, and appear to contain sub-populations with divergent expression, particularly after 8 days decidualization. Application of Drop-Seq to freshly isolated mid-luteal endometrial cells confirms the presence of distinct decidual sub-populations within the stromal compartment.

Identification of markers which can define the composition of individual whole tissue samples, including the contribution of stem cells and activated immune cells, will allow better prediction of endometria receptivity, not to mention understanding dysregulation of the tissue in patients with recurrent implantation failure or pregnancy losses.

C3.4 Aged endometrium displays perturbations of inflammation-related molecular pathways compared with fertile endometrium in the bovine species

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Advanced maternal age has been associated with decline in reproductive performances and essentially investigated at the ovary level. Nevertheless, pregnancy issue and post-natal health are determined by the active contribution of the endometrium when implantation initiates. The objective of our study was to evaluate the consequences of maternal ageing on the endometrium using bovine females generated 8.5 years apart from the same somatic cell line. Old heifers (OH group; n=8; mean age: 13.1±0.2 y) and younger females of proven fertility (primiparous cows; PC group; n=9; mean age: 4.6±0.3 y) were oestrus synchronized and endometrial biopsies were taken at Day 15 post-oestrus. Transcriptional profiles were determined (n=4 females/group) using a bovine custom oligoarray (Agilent reference: 075257) representing 23,926 unique genes. No significant differentially expressed gene was identified in the [OH group vs. PC group] comparison (adjusted p-value<0.05). Nevertheless Gene Set Enrichment Analysis (GSEA) unveils significant perturbations of various GO terms and molecular pathways in OH endometrium including "inflammation", "cytoskeleton remodelling", "myogenesis", "IFN alpha response", and "TNF alpha signaling via NFKB". To evaluate how OH and PC endometrium responds to embryonic factors, primary cultures of fibroblasts (F) and glandular epithelial (GE) cells were derived from endometrial biopsies (n=3 animals/group) and incubated with recombinant interferon-tau (roIFNT; 100 ng/mL). In primary GE cells treated with roIFNT for 1h, fold change of *MX1*and *RSAD2* transcripts was significantly lower in OH group compared to PC group (0.32 vs. 1.71 and 13.65 vs. 47.02 respectively, p-value<0.01). Our findings illustrate age-associated modifications of endometrial physiology that may modify interactions with the implanting embryo. Potential adverse consequences on establishment and progression of pregnancy as well as progeny health will deserve further studies.

C3.5 An association between foetal size and sex, and placental and endometrial angiogenesis in the pig

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Introduction: Appropriate prenatal growth and development is essential for post-natal survival and offspring growth. Inadequate foetal growth cannot be remedied post-natally; leading to severe consequences for neonatal and adult development. It is hypothesised that growth restriction occurs due to inadequate placental vascularisation.

Methods: Placental and endometrial samples associated with the lightest and closest to mean litter weight (normal-sized), male and female Large White X Landrace foetuses were obtained at gestational day (GD) 18, 30, 45, 60 and 90 (n=5 or 6 litters/GD). The mRNA expression of angiogenesis related genes (uteroferrin (ACP5), platelet endothelial cell adhesion molecule (CD31),