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HUMAN ENDOMETRIAL RECEPTIVITY AND EMBRYO-ENDOMETRIUM INTERACTIONS

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ABSTRACT

Infertility is an increasing medical and social problem affecting more than 10% of couples worldwide. Many underlying causes of human infertility have been overcome by assisted reproductive techniques; nevertheless, the implantation process remains one of the rate-limiting step as regards the success of the treatment. A prerequisite for successful implantation is the adequate preparation of a receptive endometrium and the establishment and maintenance of a viable embryo. The success of implantation further relies upon a two-way dialogue between the embryo and the endometrium. The molecular bases of these preimplantation and implantation processes in humans are not well known.

The general aim of the current thesis was to add more understanding into the complex mechanism of human embryo implantation; to identify different factors that play role in endometrial and embryo preparation for successful implantation.

In our first approach of identifying **factors important for endometrial maturation to a receptive phase**, we applied single gene analysis and genome expression analysis to fertile women and women with unexplained infertility. In the endometria of fertile women we identify previously known and new genes and pathways expressed in receptive endometrium, and that several of these genes and pathways were dysregulated in the endometria of women with no explainable reason for their fertility complications. These pathways included LIF pathway and JAK-STAT signalling cascade, coagulation cascade, inflammatory responses, lipid metabolism, and others. We also identified genetic variation in genes involved in blood coagulation to influence gene and protein expression levels in the endometrial cells, and their association with unexplained infertility was demonstrated. Further, we found pinopodes, the endometrial morphological markers, to be abundant in fertile endometria, but scarce in infertile endometria at the time of embryo implantation.

Our second study approach was to analyse **factors important for implantation-competent blastocyst development**. For that we analysed human embryos cultured *in vitro*. We found a major wave of transcriptional down-regulation in preimplantation embryos, where one possible down-regulation mechanism could operate via microRNA molecules.

Finally, we aimed to identify **interactions between receptive endometrium and blastocyst-stage embryo**. For that we applied a novel network profiling algorithm HyperModules, which combines topological module identification and functional enrichment analysis. The main curated embryo-endometrium interaction network highlighted the importance of cell adhesion molecules in the implantation process. Also cytokine-cytokine receptor interactions were identified, where osteopontin, LIF and LEP pathways were intertwining. We also identified several novel players in human embryo-endometrium interactions at the time of implantation.

The current thesis gives new insights into the processes involved in successful implantation in humans. Increasing our knowledge in the processes involved in preimplantation and implantation will facilitate the development of strategies to manipulate endometrial function, embryo development, and embryo-endometrium dialogue in order to promote successful implantation or to inhibit infertility.