CHAPTER 23

Interleukin-1 and Implantation

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Introduction

Infertility and pregnancy wastage affect one of every nine couples in Western Europe and in the United States. The molecular events of embryonic attachment to the endometrial epithelium and subsequent invasion and nidation into the stroma have long been of interest, scientifically to reproductive biologists and clinically to couples with infertility or habitual abortion and to the physicians caring for them. In order to achieve a successful pregnancy in the human, two major conditions have to be fulfilled: during the 4-5 days of transport through the fallopian tube, the embryo must undergo a series of complex maturation processes and, in the same time, a receptive endometrium must have developed. Human endometrium undergoes characteristic cyclic changes of proliferation and secretion and, without embryonic implantation, the endometrium is shed and the menstrual bleeding occurs. Uterine endometrium therefore is the anatomic prerequisite for the continuation of our species and its main purpose during the reproductive age is to communicate with, receive, nourish and protect the implanting blastocyst.1

Understanding the factors involved in preimplantation embryo development and embryo-maternal interaction which result in the complex maturation of the embryo and eutopic implantation is crucial for reproductive medicine. Attempts to overcome the low success rates of human in vitro fertilization therapy by increasing the number of embryos per transfer often result in multiple-gestation pregnancies. These are not only associated with increased evidence of maternal and neonatal complications, but are also cause for concern on the part of medical economists. The total costs for delivery and neonatal care for triplet-pregnancies were calculated with US$ 109,765 and assisted reproduction techniques (ART) were responsible for 77% of higher order pregnancies.2 On the other hand, even by increasing the number of embryos per transfer, the pregnancy rate will never be 100%.

Cytokines and Implantation

The preimplantation embryo produces several factors during its development to signal its presence to the maternal organism. The appropriate interaction between the preimplantation embryo and maternal endometrium is at least partly controlled by paracrine cytokines and this subject is extensively covered by several reviews.1,5-6 Cytokine- and growth factors and their corresponding receptors have, on the mRNA-level, been detected in blastomeres and in preimplantation embryos from different species as well as in the human endometrium throughout the menstrual cycle. Although it is known that both the endometrium and the preimplantation embryo express several of these cytokine/growth factor-receptor pairs during the time of implantation and although there is general agreement that both, endometrial and embryonic factors are involved in successful implantation, there is only limited knowledge about the actual role of these factors. A better understanding of these factors during early embryonic

The interleukin-1-system (Fig. 1) is composed of two agonists, Interleukin-1α (IL-1α) and interleukin-1β (IL-1β), one antagonist, the Interleukin-1 receptor antagonist (IL-1ra) and two membrane-bound receptors, Interleukin-1 receptor type I (IL-1R tI) and II (IL-1R tII). All components of the IL-1 family in humans are located on chromosome 2 and the protein-, DNA- and RNA-structures are all well characterized for many species. Both agonists are initially synthesized as precursor proteins of 31kDa. The mature proteins have a molecular weight of 17kDa and although the amino acid sequences have a similarity of only ~22%, they induce the same biological responses. There is also a high similarity between the cDNA-sequences of IL-1α and -β in mice and humans. Interleukin-1 receptors type I and II both possess a transmembrane domain and their extracellular portions are homologous with similar binding affinities for the agonists and antagonist; there is also a soluble form of the IL-1R tII. The IL-1 receptor type I is found in low numbers on almost all cell surfaces whereas IL-1R tII is found primarily on white blood cells. Only the binding of either IL-1α or -β to the IL-1 receptor type I results in signal transduction, with receptor type II and the soluble IL-1 receptor acting as competitors of the receptor type I. The IL-1 receptor antagonist binds with a high affinity to both receptors and prevents signal transduction by IL-1α and -β.