Implantation

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1. **TRANSPORT** The blastocyst arrives in the uterus 132 to 144 hours after fertilization (Findlay 1984).

2. **ORIENTATION** The inner cell mass is oriented towards the endometrial epithelial lining.

3. **HATCHING** The zona pellucida dissolves possibly because of the secretion of proteases by trophectodermal cells.

4. **APPOSITION** The blastocyst is now in close contact with the endometrial lining but no connections have been established. The embryo can still be dislodged by washing.

5. **ADHESION** Connections of an unknown nature are established between the embryo and the endometrial epithelium. The embryo cannot be dislodged anymore.

Figure 1a
6. **INVASION** Thin folds of trophectodermal cells intrude inbetween the endometrial epithelial cells.

7. **DIGESTION** At the tips of the invadopodia, integrins (fig.) anchor the trophoblast to the basement membrane. This binding triggers the secretion of proteases which digest the basement membrane.

8. **SYNCYTIALISATION** Some trophectodermal cells fuse to form syncytia. These syncytia proliferate and invade the endometrial extracellular matrix.

9. **VILLOUS FORMATION** The former trophectodermal cells, now called cytotrophoblastic cells migrate inbetween the syncytia followed by the fetal stoma. This will lead to the formation of the placental villi.

*Figure 1b*
PLACENTAL CELLS

Syncytiotrophoblast (STB) ← Cytotrophoblast (CTB)
- Villous STB
- Extravillous STB
- Villous CTB
- Extavillous CTB

- Intravascular
- Chorionic plate
- Fetal membranes
- Septum
- Cell columns (Anch. villi)
- Cell columns (Cell islands)

Figure 2
Figure 3
Figure 4
| MMP-1 | Intersti.Collase | 54007 | 469 | 218 | Col I, II, III, VII, X | 11q22-q23 |
| MMP-2 | Intersti.Collase | 73882 | 660 | 403 | Col IV, V, VII, X, Gelatin | 16q13 |
| MMP-3 | ST-1 | 53977 | 477 | 218 | Col III, IV, IX, X, Gelatin, Laminin | 11q23 |
| MMP-7 | PUMP-I | 29677 | 267 | 214 | Casein, Fibronectin, Gelatin | 11q21-q22 |
| MMP-8 | Neutrophil Collase | 53412 | 467 | 217 | Col I, III | 11q21-q22 |
| MMP-9 | Gelatinase B | 78427 | 707 | 401 | Col IV, V, Gelatin | 20q11.2-q13.1 |
| MMP-10 | ST-2 | 54151 | 476 | 217 | Col II, IV, V, Fibronectin, Gelatin | 11q22.3-q23 |
| MMP-11 | ST-3 | 54595 | 488 | 215 | Col IV | 22q11.2 |
| MMP-13 | Collagenase-3 | 53819 | 471 | 222 | Col I | 11q22.3 |
| MMP-14 | MT1-MMP | 65883 | 582 | 243 | MMP-2 | 14q11-q12 |
| MMP-15 | MT2-MMP | 75807 | 669 | 259 | MMP-2 |
| MMP-16 | MT3-MMP | 69158 | 604 | 246 | MMP-2 |

Figure 5
THE PROMOTER REGION OF THE HUMAN MMP-9 GENE

CIS - Regulatory Elements

NFkB   binds p50-p65 complexes (products of REL oncogene family).
SP-1   binds the transcription factor SP-1.
ets    binds ETS-1 or ETS-2 proteins (products of c-ets oncogene).
TRE    TPA responsive element, binds Jun and Fos complexes the products of c-jun and c-fos oncogenes.
TIE    TGF beta inhibitory elements binds TGF beta.
NIP    binds NIP protein.
RCE    Retinoblastoma control element binds p105^{RB1} the product of RB1 oncogene.
TATA   binds an octameric complex of transcription factors.

Figure 6
1. Membrane receptors are coupled to the G protein complex (ras oncogene products).
2. Upon binding of the ligand to the receptor, the G protein complex is activated.
3. GTP binds to protein Gγ.
5. The Gγ protein activates phospholipase C (PLC).
6. Active PLC cleaves its substrate into inositol tri phosphate (IP3) and diacyl glycerol (DAG).
7. DAG activates protein kinase C (PKC). This enzyme can be directly activated by TPA.
8. Active PKC phosphorylates Jun in its trans-activation domain (N terminus).
9. Phosphorylated jun binds Fos, this AP-1 complex binds a specific DNA sequence known as TRE.
10. Active PKC phosphorylates also an inhibitory protein (IP) which cannot inhibit anymore the binding of Jun to the DNA.
11. Jun can also bind Jun B (another oncogene product from the same gene family) and this complex is unable to bind to the DNA.

Figure 7