

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

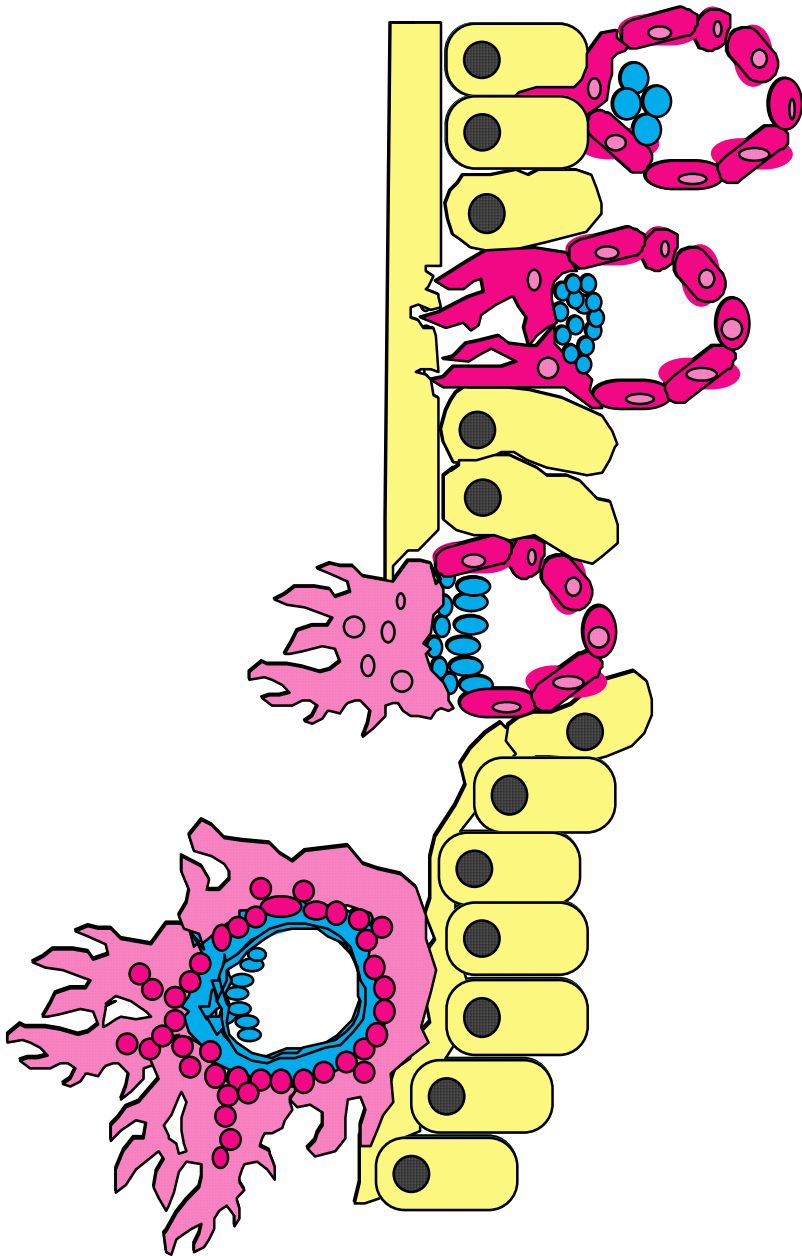
2. ORIENTATION The inner cell mass is oriented towards the endometrial epithelial lining.

3. HATCHING The zona pellucida dissolves possibly because of the secretion of proteases by trophoblast 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 trophoctodermal 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 trophoctodermal cells fuse to form syncytia. These syncytia proliferate and invade the endometrial extracellular matrix.

9. VILLOUS FORMATION The former trophoctodermal 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

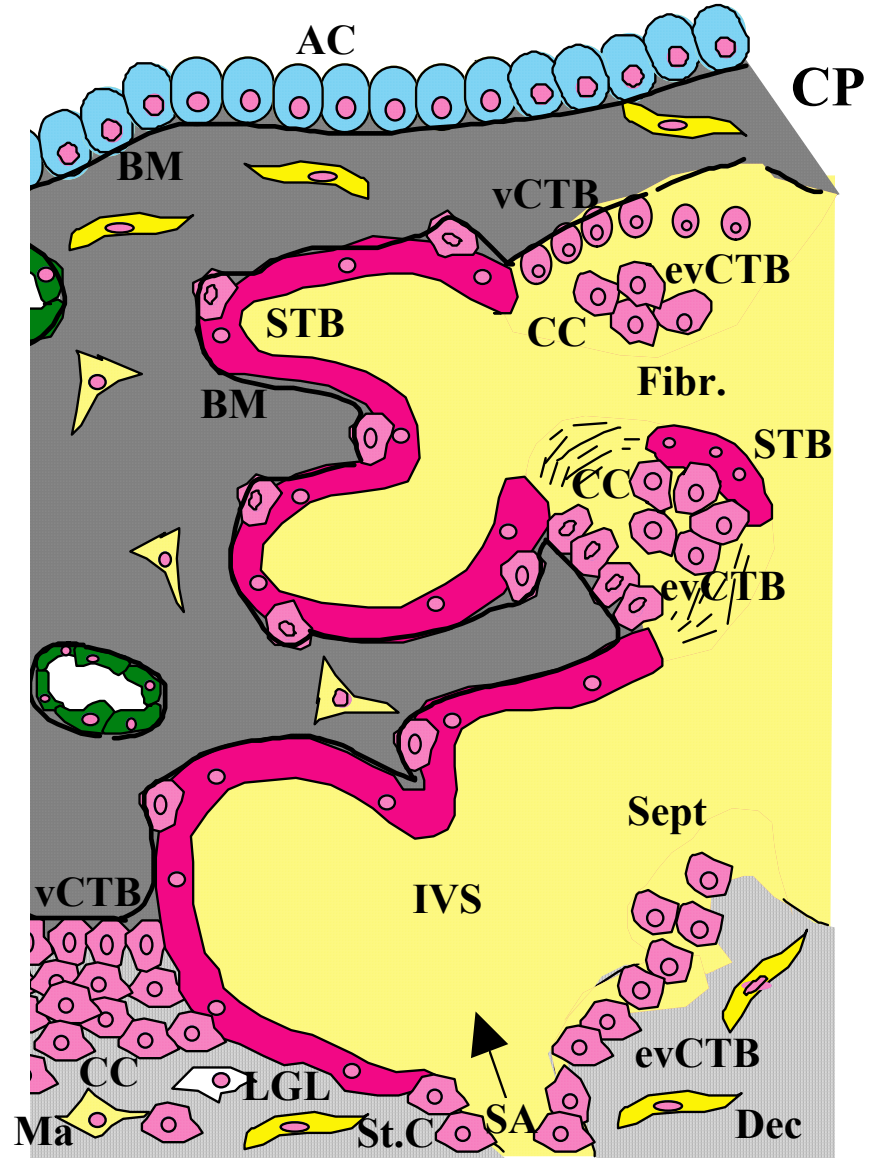
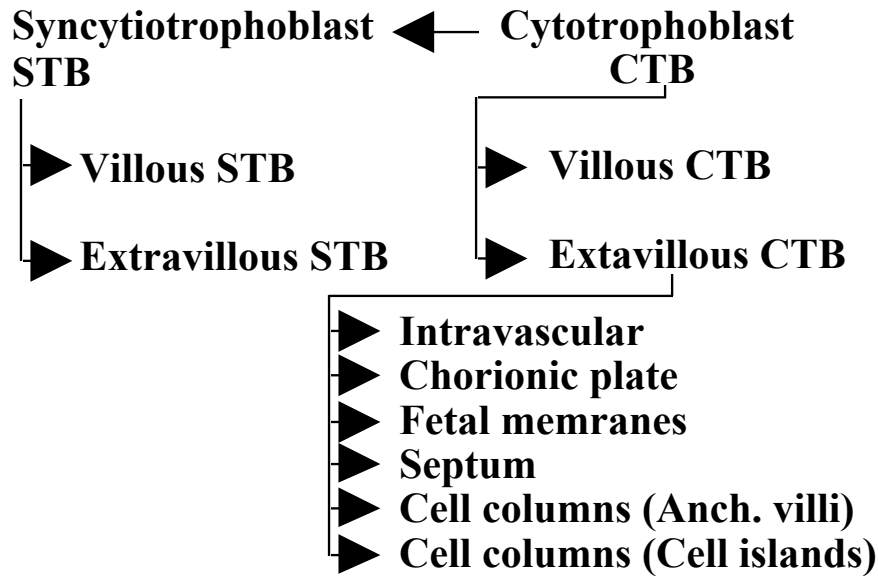


Figure 2

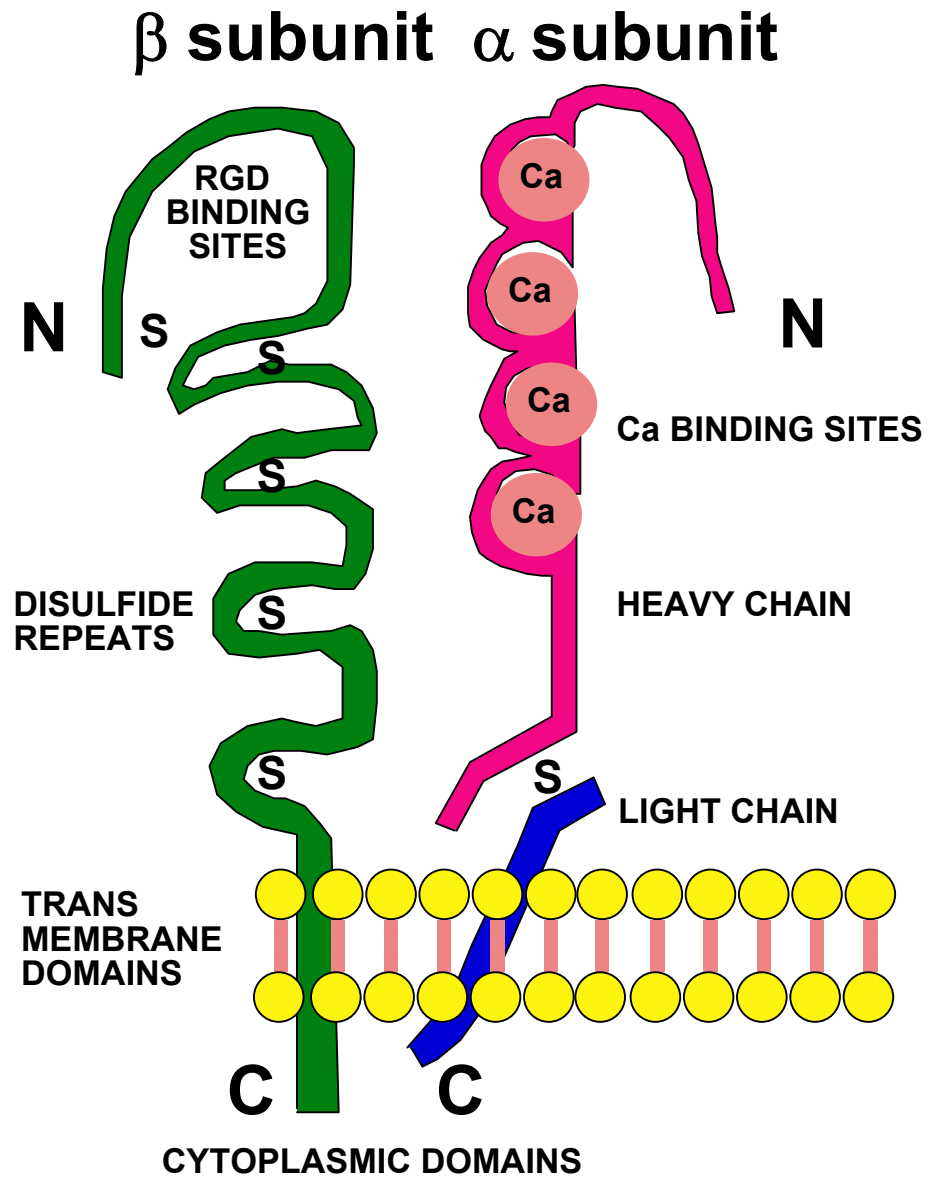


Figure 3

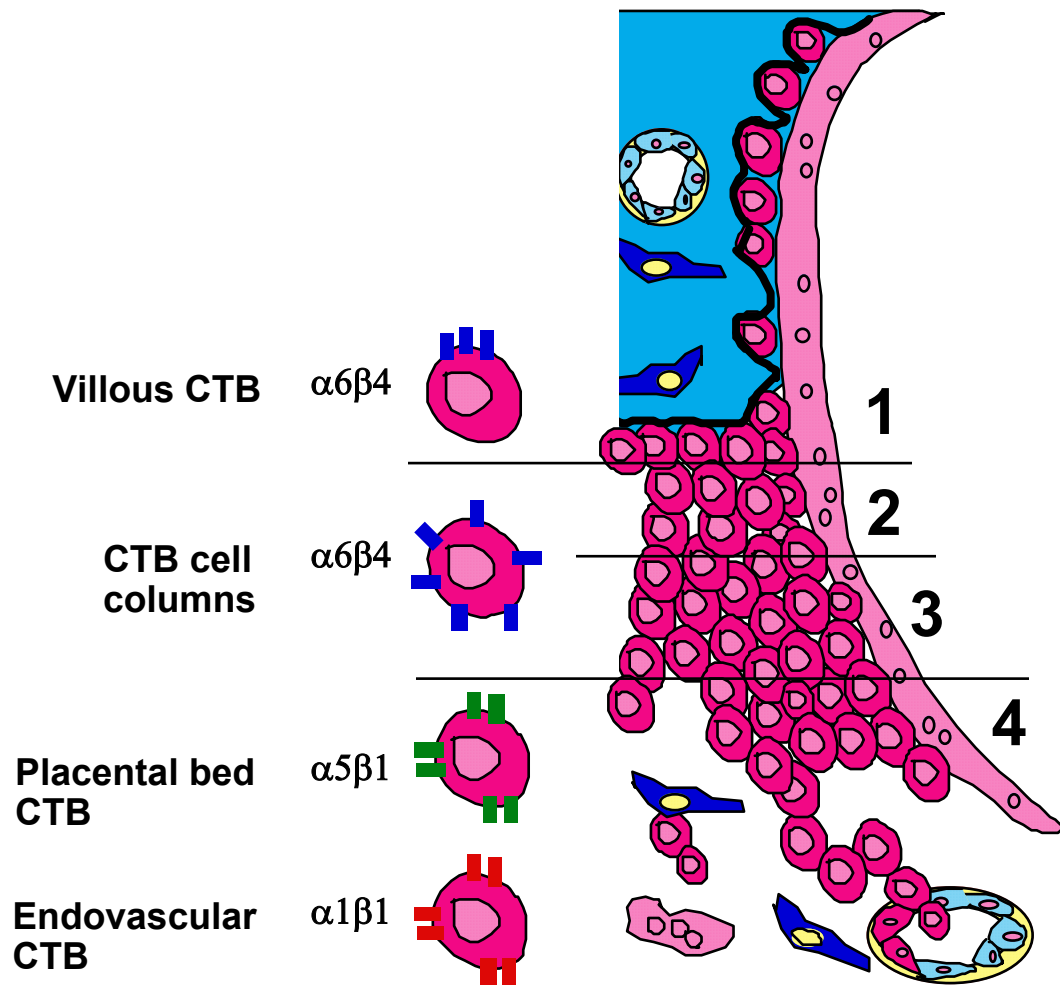
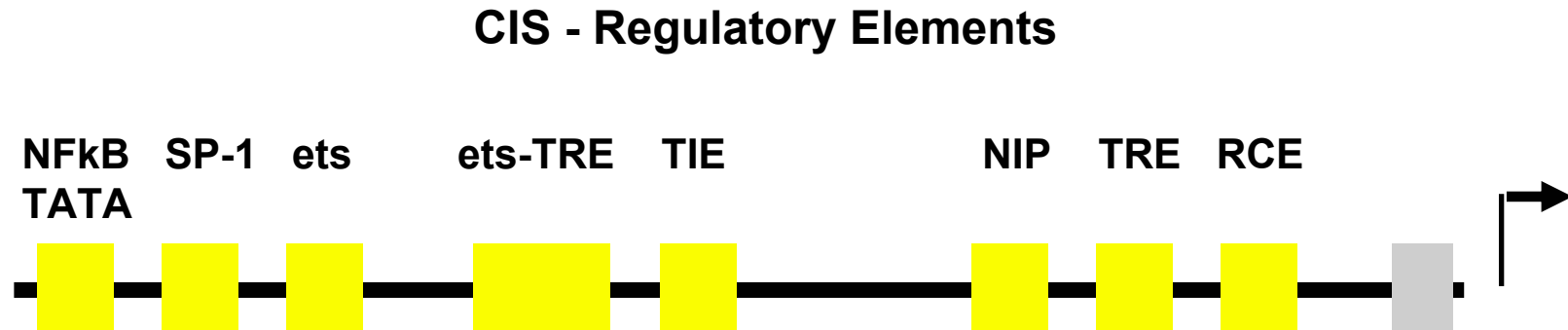


Figure 4

	Other names	M.W.	# a.a.	Zinc at pos.	Substrates	Location of gene
MMP-1	Intersti.Collase	54007	469	218	Col I, II, III,VII, X	11q22-q23
	Fibrobl. Collase				MMP-5, Entactin	
MMP-2	Intersti.Collase	73882	660	403	Col IV, V, VII, X, Gelatin	16q13
	72kD gelatinase				Fibronectin, Elastin	
MMP-3	ST-1	53977	477	218	Col III, IV,IX, X, Gelatin, Laminin	11q23
	Transin-1				Fibronectin, Elastin, Casein	
MMP-7	PUMP-I	29677	267	214	Casein,Fibronectin, Gelatin	11q21-q22
	Matrilysin					
MMP-8	Neutophil Collase	53412	467	217	Col I, III	11q21-q22
	PMNL collase					
MMP-9	Gelatinase B	78427	707	401	Col IV, V, Gelatin	20q11.2-q13.1
	92 kD Gelatinase					
MMP-10	ST-2	54151	476	217	Col II, IV, V, Fibronectin, Gelatin	11q22.3-q23
	Transin-2					
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	14 q11-q12
	MMP-X1					
MMP-15	MT2-MMP	75807	669	259	MMP-2	
MMP-16	MT3-MMP	69158	604	246	MMP-2	
	MMP-X2					

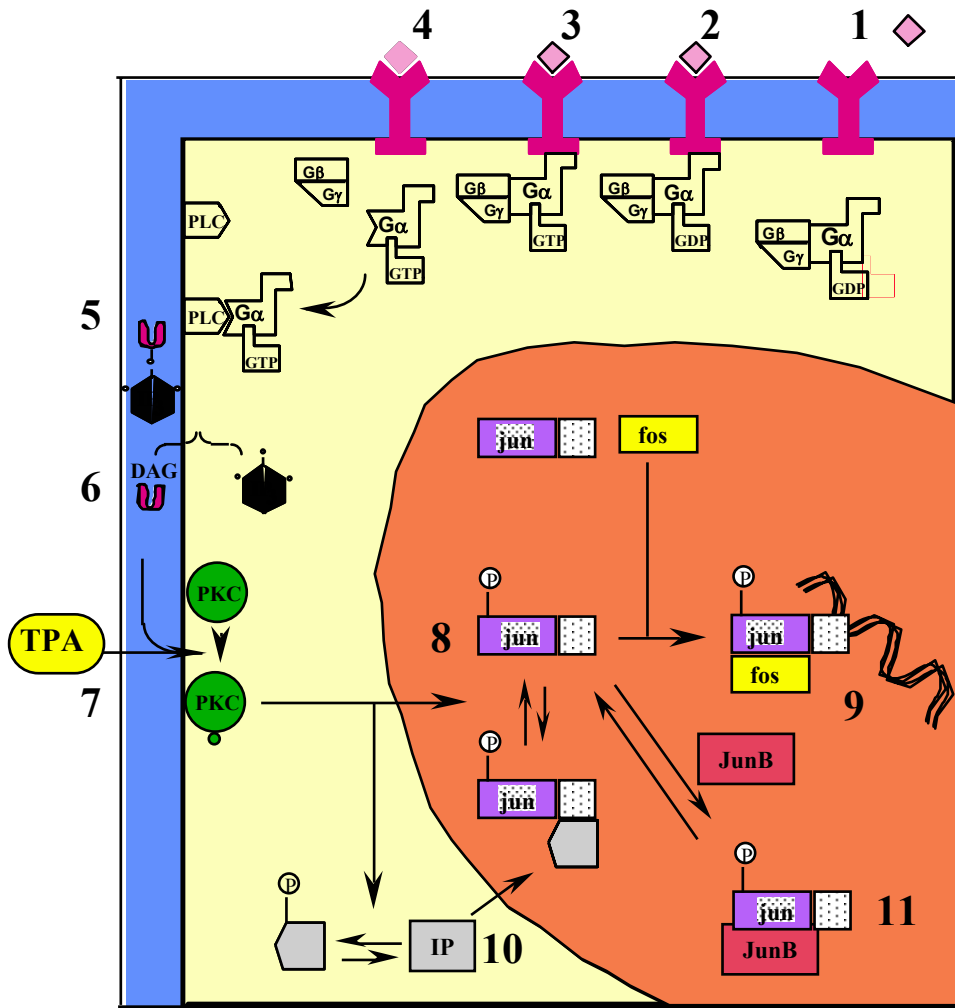
Figure 5

THE PROMOTER REGION OF THE HUMAN MMP-9 GENE



- 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 G α .
4. The G protein complex dissociates.
5. The G γ protein activates phospholipase C (PLC).
6. Active PLC cleaves its substrate into inositol tri phosphate (IP_3) 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