IN SUMMARY
PLACENTATION

PLACENTA

General facts

- Mammalian organ vital for fetal life
- Acts as interface between fetal and maternal environments
- Source of pregnancy-associated hormones and growth factors
- Protects the fetal "allograft" from maternal immune system

Development of the human placenta

- The placenta forms from zygotic tissues and the first cell type to differentiate is the trophoblast
- By the end of the third week the placenta is functioning
- The human placental cell types include:
  - –Cytotrophoblast
  - –Synctiotrophoblast
  - –Intermediate trophoblast
  - –Stroma - macrophages (Hofbauer cells), fibrocytes, Wharton's jelly
  - –Vascular structure - endothelium

Implantation

- After ovulation
  - –glands become tortuous
  - –spiral arteries form
  - –endometrium thickens
- pinopods, microvilli, apical protrusions present at 20-23 days
- implantation occurs during this time
- pinopods
  - –absorb molecules and fluid from lumen
  - –increase apposition of embryo and endometrium
  - –reduce potential cavity

- Ovum captured in distal portion of tube
- Fertilization occurs
- Enters uterus 4 days after ovulation
- Cleavage occurs during these 4 days but no change in size (no cell growth) - 150um
- Inner cell mass --> embryo
- Trophoblast ---> placenta
- Cell growth then begins

- Invasion
  - –between uterine epithelium (intrusive penetration)
    - •ferret, guinea pig, rhesus monkey
  - –replace epithelial cells (displacement penetration)
    - •mouse, rat
  - –fuse with epithelial cells (fusion penetration)
    - •rabbits
- Human mode unknown but probably intrusive
- attaches to epithelium and heads for decidua
- Cytotrophoblasts fuse to form syncytium
- Penetration continues for 4 days
- Stroma undergoes changes (not just displaced)

- Implantation occurs 7-8 days after ovulation

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- Embryo “targets” hypoepithelial vessels on surface of endometrium
- Surface is made receptive for the embryo
- Immediate
  - –human
- Delayed
  - –facultative (rat, red kangaroo only during stress)
  - –facultative (Alaska fur seal, mink, bear always)
  - –free floating morula/blastocyst with min. met. act.
  - –Light cycle control duration of delay

Immature Chorionic Villi

Trophoblast cell types

- Cytotrophoblast
  - –Stem cell
  - –Mononuclear/euploid
  - –epithelial
- Intermediate trophoblast
  - –Invasive/implantation site cell
  - –Mono-multinucleate
  - –hPL>hCG
  - –proteases
- Syncytiotrophoblast
  - –Terminally differentiated
  - –Polynucleated-polyploid
  - –hCG> hPL
  - –transport

- Murine placental development
- E3.5 trophectoderm (epithelial cells) differentiates:
  - –Extraembryhonic ectoderm
  - –Extraplacental cone
  - –Trophoblast giant cells

Trophectoderm differentiation

- Control over the initial cell fate decision is unclear
- After blastocoel forms, signalling between the ICM and the trophectoderm are critical
  - –Fgf4/Fgfr2

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Early trophectoderm differentiation

- Trophectoderm spatially most distant from ICM become TGC
- ICM expresses Fgf4, trophectoderm expressed Fgfr2
- Fgf4 ko embryos are lethal YET Fgf4 -/- stem cells are viable
- Oct4 ko lack ICM but make trophectoderm if Fgf4 given
- Fgfr dominant negative constructs block trophoblast proliferation
- Trophoblast "stem cells" require Fgf4, withdrawn will differentiate to TGC

Branching

- As the trophoblast grows it branches and increases its surface area
- Molecules involved in this process are same as involved in branching morphogenesis in other organs (e.g. lung, kidney)
- Initiation of branching - Gcm1
- Branching morphogenesis - Fgf and others downstream/ signal transduction: Grb2, Gab1, Sos1 Mek1
- Wnt canonical pathway via Tcf1 and Lef1

Vasculogenesis

- Coordination of vascular pattern with villous pattern varies amongst species
  - Murine the events are simultaneous
  - In human, the villi form first then vessels "come in"
- Eptihelial-mesenchymal interactions are key
- Trophoblast factor - Esx1
- Hypoxia inducible factors important
  - Hif1b1
  - Vegf
  - Epas

Immunobiology of pregnancy

- Mother's immune system has to protect the mother and fetus against pathogens and prevent the rejection of the semi-allergeneic feto-placental unit
- Potential for repeated pregnancies with same paternity potentially triggering immune memory

Innate vs Adaptive Immunity

- Fetal alloantigens are recognized by maternal adaptive immune system
- Innate immune response during implantation involves complement activation and neutrophil infiltration

Controlled complement activation

- Complement regulatory proteins prevent overdrive of complement activation in successful pregnancies
- Complement mediated cell lysis is regulated by factors:
  - DAF/CD55
  - MCP/CD46
  - Crry

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Complement

- C3 deposition at maternal-fetal interface results in hemorrhagic necrosis and neutrophil infiltration leading to fetal resorption
- Crry -/- abort
- Crry -/- crossed with C3 -/- produce viable fetuses
- C3 deficient mothers have no fetal injury even when injected with aPL which results in antibody deposition in the decidua

T-Cell dependent inflammation inhibited by IDO

- Tryptophan is needed for cell proliferation and is lower in pregnant than in non-pregnant women
- IDO degrades tryptophan
- IDO is expressed by syncytiotrophoblast, macrophages, and antigen presenting cells
- Macrophages suppress T cell activity due to degradation of tryptophan by IDO
- Treatment with an IDO inhibitor leads to inflammation, complement deposition and hemorrhagic necrosis at fetomaternal interface

Role of HLA-G

- Nonclassical HLA class I molecule expressed in trophoblasts, amnion, and thymic epithelial cells
- 7 distinct protein isoforms each encoded by a specific alternatively spliced transcript
- 4 are membrane bound and 3 are soluble
- Inhibit NK cell mediated cytolysis and Ag specific CD8+ T cell mediated cytolysis

HLA-G and Implantation

- Normally highly expressed by invading trophoblast
- Greatly reduced in trophoblasts from spontaneous abortions and in patients with pre-eclampsia
- Zygotic expression of soluble HLA-G is required for blastocyst attachment

Adhesion molecules

- Integrins
  - cell to cell adhesion receptors
  - cell-to-cell matrix reactions
  - 21 different types
  - anchor cells to specific locations
  - transmit information to cells
- Immunologic homing
- Metastatic spread
- Healing

- –Heterodimers composed of α and β subunits
- –Ligand specificity a function of $\alpha\beta$ heterodimer
- –May bind to several ligands
- –Ligand may bind to several heterodimers

•constituitivly expressed
•phasic and hormonally regulated

- –infertility ? Related to reduced endometrial expression of β_3
- –defect in embryonic expression of β_1 causes involution of inner cell mass but preserves trophoblast
- –polarity

•Distribution of the integrins either promotes or retards attachment

- –Switching

•Early trophoblast exhibits $\alpha_5\beta_1$ but later changes to $\alpha_1\beta_1$
•May regulate invasiveness

FUNDAMENTAL QUESTIONS

1. What cell types are seen in the human placenta?
2. How does a human placenta differ from that of a dog? rabbit?
3. Describe the process of implantation?
4. How is invasion accomplished?
5. What types of trophoblast are seen?
6. Why is the placenta not rejected?
7. Describe the branching process of the placenta?
8. What is an integrin? How do integrins act in placental development?