Angiogenesis in Human Development

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BACKGROUND READING

Vascular Development

"Signaling Vascular Morphogenesis and Maintenance"

VEGF Signaling

"VEGF Receptor Signaling—The control of vascular function"

Notch and arterial specification

"Notch and arterial specification during development"
Watanabe and Enari, Nature 419, 124-129 (2002)

Lymphatic Development

"Signaling in lymphatic development"
Guillen-Olivas, Nat Rev Immunology 5, 265-276 (2005)

Angiogenic Factors

Wnt and retinal angiogenesis

"Wnt and retinal angiogenesis"
Nestor Masckauchan and Jan Kitajewski, Physiology Molecular Biology of Cell (2003)

Vascular Development

- Vasculogenesis = de novo tube formation
- Angiogenesis = sprouting of new tubes off of pre-existing tubes

Cell Types:

- Endothelial Cell = cell type that makes up and lines blood vessels
- Mural Cells = specialized cells that surround blood vessels
  - Pericytes
  - Smooth muscle cells

Angiogenic Factors:

- Vascular Endothelial Growth Factor (VEGF-A, VEGF-B, PlGF, VEGF-C...)
- Angiopoietins (Ang 1, Ang 2, ...)
- Notch ligands

Lymphatic vessel

blood vessel

pericyte

Endothelial cell
**Vascular Development**

**VASCULOGENESIS**

**ANGIOGENESIS**

**Cellular steps in Angiogenesis**

1. Biochemical Response and Preparation
2. Sprout Initiation
3. Migration
4. Proliferation
5. Survival
6. Tube Formation
7. Maturation
8. Completion

**Angiogenesis - Basement Membrane Breakdown**

**Angiogenesis - Endothelial Cell Migration**

**Angiogenic Stimulus (VEGF)**
**Angiogenesis - Vascular Maturation**

- **VEGF**
  - Endothelial cell-cell junctions
  - Negative Feedback
  - Smooth Muscle Cells
  - Basement Membrane
  - Endothelium

**VEGF and VEGF Receptors**

- VEGF-B and PIGF
  - VEGF Receptor-1
  - specialized angiogenic factor
  - endothelial specific signaling

- VEGF-C and VEGF-D
  - lymphangiogenic factor
  - VEGF Receptor-3
  - lymphatic endothelial specific signaling

**Promotes:**
- Proliferation
- Migration
- Survival
VEGF is a hypoxia induced gene
Mechanism for producing angiogenic factor in conditions of low tissue oxygen

Notch drives cell fate determination

Notch/Notch ligand interaction:
- mechanism for setting and maintaining state of differentiation
- fates locked in via lateral inhibition

Notch drives cell fate differentiation

Notch/Notch ligand interaction:
- mechanism for driving state of differentiation
- fates locked in via lateral inhibition
Notch drives cell fate differentiation

Notch restricts endothelial sprouting through feedback to VEGF signaling

Wild-type  Notch Mutant  Normal  Too much Notch
Endothelial Specification

Vascular Specification

Vessels specialization during development
1) Arterial-Venous Vessels
2) Lymphatic Vessels
3) Tissue specific vessels

Notch drives cell fate differentiation

A molecular pathway for arterial-venous fate determination

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VEGF and VEGF Receptors

Structure of blood and lymphatic vasculature in dermis

Figure 2: Blood and lymphatic vessels in mouse ear. a: Whole mount immunohistochemistry labeling of lymphatic vessels (LYVE-1) and blood vessels (PECAM-1) grown in mouse ear. b. Transgenic expression of the VEGF-C mutant C562G in the skin leads to enlargement of the lymphatic vessels, whereas only a few lymphatic ECs are present in the wild-type (control). We thank G. Dusso for the staining and D. Jackson for the LYVE-1 antibody.
Normal intraretinal vasculature

Fig. 20. A view of the fovea of the eye and of the retina in a patient who has senile macular degeneration.

Retinopathy of Prematurity

![Diagram of normal intraretinal vasculature](Image)

Retinopathy of Prematurity

![Diagram of retinopathy of prematurity](Image)
**FEVR - Familial Exudative Vitreoretinopathy**

- Autosomal dominant, recessive, and X-linked forms; variable phenotype
- Clinical characteristics:
  - mild to severe vision loss
  - retina: avascular peripheral retina, exudates, neovascularization, fibrovascular masses, traction or rhegmatogenous retinal detachment
  - vitreous: posterior vitreous detachment, fibrovascular membranes, hemorrhage
  - other: cataract, neovascular glaucoma

**Autosomal dominant FEVR mutations**

In the cysteine-rich domain (CRD) of Fz4

**Retinal defects in FEVR patients heterozygous for Fz4 M157V**

Frizzled-4 is a Wnt receptor

Intraocular hemorrhage in Fz4(-/-) mice

Absence of intra-retinal capillaries in Fz4(-/-) mice
Norrie Disease

- First described by Norrie (1927) and analyzed systematically by Mette Warburg [Acta Ophthalmologica 39: 757-772 (1961); 41: 134-146 (1963); 89:1-147 (1966)]
- X-linked recessive with variable phenotype
- Clinical characteristics:
  - Moderate vision loss to congenital blindness
  - Retina: retinal folding and detachment, retinal degeneration, fibrovascular masses, vitreoretinal hemorrhage
  - Vitreous: persistent primary vitreous
  - Other: progressive sensorineural deafness

Norrin is a ligand for Frizzled-4

Molecular genetics of Norrie Disease and FEVR

- FEVR

- Norrie disease
  - Gene identified by Berger et al. and Chen et al. [Nature Genetics 1: 199-203 and 204-208 (1992)]
  - The encoded protein is small (133 amino acids in length), has the same pattern of cysteines as seen in transforming growth factor beta, and begins with a signal sequence (i.e. it looks like a secreted protein). No known biochemical function.

Vessel component to human diseases

- Tumor angiogenesis
- Tumor lymphangiogenesis, metastasis
- Diabetic vascular complication
  - Diabetic retinopathy
  - Stroke
  - Ischemia
  - Wound repair
- Heart disease
  - Occluded vessels
  - Rebuilding vessels of damaged heart tissue
- Obesity
- Lymphedema
- Blindness
  - Wet Macular Degeneration
  - Retinopathy of Prematurity