Angiogenesis in Human Development

Jan Kitajewski *ICRC 916, ph 851-4688, email: jkk9*

BACKGROUND READING:

Vascular Development

"Signaling Vascular Morphogenesis and Maintenance"
Douglas Hanahan. *Science* 277: 48-50. in Perspectives. (1997)

VEGF Signaling

"VEGF Receptor Signaling – in control of vascular function"
Ollsson, Dimburg, Krueger, and Lena Claesson-Welsh. Nat. Rev. Mol. Cell Biol. 7: 359-71 (2006)

Notch and arterial specification

"Arterial Venous Specification During Development"
Matthew Swift and Brant M. Weinstein . *Circ. Res.* 104: 576-588 (2009)

Lymphatic Development

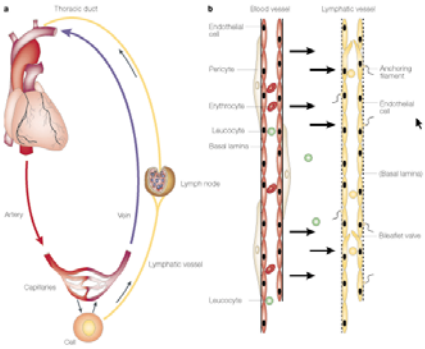
"Lymphatic Vascular Development"
Guillermo Oliver. *Nature Rev Immunology* 4: 35-45 (2004)

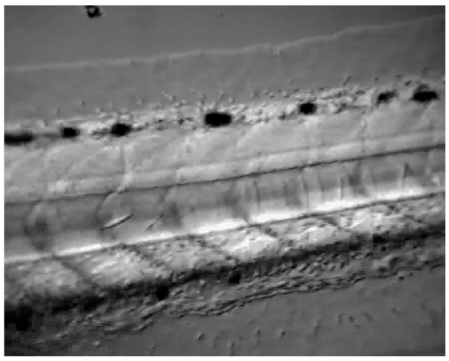
Wnts and retinal angiogenesis

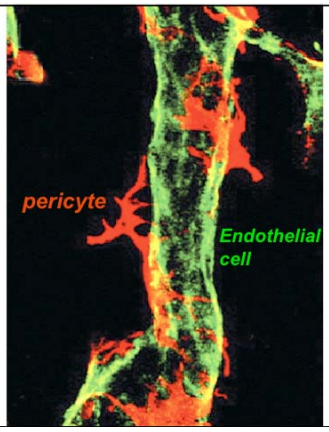
"Wnt/Frizzled Signaling in the Vasculature: New Angiogenic Factors in Sight"
Nestor Masckauchán and Jan Kitajewski. *Physiology* 21: 181-188 (2006)

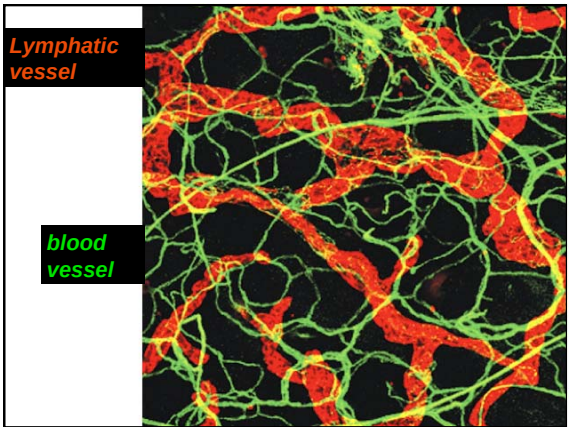
Vascular Development

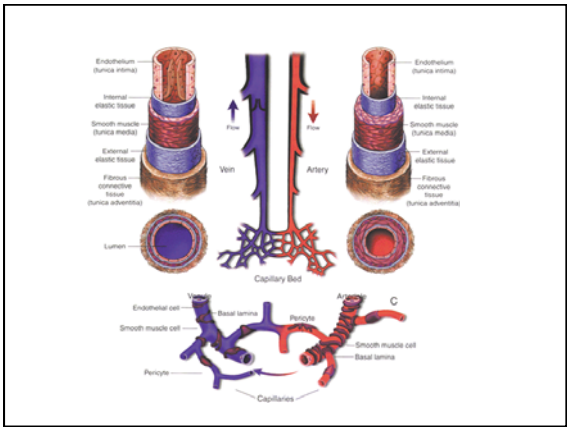
- Vasculogenesis = de novo tube formation
- Angiogenesis = sprouting of new tubes off of pre-existing tubes
- Cell types
  - Endothelial Cell = cell type that makes up and lines blood vessels
  - Mural Cells = specialized cells that surround blood vessels
    - Pericytes
    - Smooth muscle cells
- **Angiogenic Factors**
  - Vascular Endothelial Growth Factor (VEGF-A, VEGF-B, PlGF, VEGF-C.....)
  - Angiopoietins (Ang 1, Ang2, ...)
  - Notch ligands (Jagged1, Delta4)

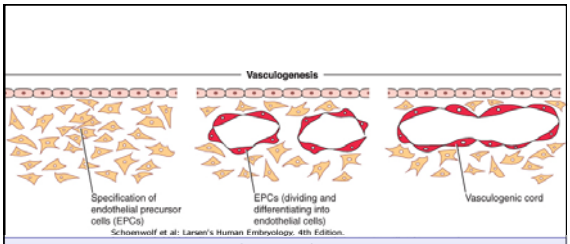






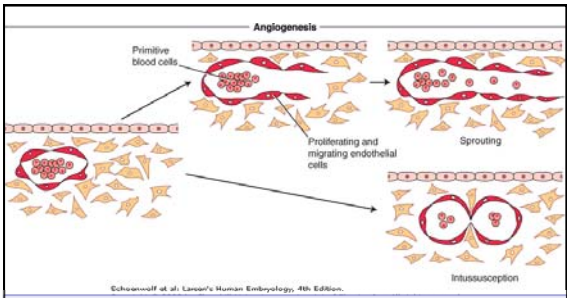






Vascular Development

VASCULOGENESIS



Vascular Development

ANGIOGENESIS

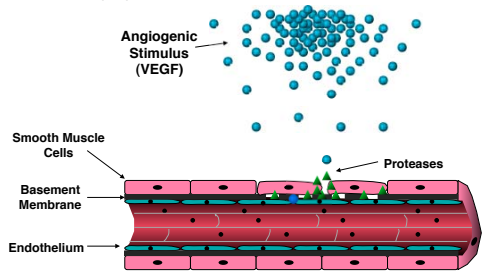
Vascular Development

ANGIOGENESIS

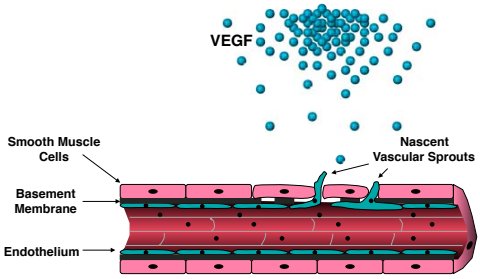
Cellular steps in Angiogenesis

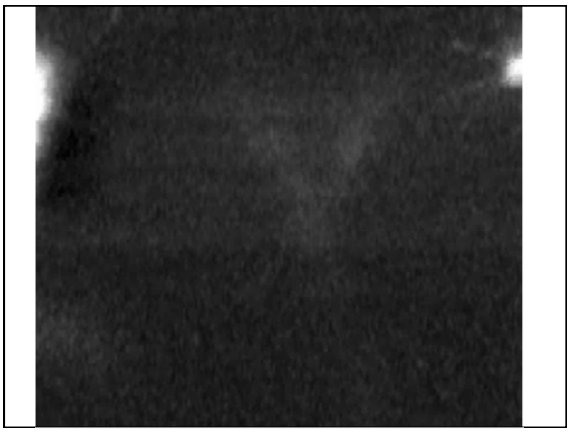
1) Biochemical Response and Preparation
2) Sprout initiation
3) Migration
4) Proliferation
5) Survival
6) Tube Formation
7) Maturation
8) Completion
9) Blood Flow

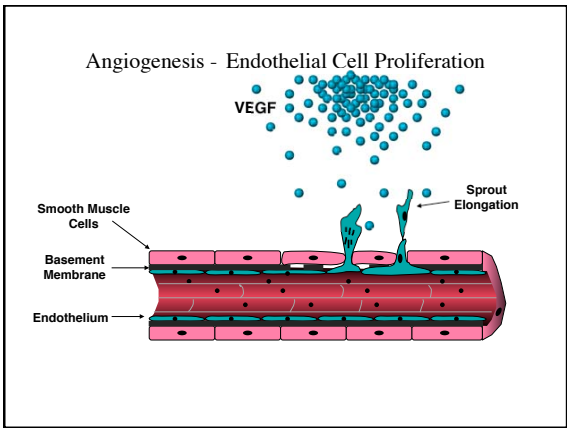
Angiogenesis - Basement Membrane Breakdown

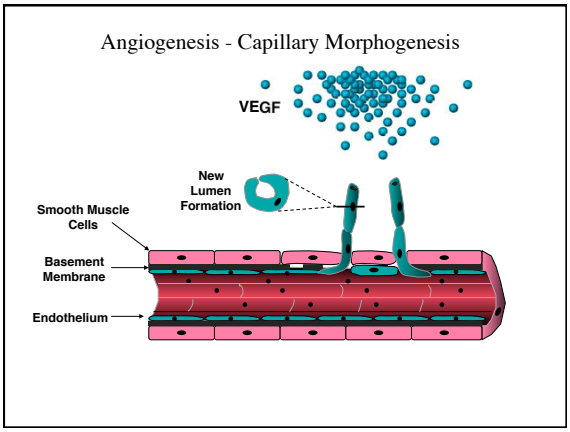


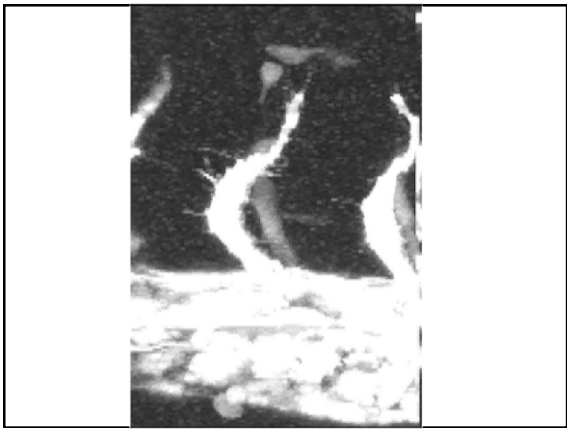
Angiogenesis - Endothelial Cell Migration

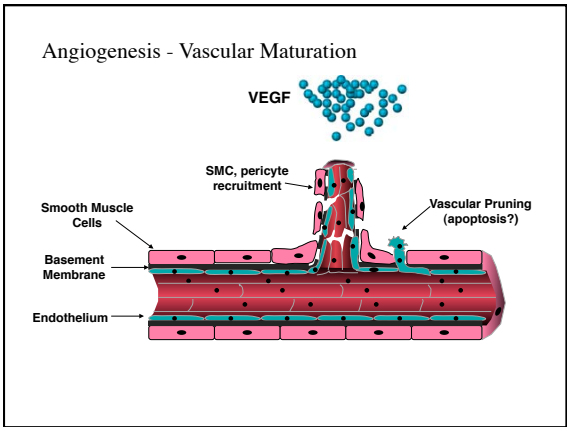


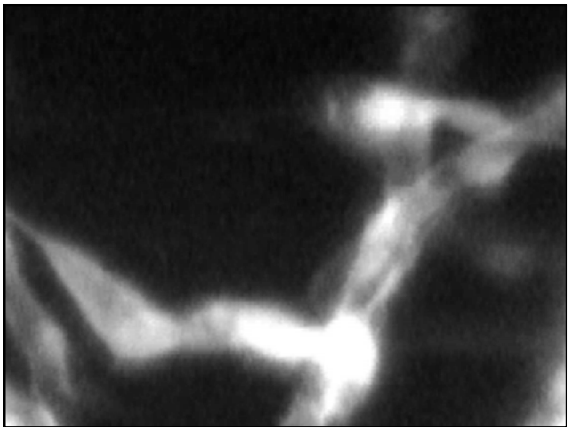


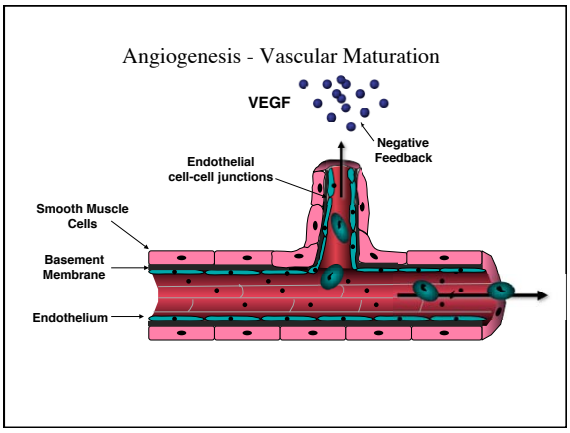

Angiogenesis - Endothelial Cell Proliferation
VEGF
Sprout Elongation
Smooth Muscle Cells
Basement Membrane
Endothelium

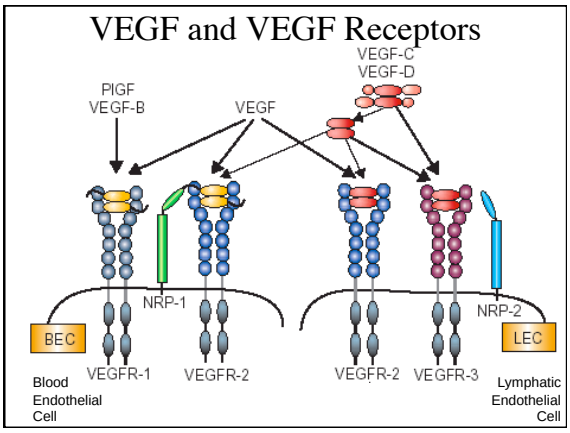

Angiogenesis - Capillary Morphogenesis
VEGF
New Lumen Formation
Smooth Muscle Cells
Basement Membrane
Endothelium



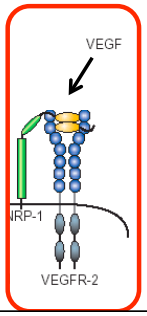

Angiogenesis - Vascular Maturation
VEGF
SMC, pericyte recruitment
Vascular Pruning (apoptosis?)
Smooth Muscle Cells
Basement Membrane
Endothelium



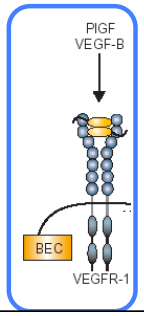




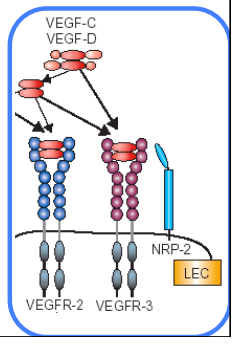
VEGF = VEGF-A angiogenic factor
VEGF Receptor-2 endothelial-specific signaling receptor



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

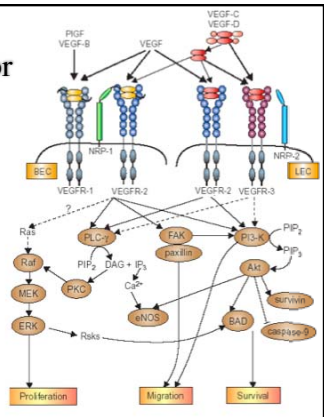


VEGF-C and VEGF-D lymphangiogenic factor
VEGF Receptor-3 lymphatic endothelial specific signaling



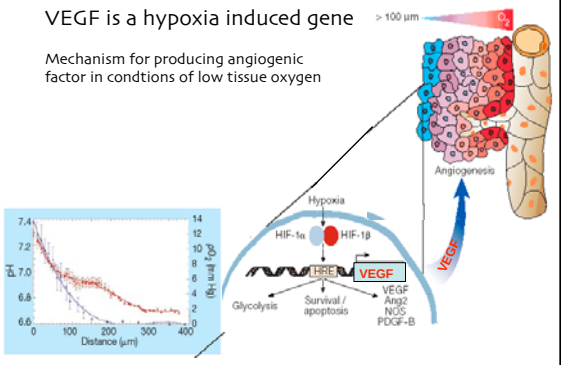
VEGF-receptor signaling

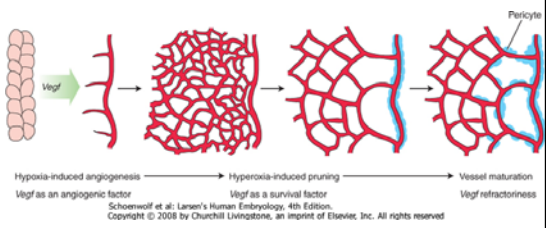
Promotes:
Proliferation
Migration
Survival

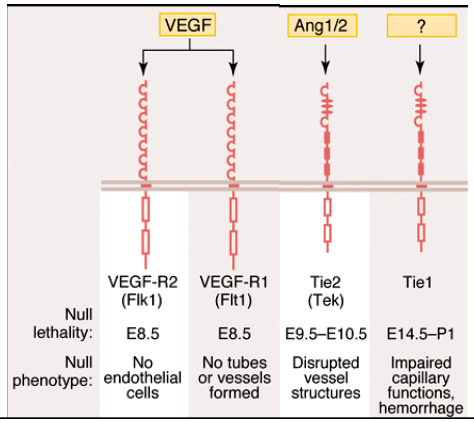


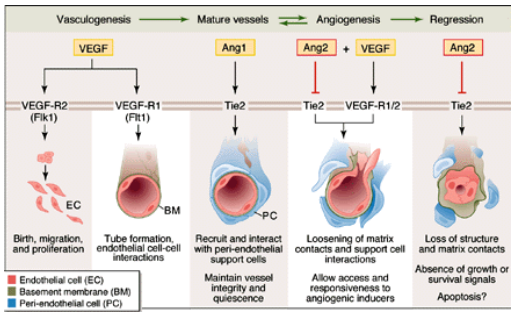
VEGF is a hypoxia induced gene

Mechanism for producing angiogenic factor in condtions of low tissue oxygen









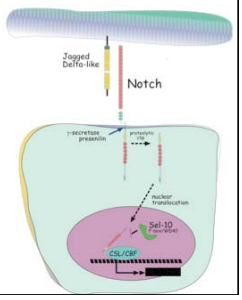
Notch drives cell fate determination

Notch/Notch ligand interaction:

-mechanism for setting and maintaining state of differentiation

-fates locked in via lateral inhibition

-



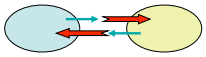
Notch drives cell fate differentiation

Notch/Notch ligand interaction:

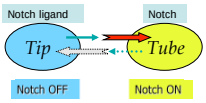
-mechanism for driving state of differentiation

-fates locked in via lateral inhibition

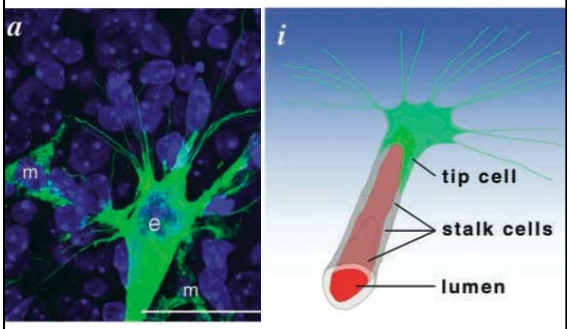
Notch drives cell fate differentiation



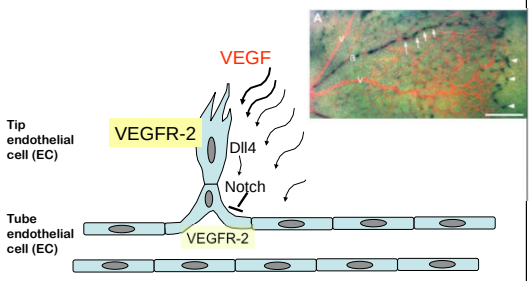
Notch drives cell fate differentiation

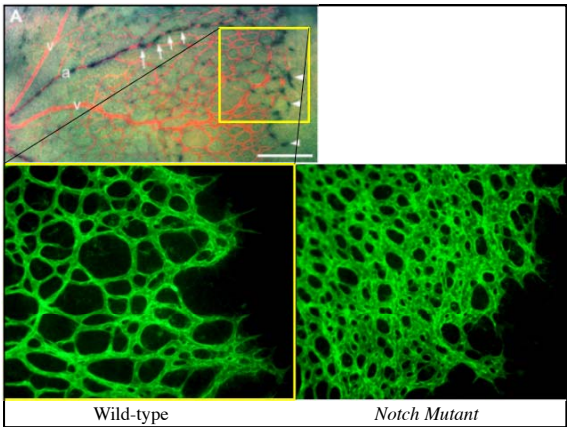


Notch restricts tip cell specification

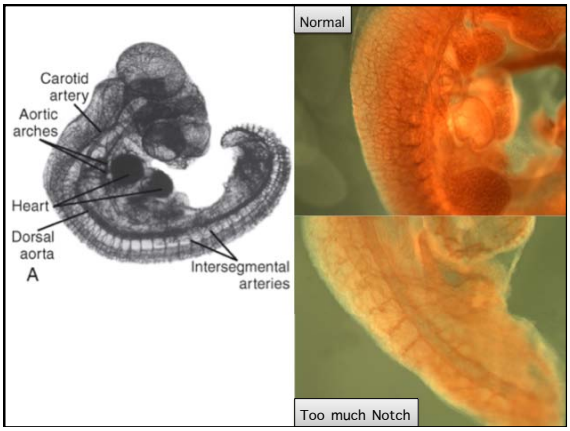


Notch restricts endothelial sprouting through feedback to VEGF signaling

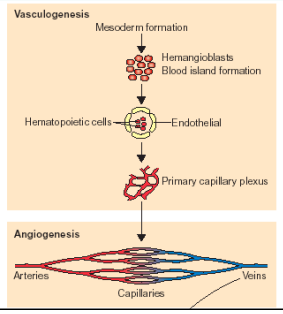


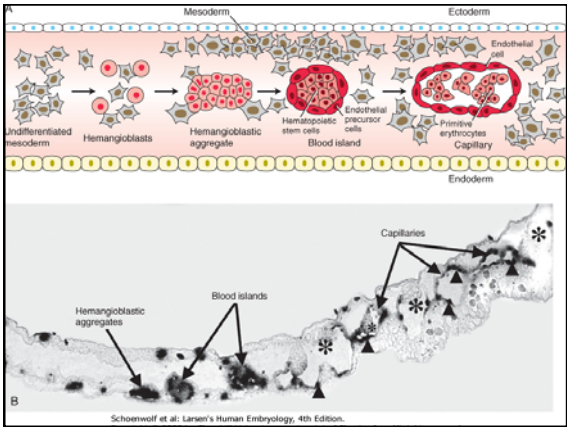


Wild-type *Notch Mutant*



Endothelial Specification



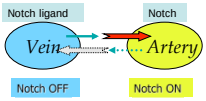


Vascular Specification

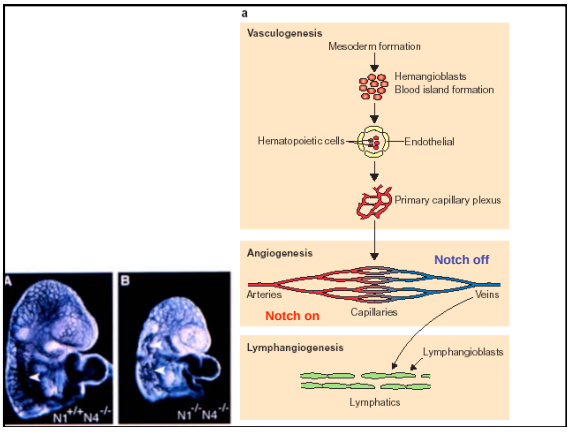
Vessels specialization during development

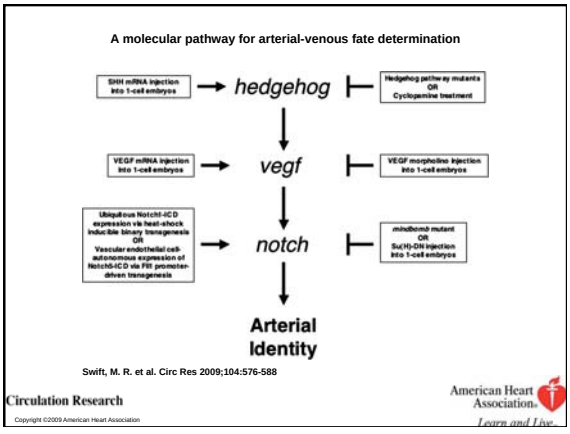
1) Arterial-Venous Vessels
2) Lymphatic Vessels
3) Tissue specific vessels

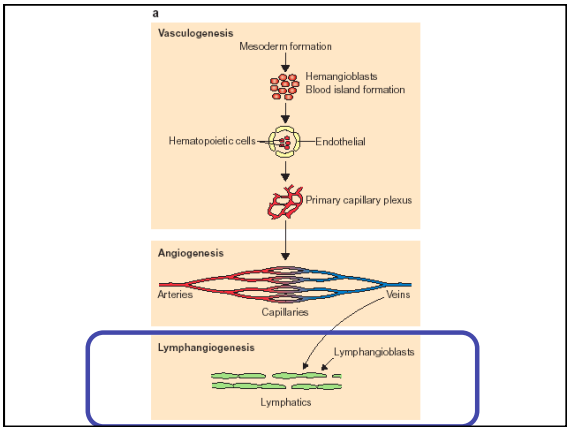
Notch drives cell fate differentiation

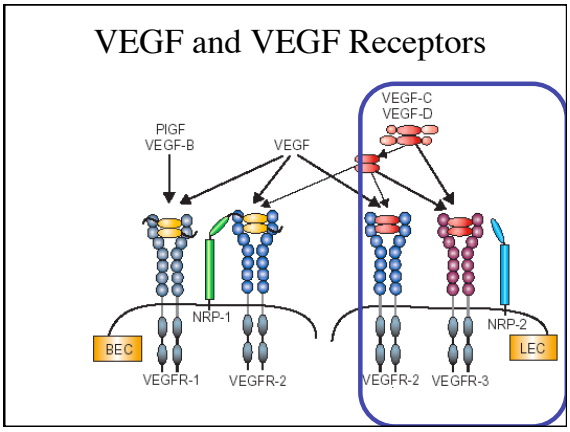


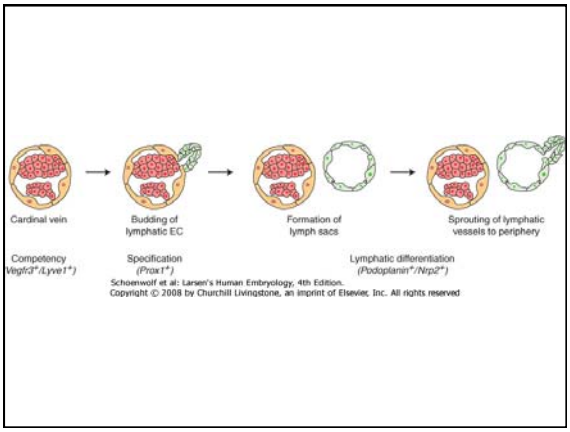
Notch promotes arterial specification






a
Vasculogenesis
Mesoderm formation
Hemangioblasts
Blood island formation
Hematopoietic cells
Endothelial
Primary capillary plexus
Angiogenesis
Arteries
Veins
Capillaries
Lymphangiogenesis
Lymphangioblasts
Lymphatics


VEGF and VEGF Receptors
PlGF
VEGF-B
VEGF
VEGF-C
VEGF-D
NRP-1
NRP-2
BEC
LEC
VEGFR-1
VEGFR-2
VEGFR-2
VEGFR-3


Cardinal vein
Budding of lymphatic EC
Formation of lymph sacs
Sprouting of lymphatic vessels to periphery
Competency
Vegfr3+/Lyve1+
Specification
(Prox1+)
Lymphatic differentiation
(Podoplanin+/Nrp2+)
Schoenwolf et al: Larsen's Human Embryology, 4th Edition.
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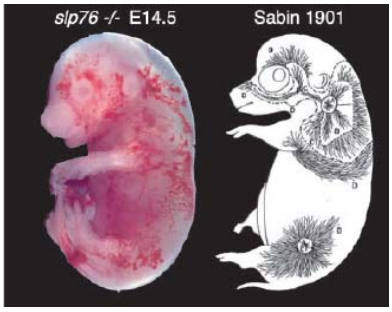
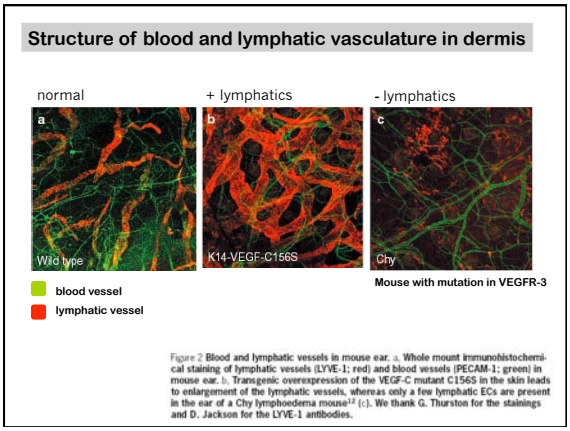
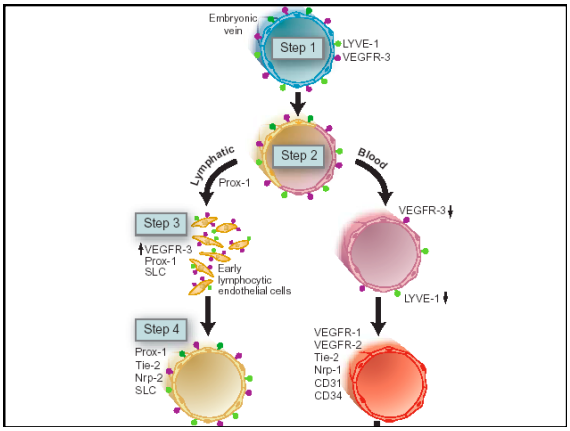
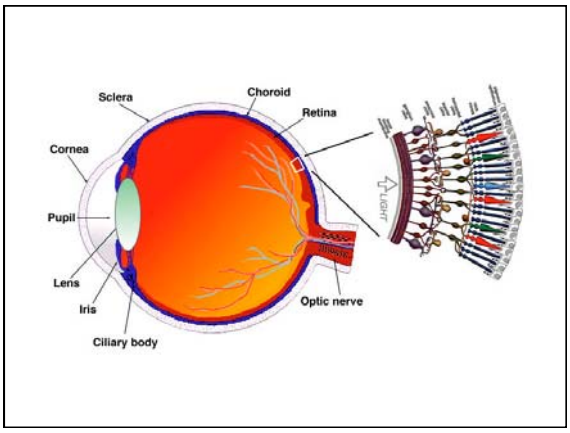
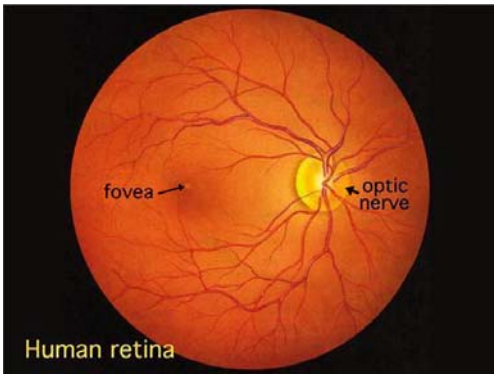
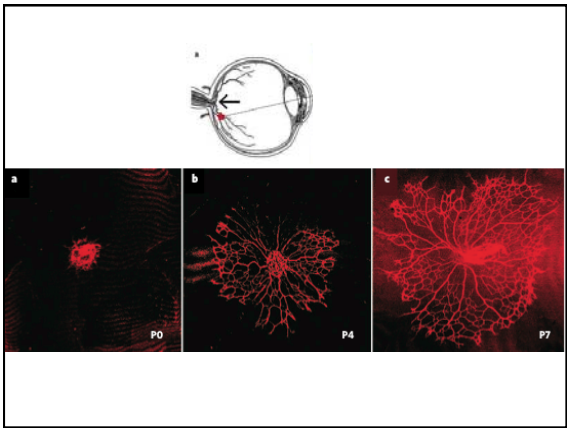

slp76 -/- E14.5
Sabin 1901


Structure of blood and lymphatic vasculature in dermis
normal
+ lymphatics
- lymphatics
a
b
c
Wild type
K14-VEGF-C156S
Chy
Mouse with mutation in VEGFR-3
blood vessel
lymphatic vessel
Figure 2 Blood and lymphatic vessels in mouse ear. a, Whole mount immunohistochemical staining of lymphatic vessels (LYVE-1; red) and blood vessels (PECAM-1; green) in mouse ear. b, Transgenic overexpression of the VEGF-C mutant C156S in the skin leads to enlargement of the lymphatic vessels, whereas only a few lymphatic ECs are present in the ear of a Chy lymphoedema mouse[12] (c). We thank G. Thurston for the stainings and D. Jackson for the LYVE-1 antibodies.


Embryonic vein
Step 1
LYVE-1
VEGFR-3
Step 2
Lymphatic
Blood
Prox-1
Step 3
VEGFR-3
Prox-1
SLC
Early lymphocytic endothelial cells
VEGFR-3
LYVE-1
Step 4
Prox-1
Tie-2
Nrp-2
SLC
VEGFR-1
VEGFR-2
Tie-2
Nrp-1
CD31
CD34







Normal intraretinal vasculature

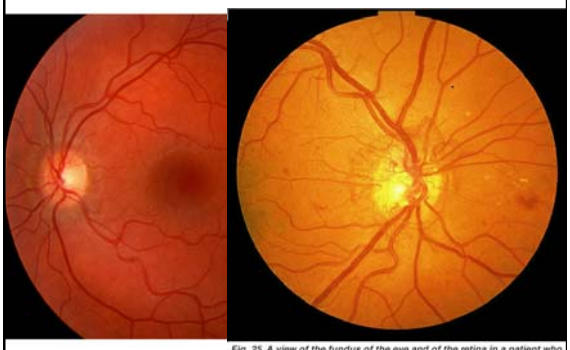
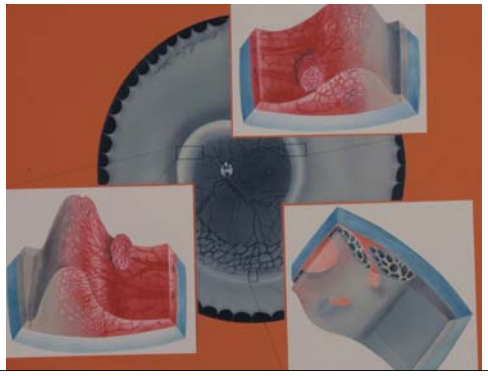


Fig. 25. A view of the fundus of the eye and of the retina in a patient who has advanced diabetic retinopathy.

Retinopathy of Prematurity



Retinopathy of Prematurity

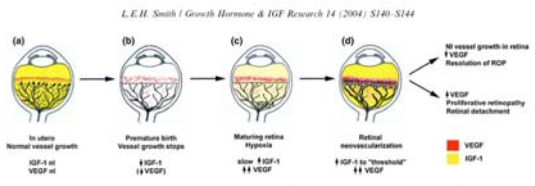
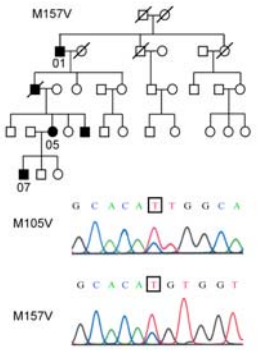


Fig. 1. Mechanism for retinopathy of prematurity (ROP) (Reprinted, with permission, from [37]).

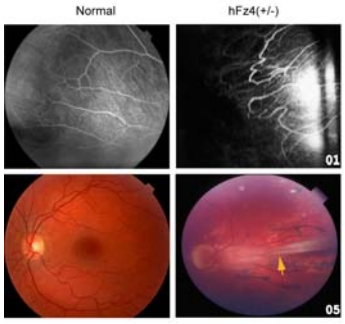
FEVR- Familial Exudative Vitreoretinopathy

- First described by Criswick and Schepens [Am. J. Ophthalmol. 68: 578-594 (1969)]
- 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

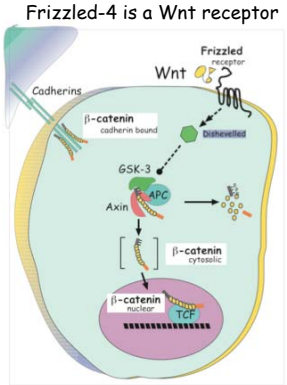
Autosomal dominant FEVR mutations In the cysteine-rich domain (CRD) of Fz4



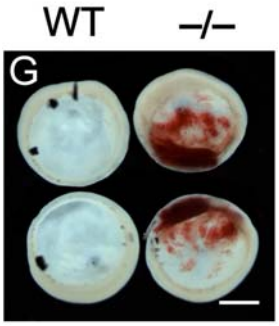
Retinal defects in FEVR patients heterozygous for Fz4 M157V



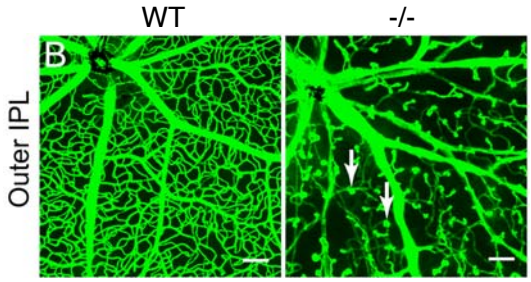
Frizzled-4 is a Wnt receptor



Intraocular hemorrhage in Fz4(-/-) mice

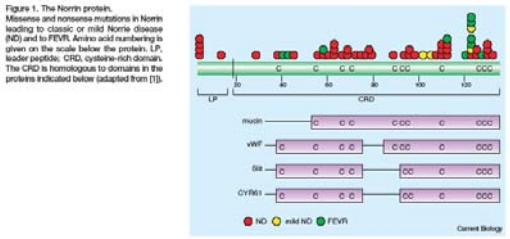


Absence of intra-retinal capillaries in Fz4(-/-) mice

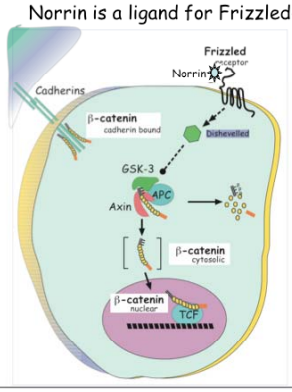


Norrie Disease

- 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
  One autosomal dominant FEVR gene identified by Robaitaille et al [Nature Genetics 32: 326-330 (2002)] encodes Frizzled4, a putative Wnt receptor. A second autosomal dominant FEVR locus encodes the Wnt co-receptor Lrp5 [Toomes et al [IOVS 45: 2083-2090 (2004)]; Jiao et al [Am J Hum Genet 75: 878-884 (2004)].
- 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 *(treatment available ?)*
- 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 *(treatment available)*
  - Retinopathy of Prematurity