

Angiogenesis in Human Development

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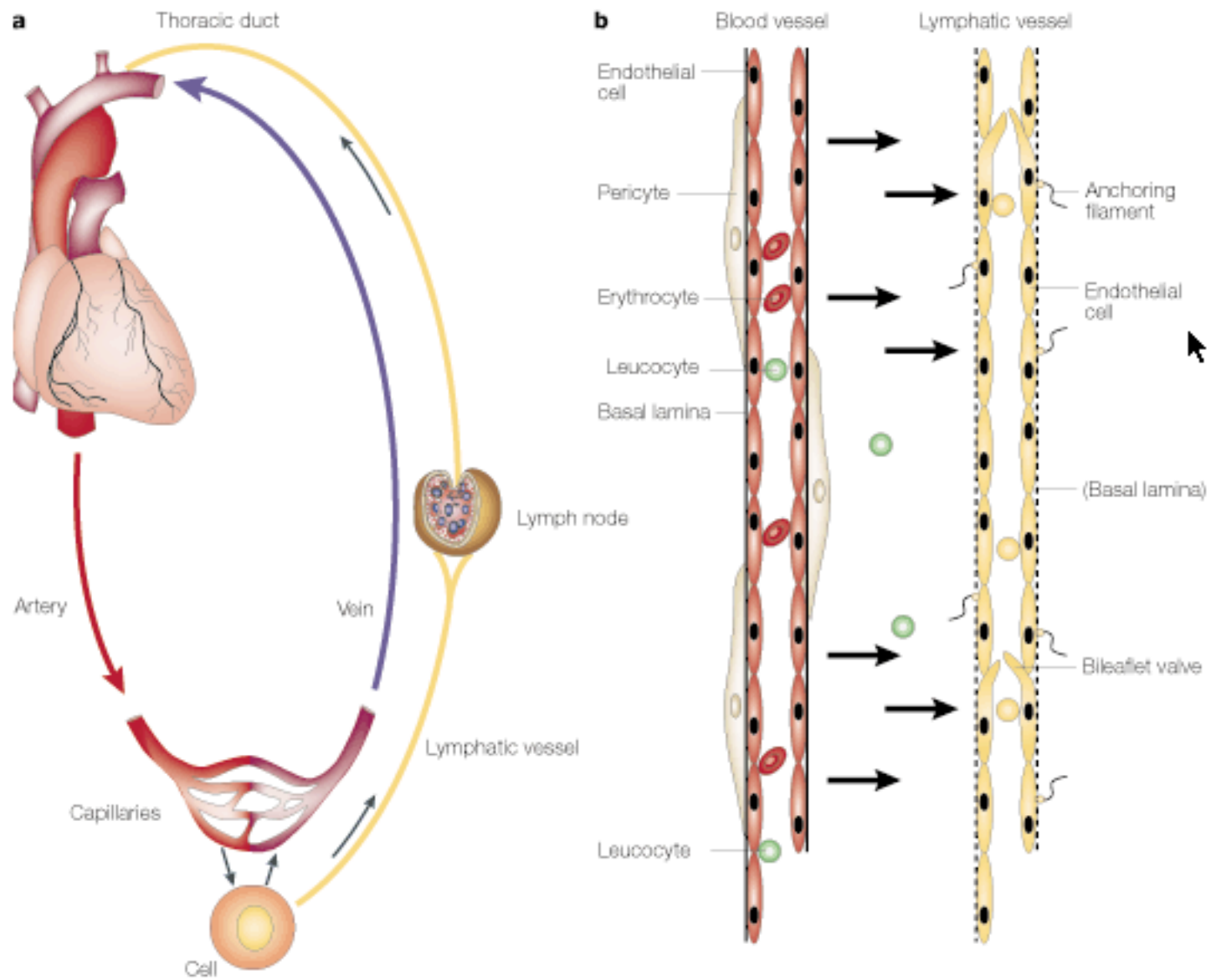
BACKGROUND READING:

Vascular Development

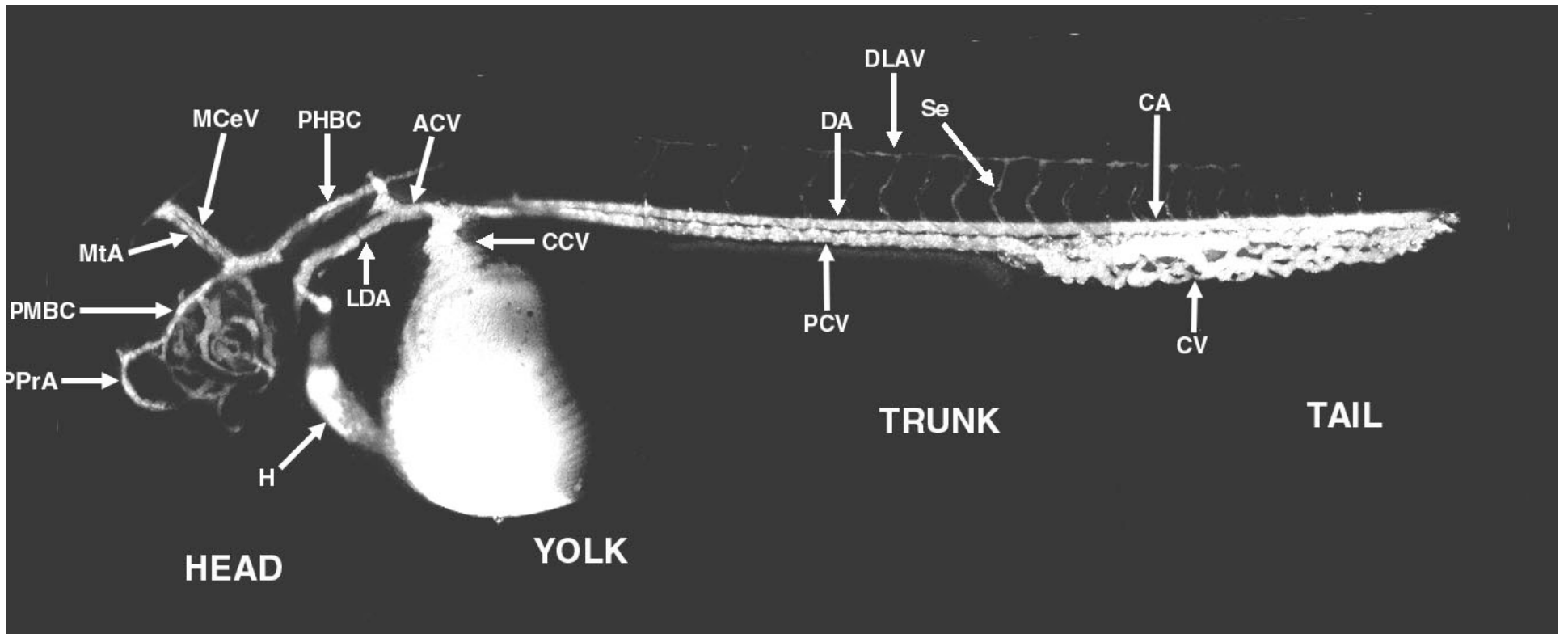
“Signaling Vascular Morphogenesis and Maintenance”
Douglas Hanahan. *Science* 277: 48-50. in Perspectives. (1997)

Vascular Development

- **Vasculogenesis** = de novo tube formation
- **Angiogenesis** = sprouting of new tubes off of pre-existing tubes
- **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, VEGF-D)
 - Angiopoietins (Ang 1, Ang2,
 - Notch ligands (Jagged1, Delta4)



2.5 day



Nature Biotechnology **22**, 595 - 599 (2004)

Chemical suppression of a genetic mutation in a zebrafish model of aortic coarctation

Randall T Peterson¹, Stanley Y Shaw^{1, 2}, Travis A Peterson¹, David J Milan¹, Tao P Zhong^{1, 3}, Stuart L Schreiber², Calum A MacRae¹ & Mark C Fishman^{1, 4}

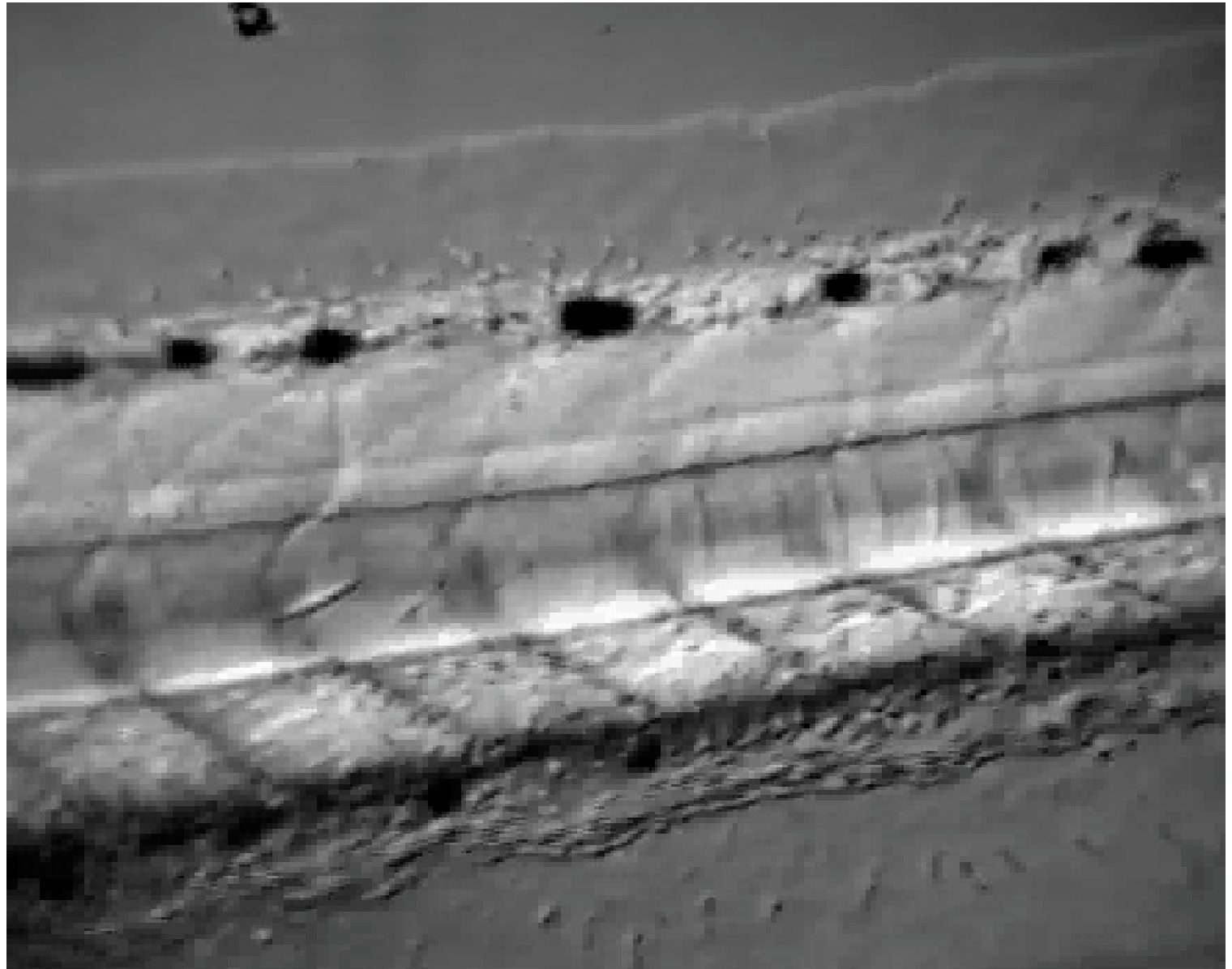
1 Developmental Biology Laboratory, Cardiovascular Research Center, Massachusetts General Hospital

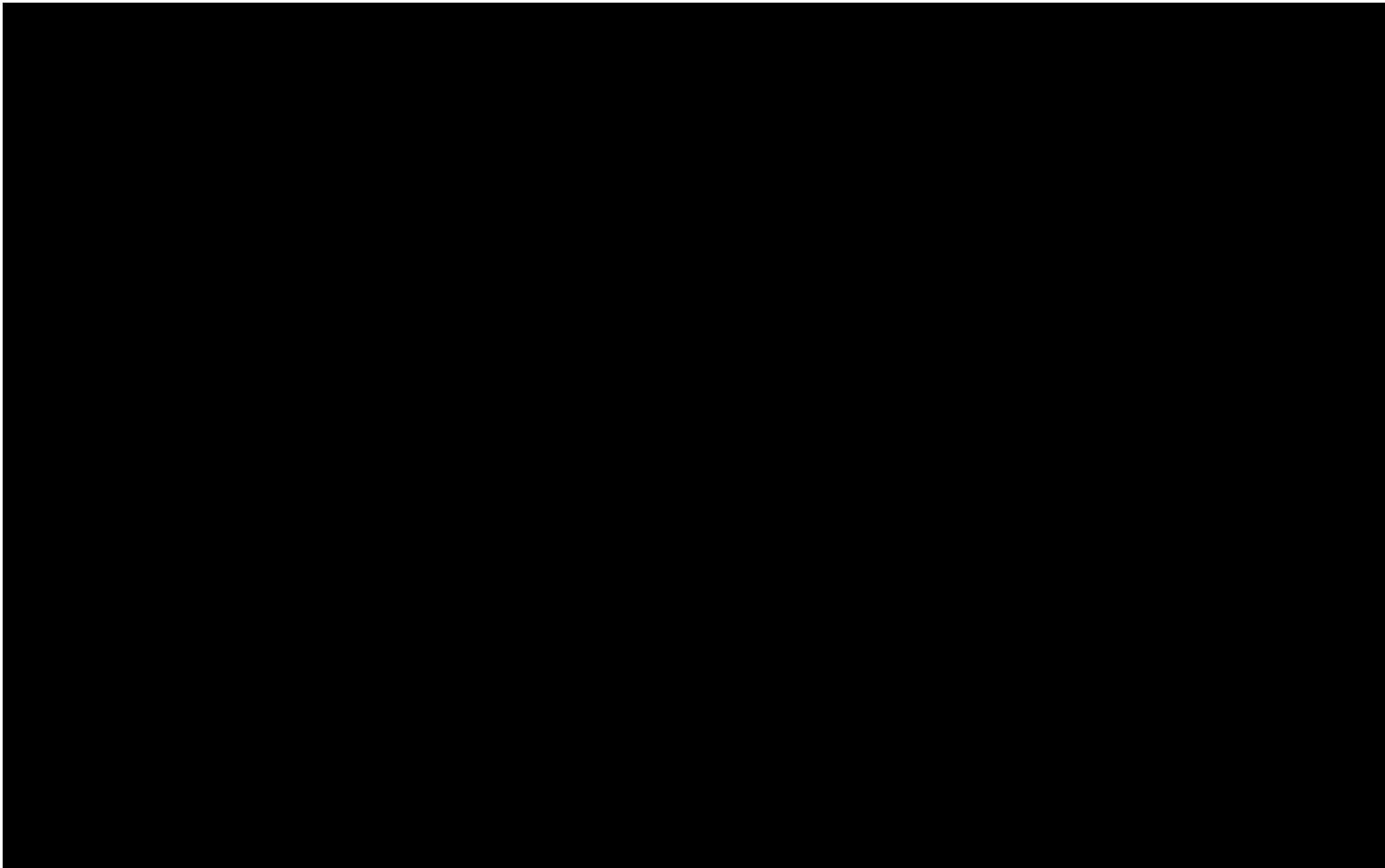
Nature Chemical Biology **1**, 263-264 (2005)

High-throughput assay for small molecules that modulate zebrafish embryonic heart rate.

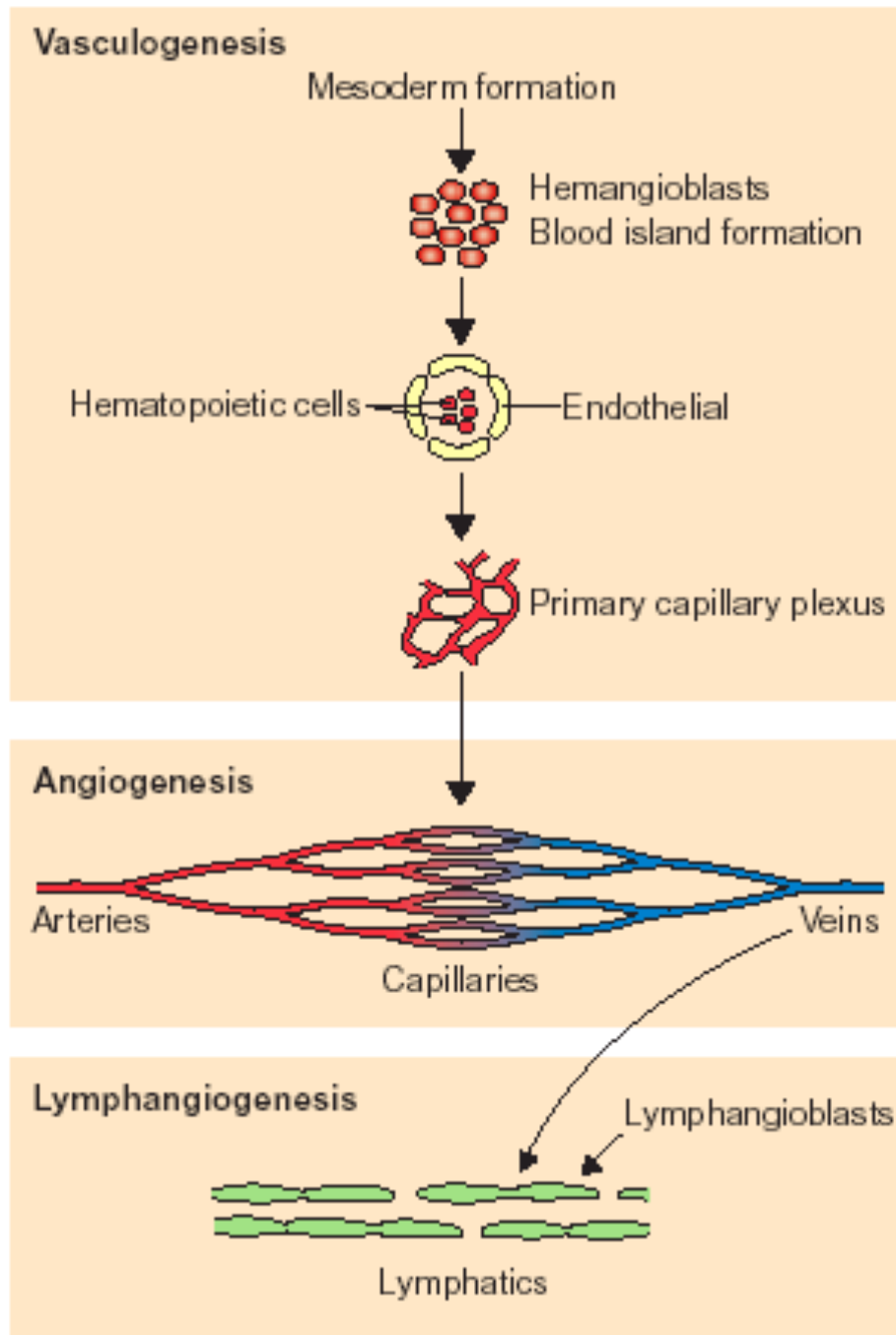
Burns CG, David J Milan, Grande DJ, Rottbauer W, Calum A MacRae & Mark C Fishman

Developmental Biology Laboratory, Cardiovascular Research Center, Massachusetts General Hospital

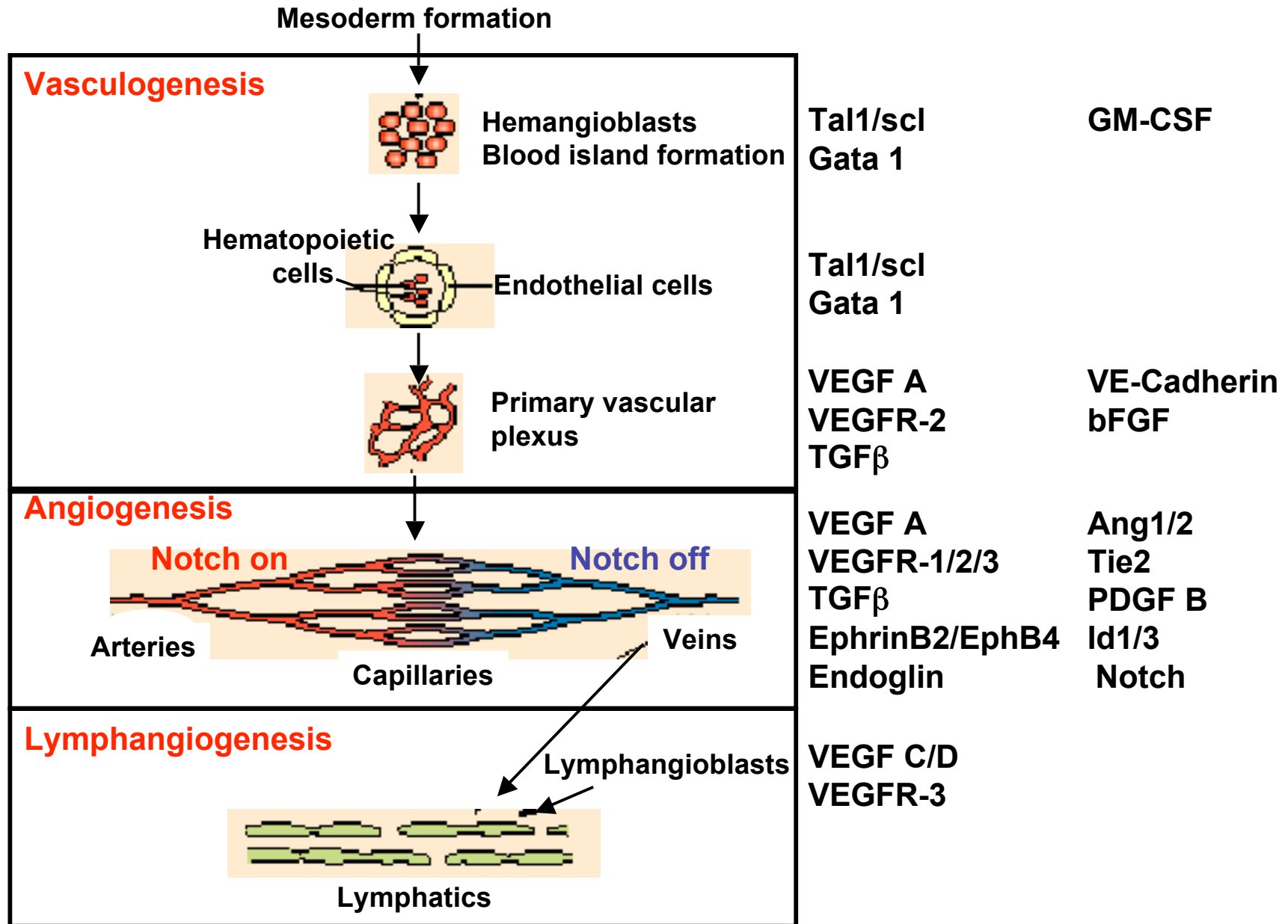


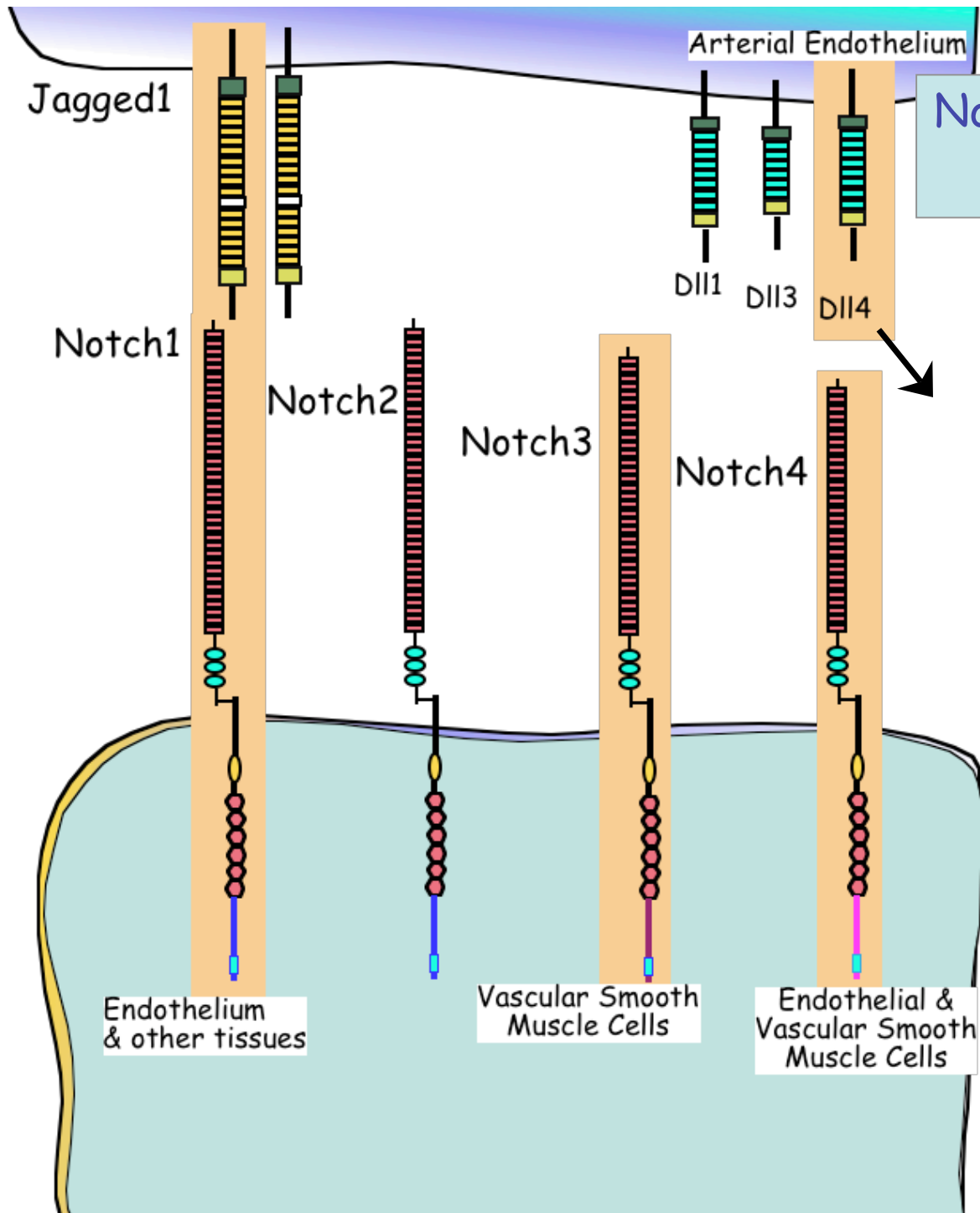


a

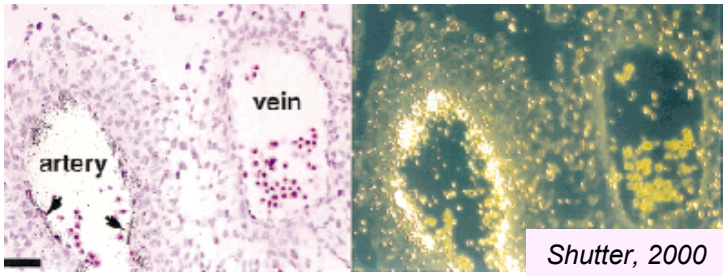
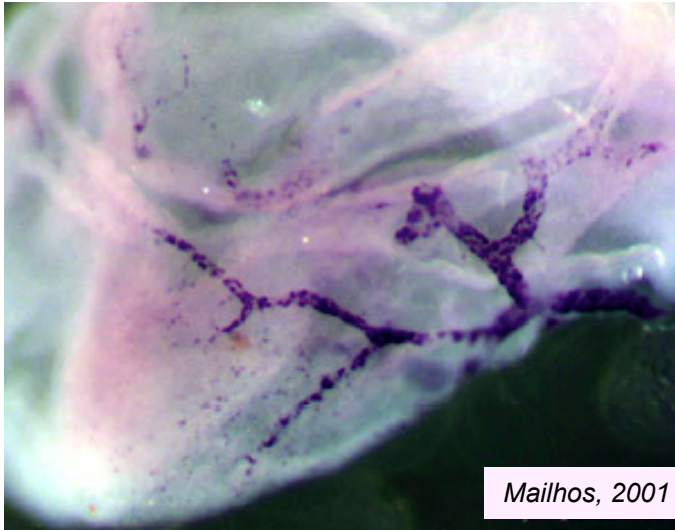


Vascular Development

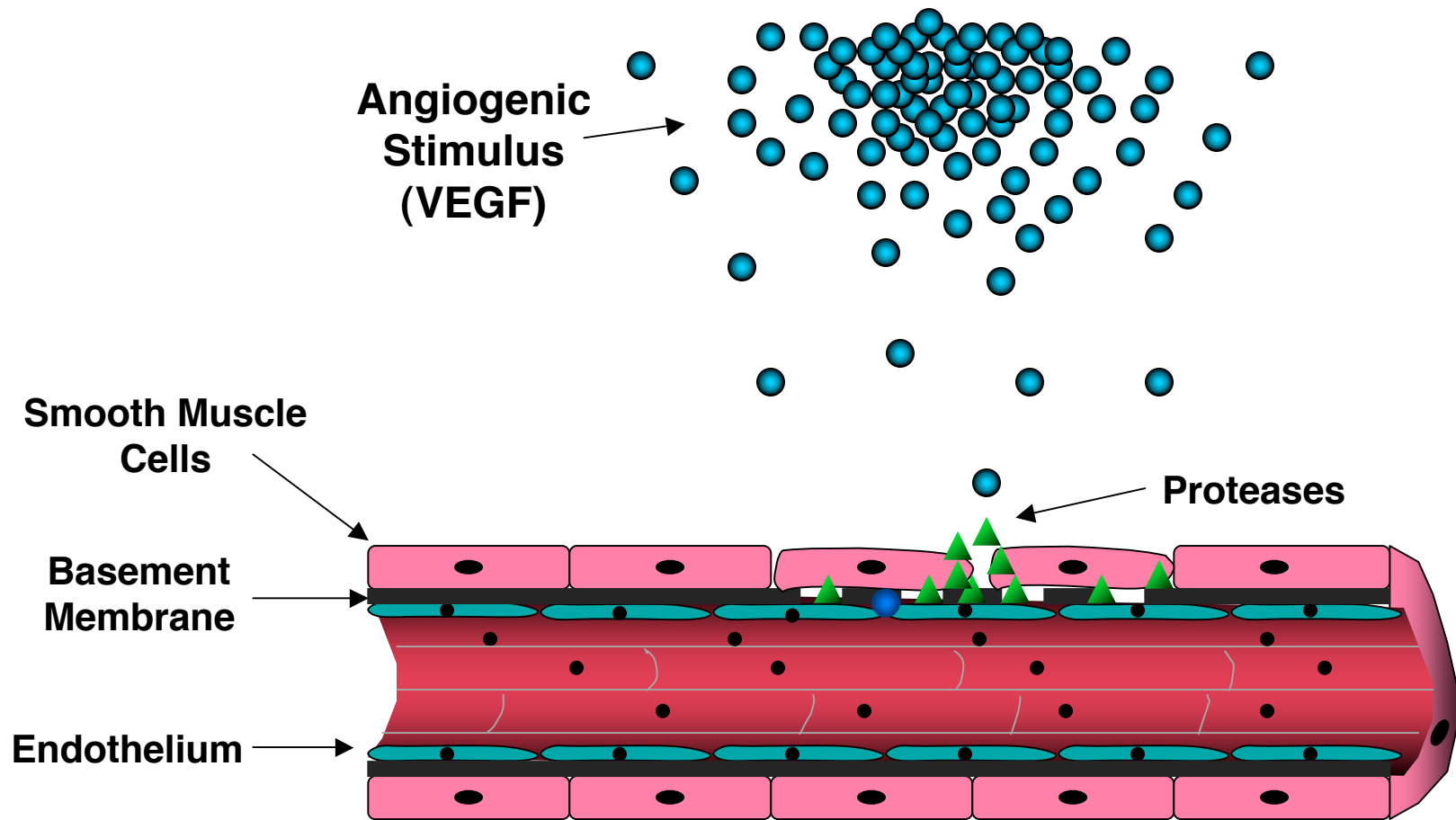




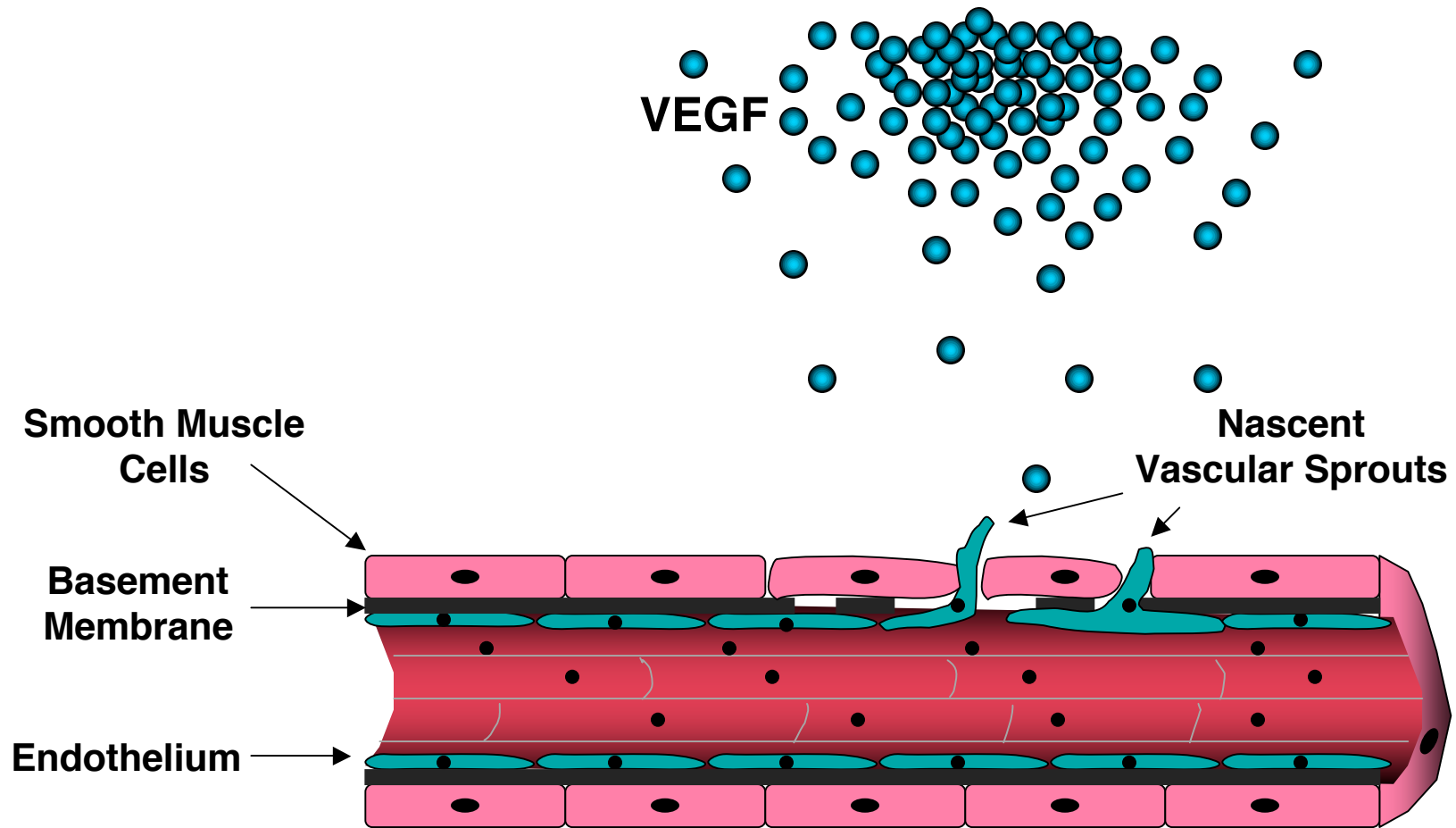
Notch/Notch ligands expressed in arterial endothelium

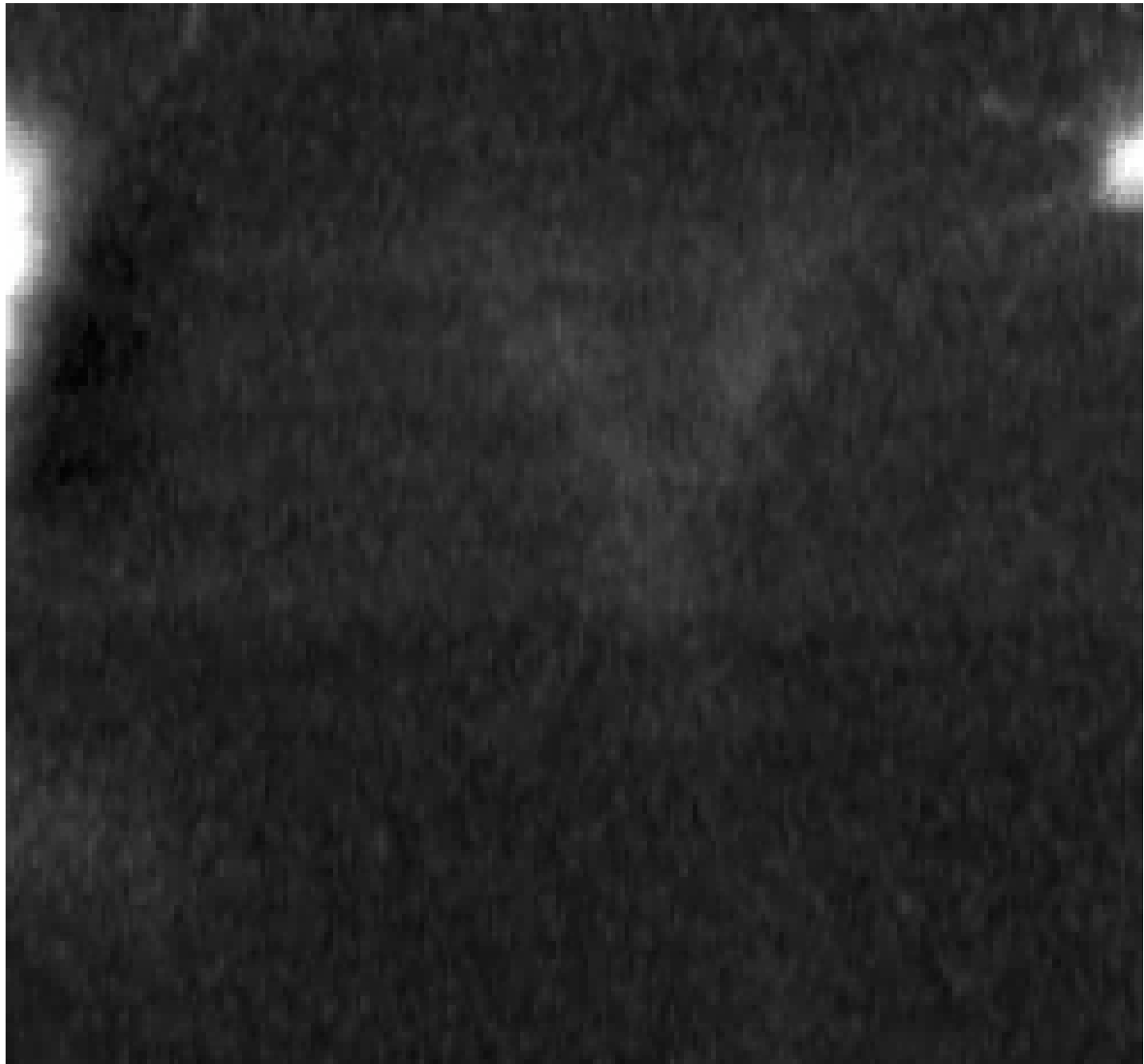


Angiogenesis - Basement Membrane Breakdown

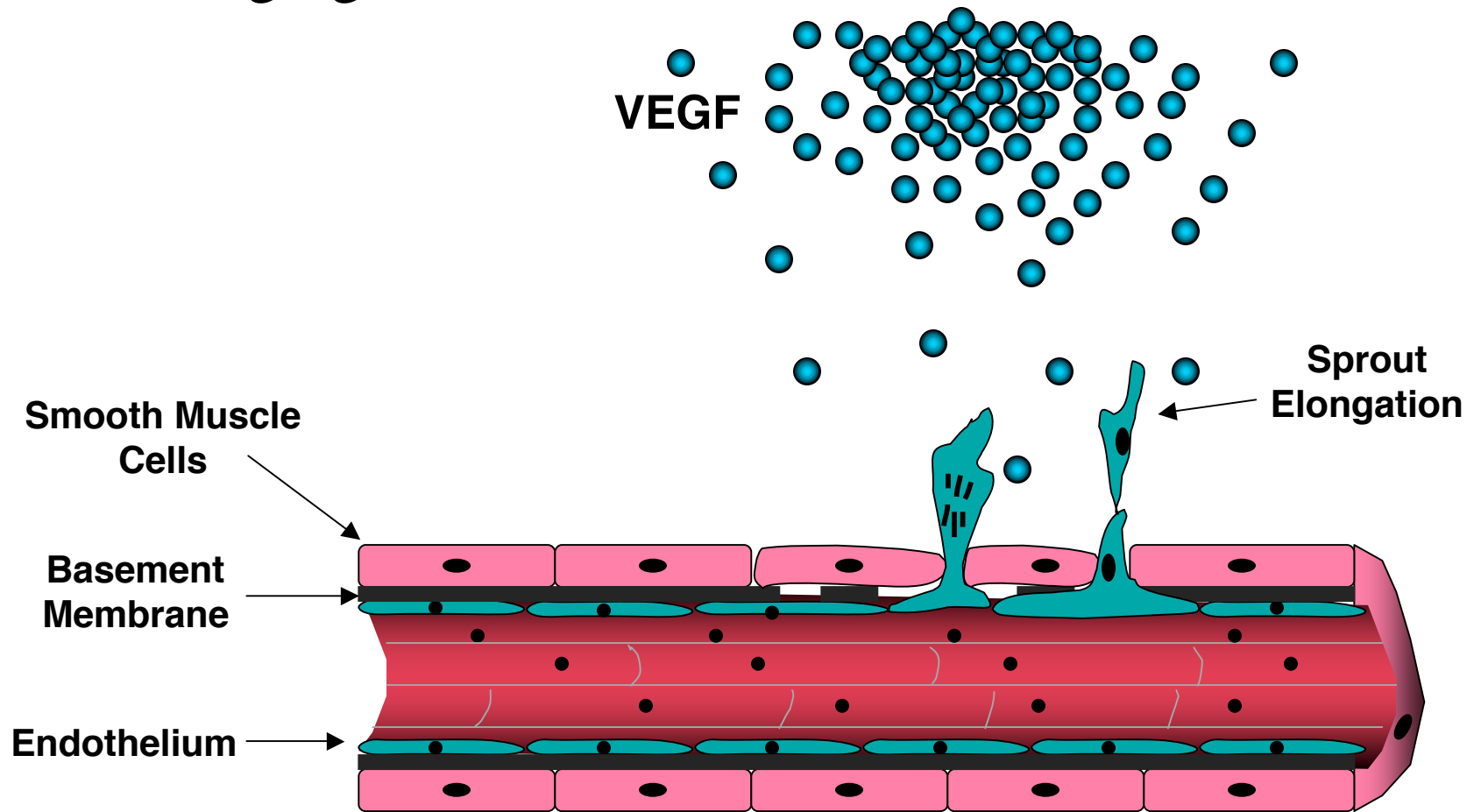


Angiogenesis - Endothelial Cell Migration

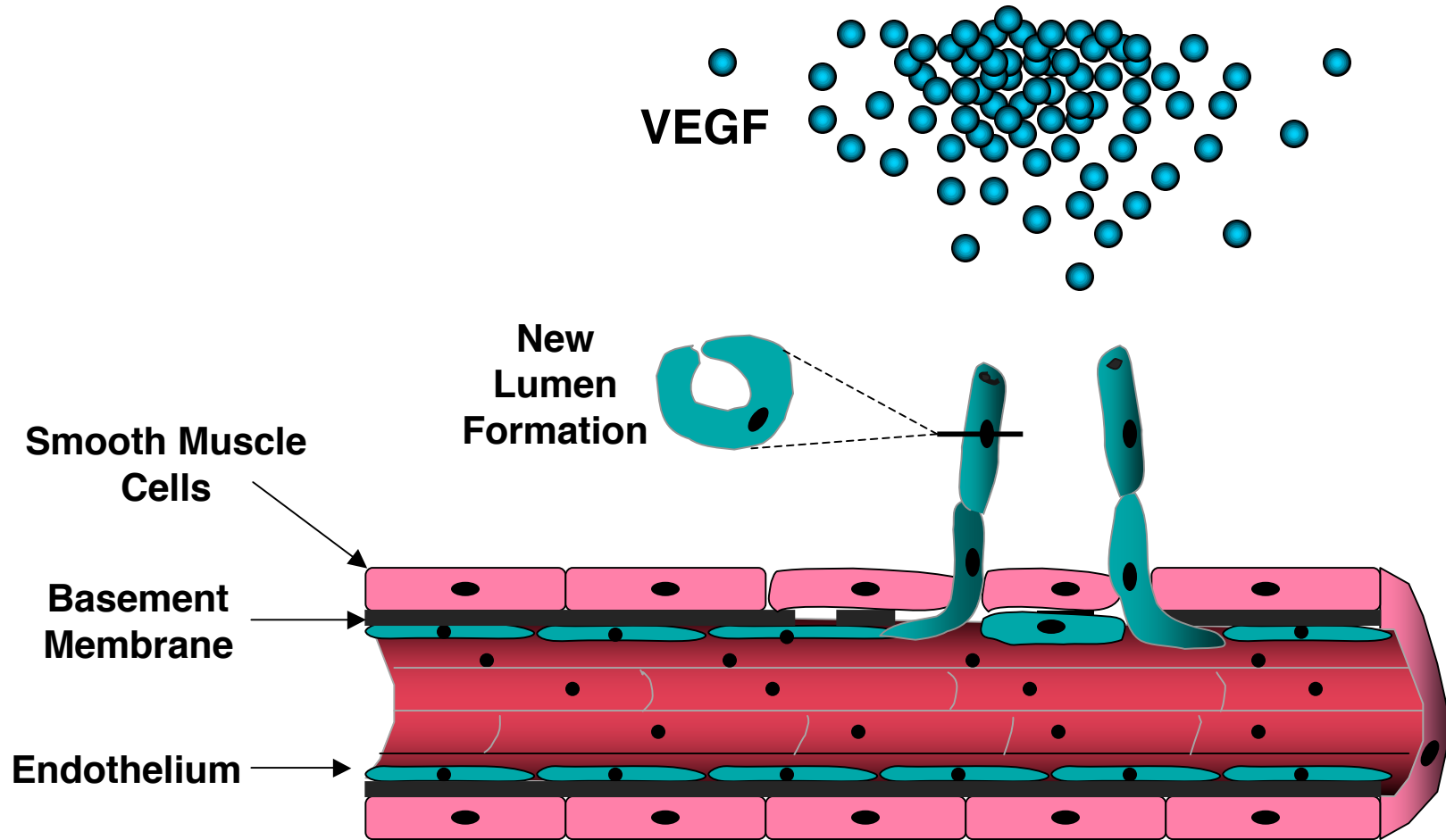


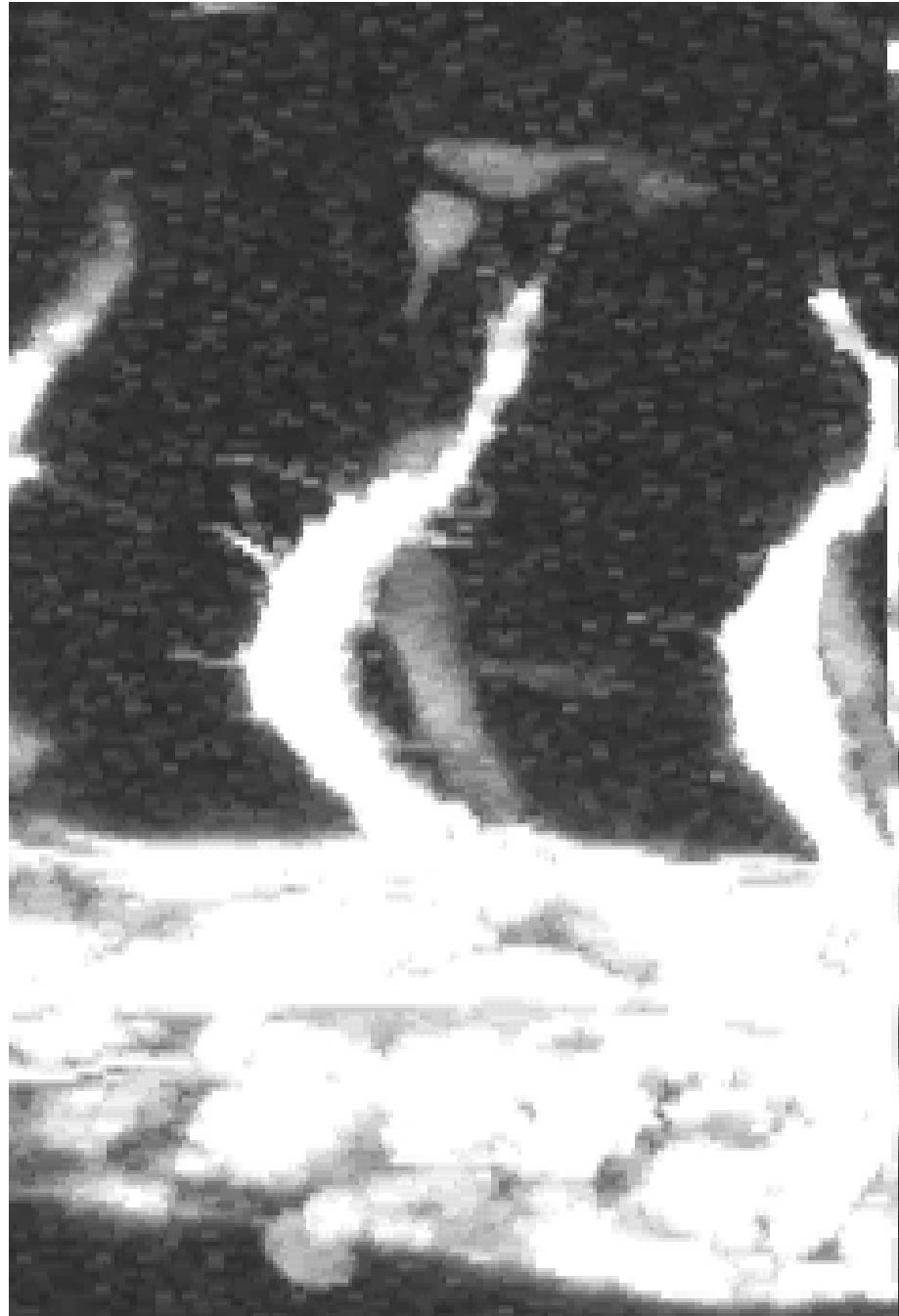


Angiogenesis - Endothelial Cell Proliferation

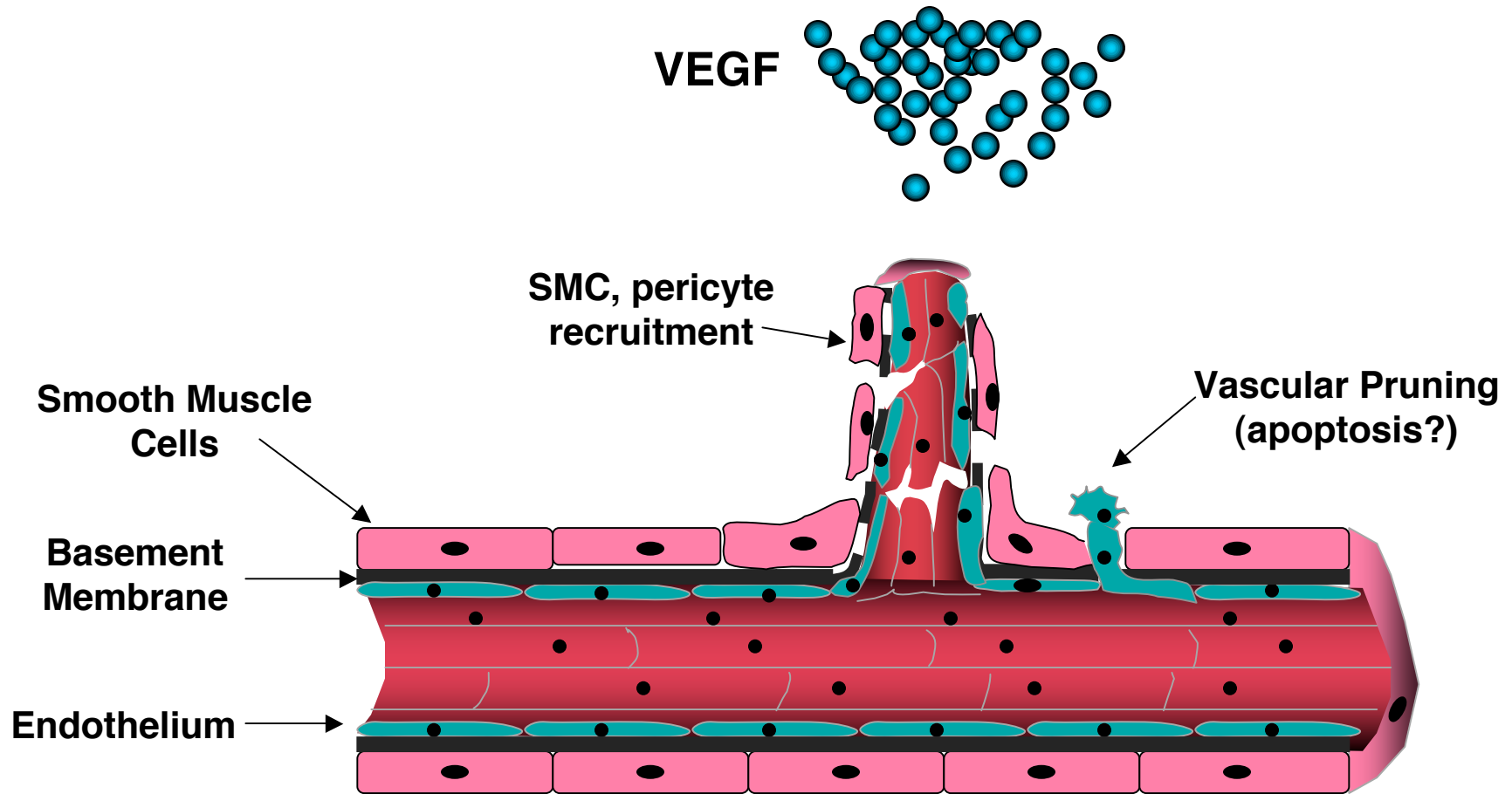


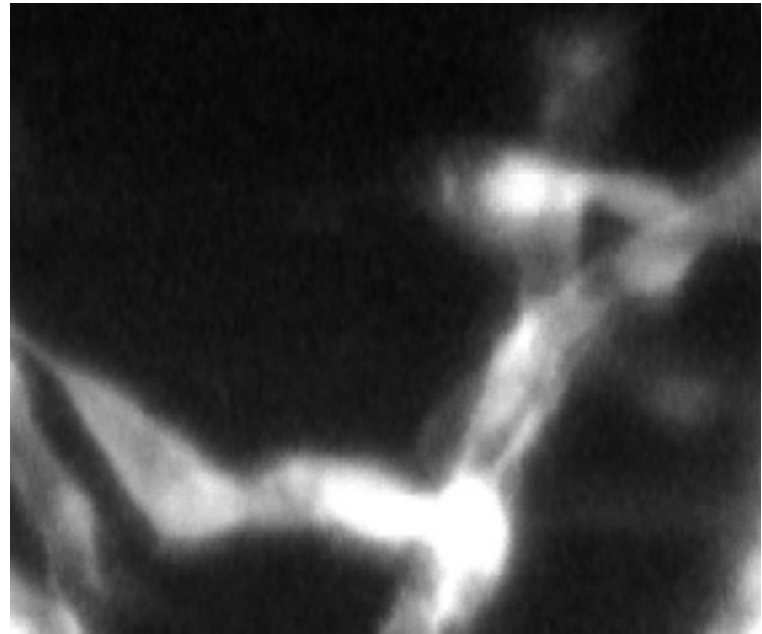
Angiogenesis - Capillary Morphogenesis



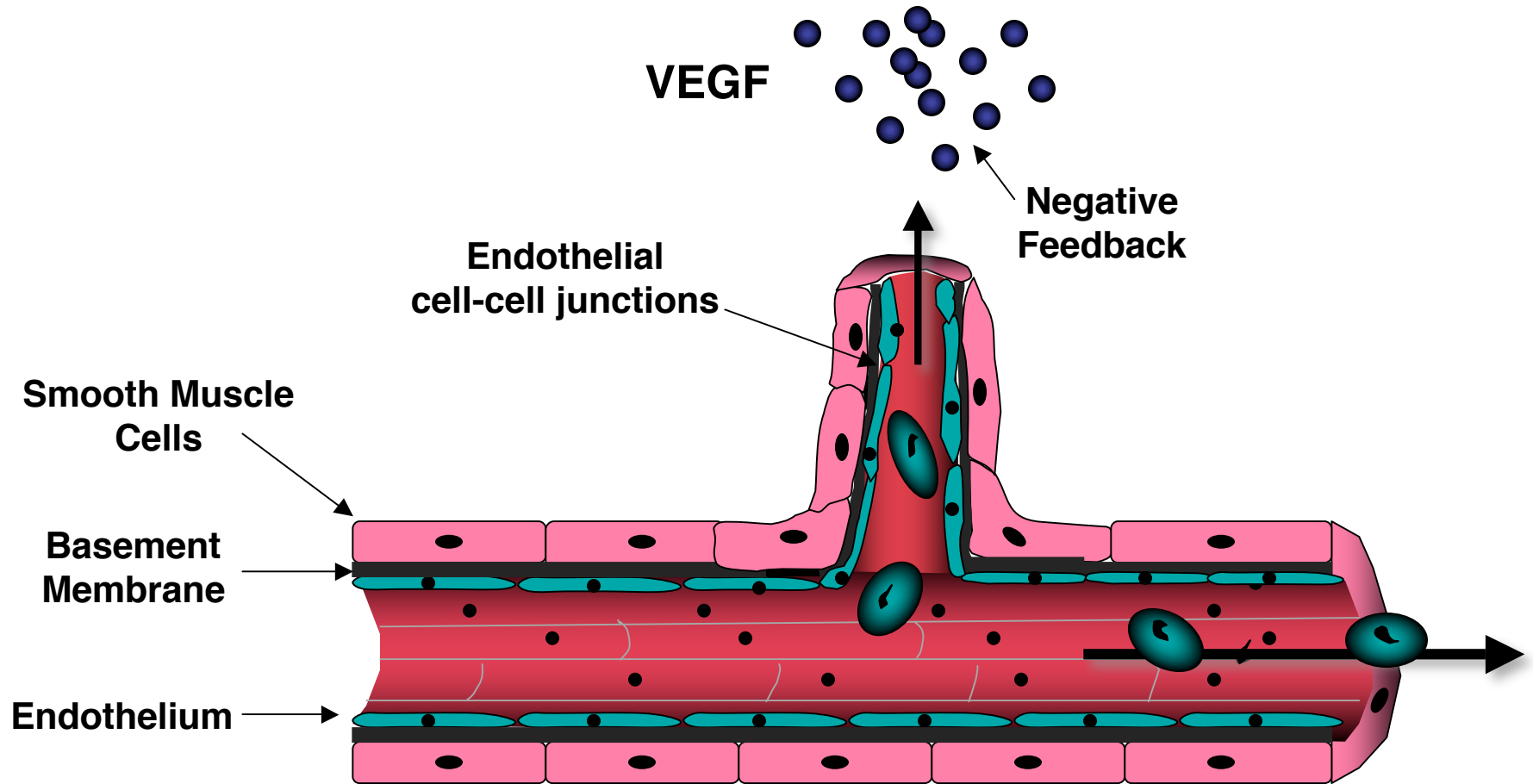


Angiogenesis - Vascular Maturation

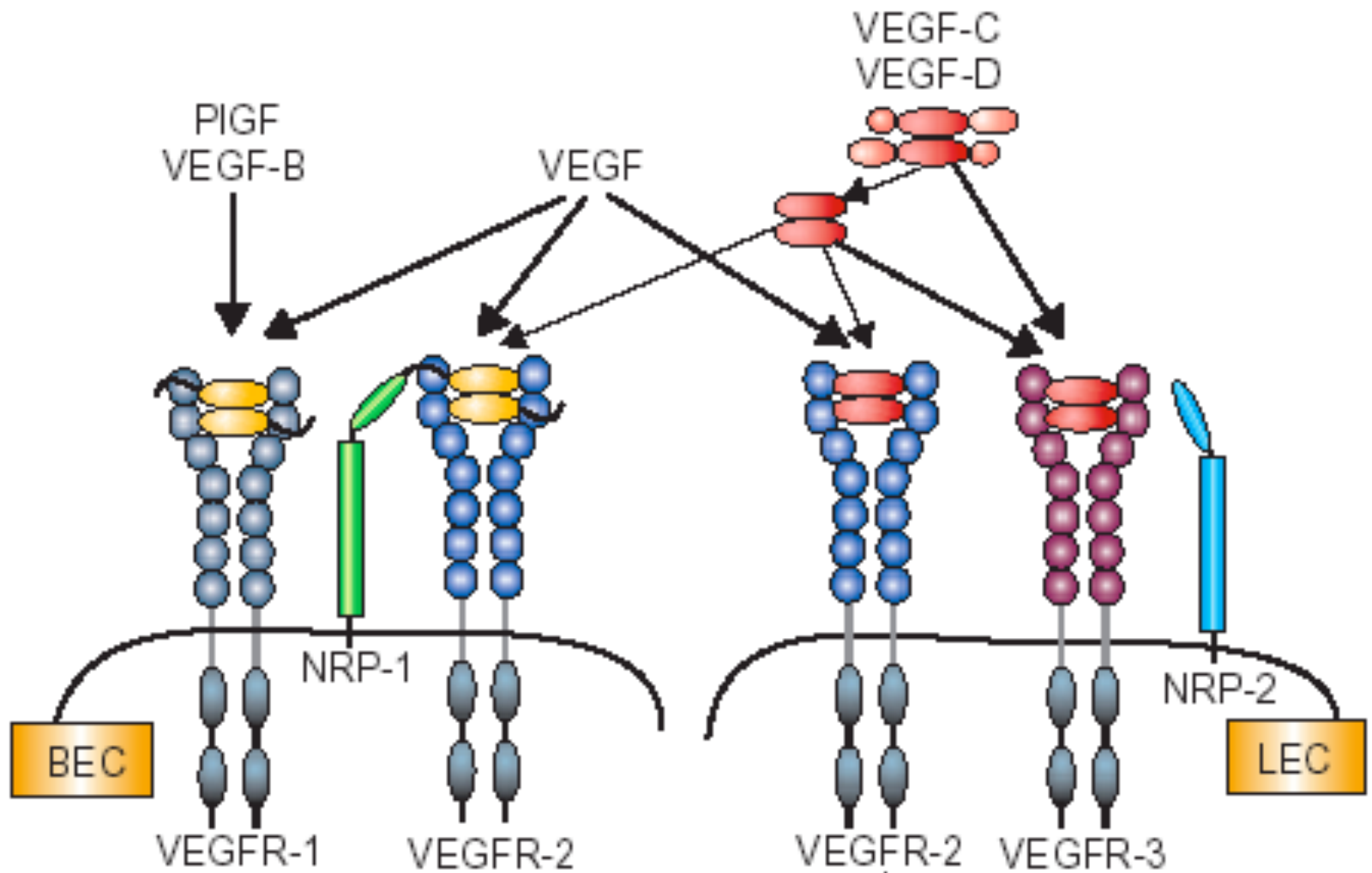




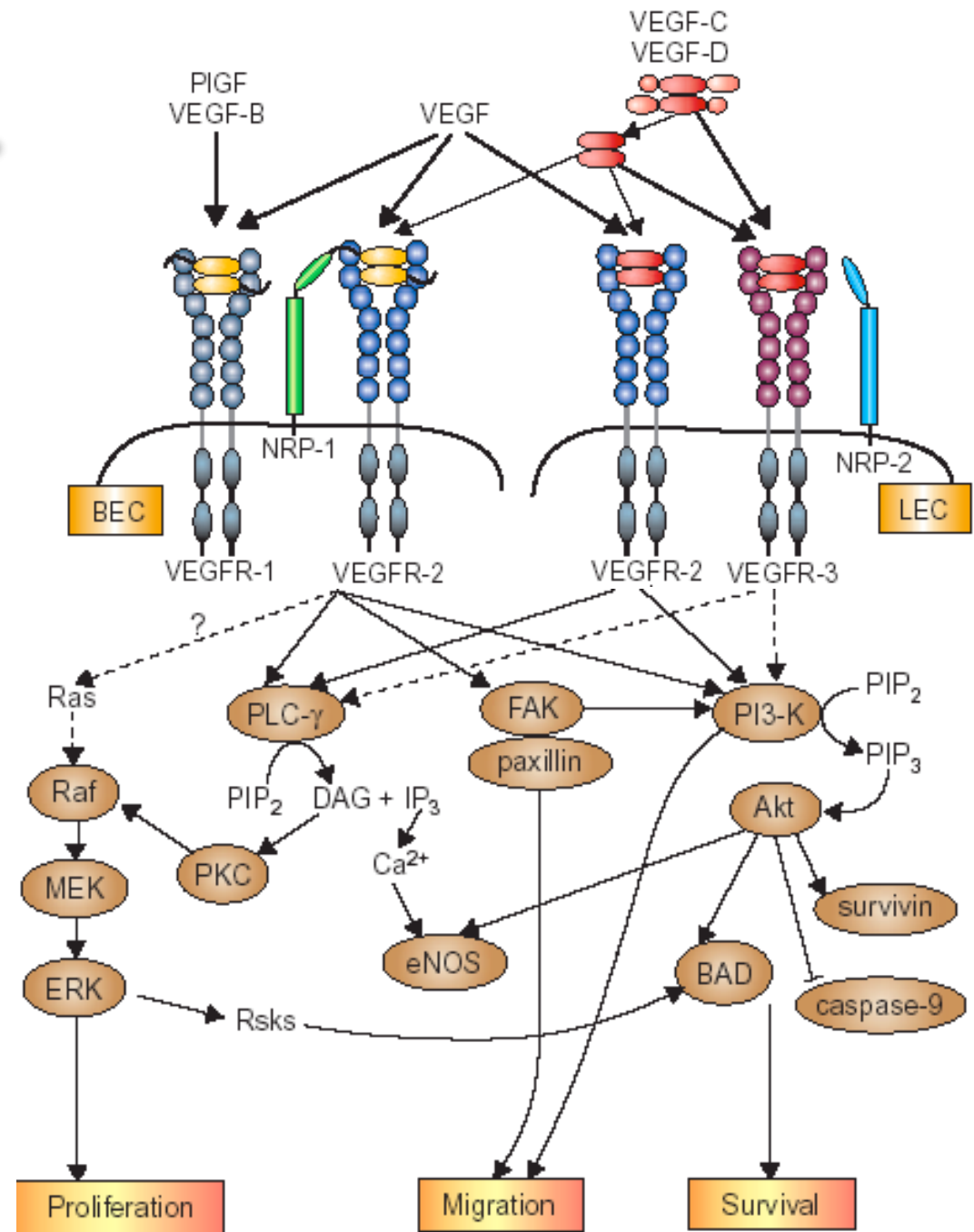
Angiogenesis - Vascular Maturation

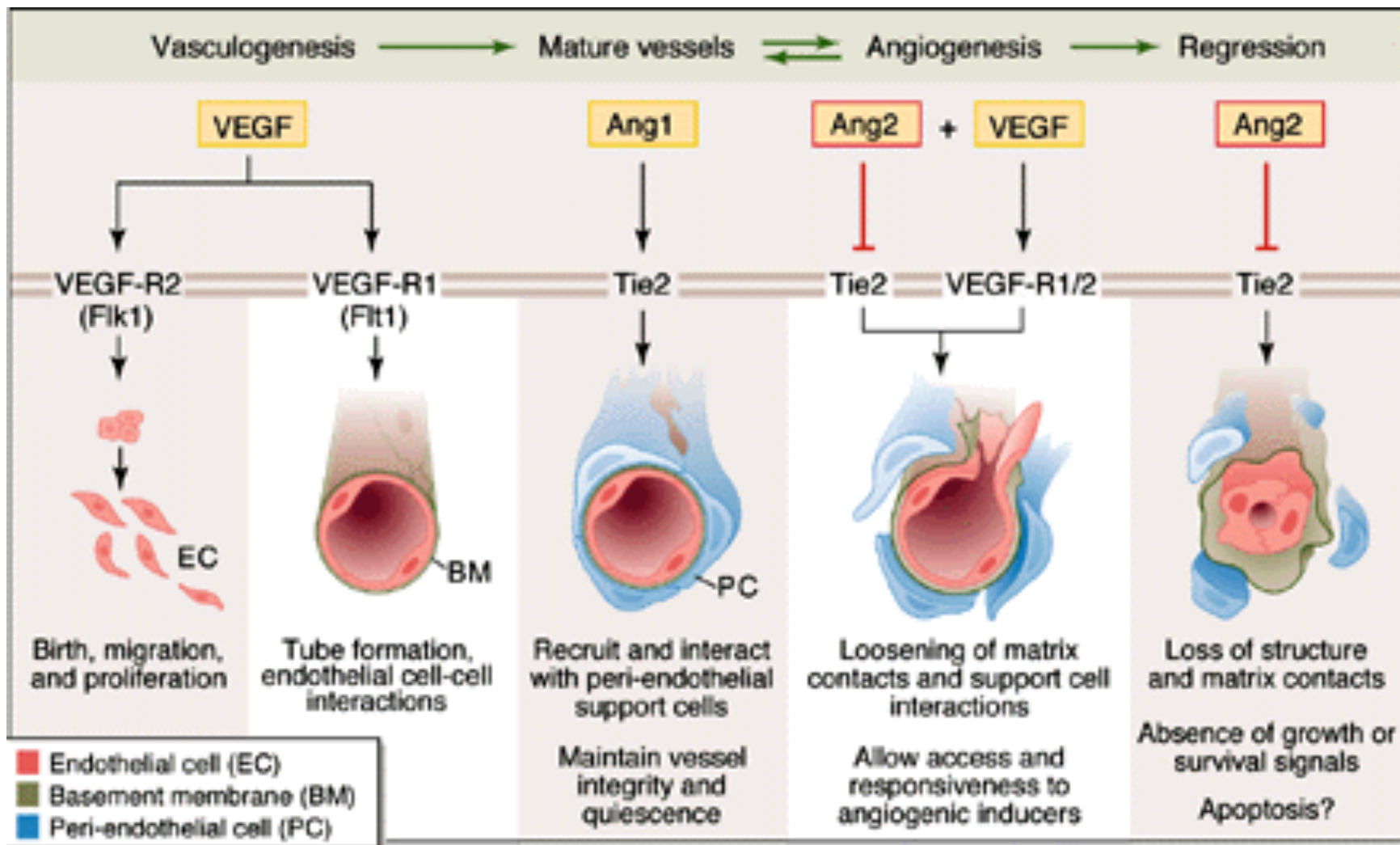


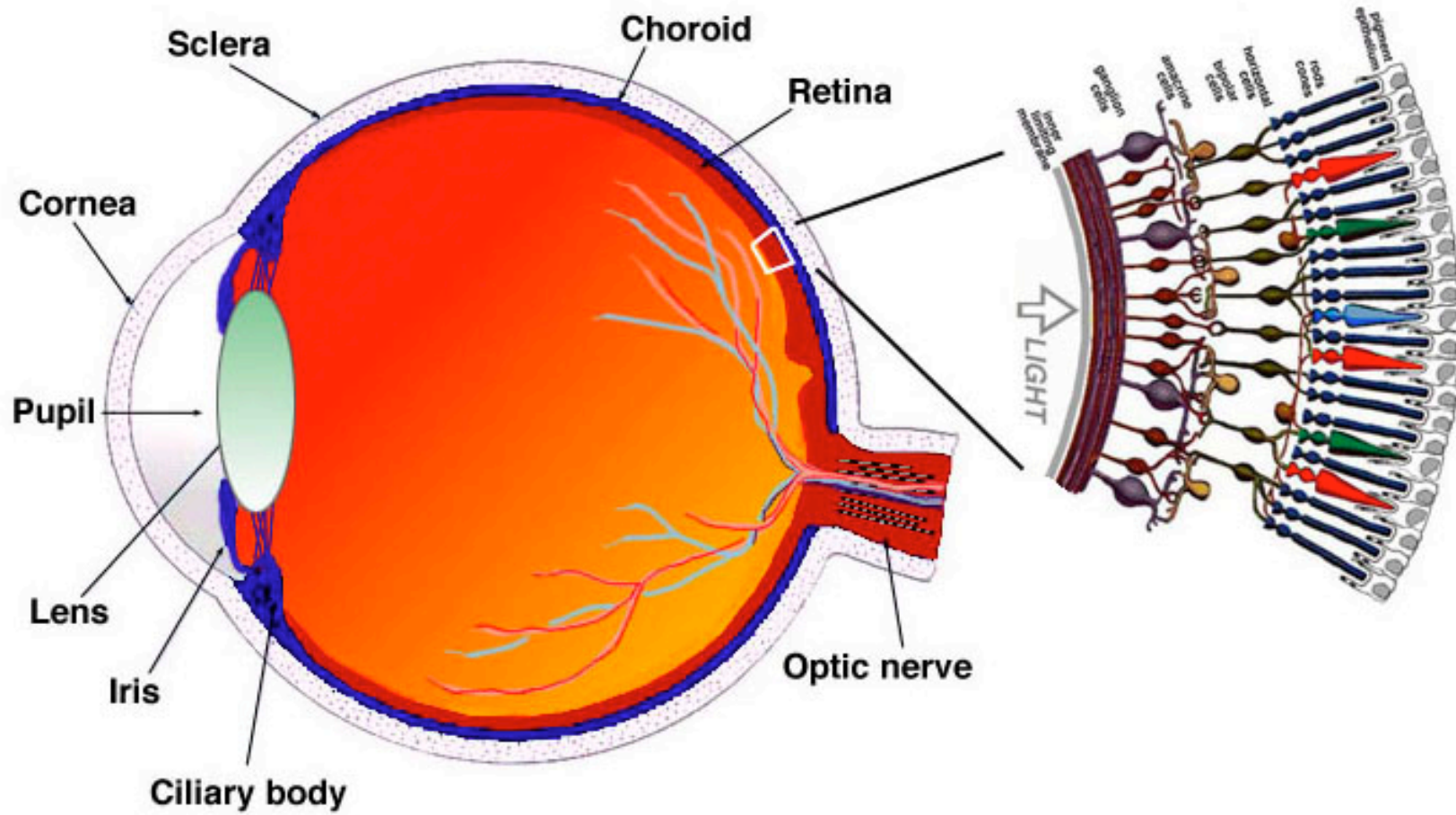
VEGF and VEGF Receptors

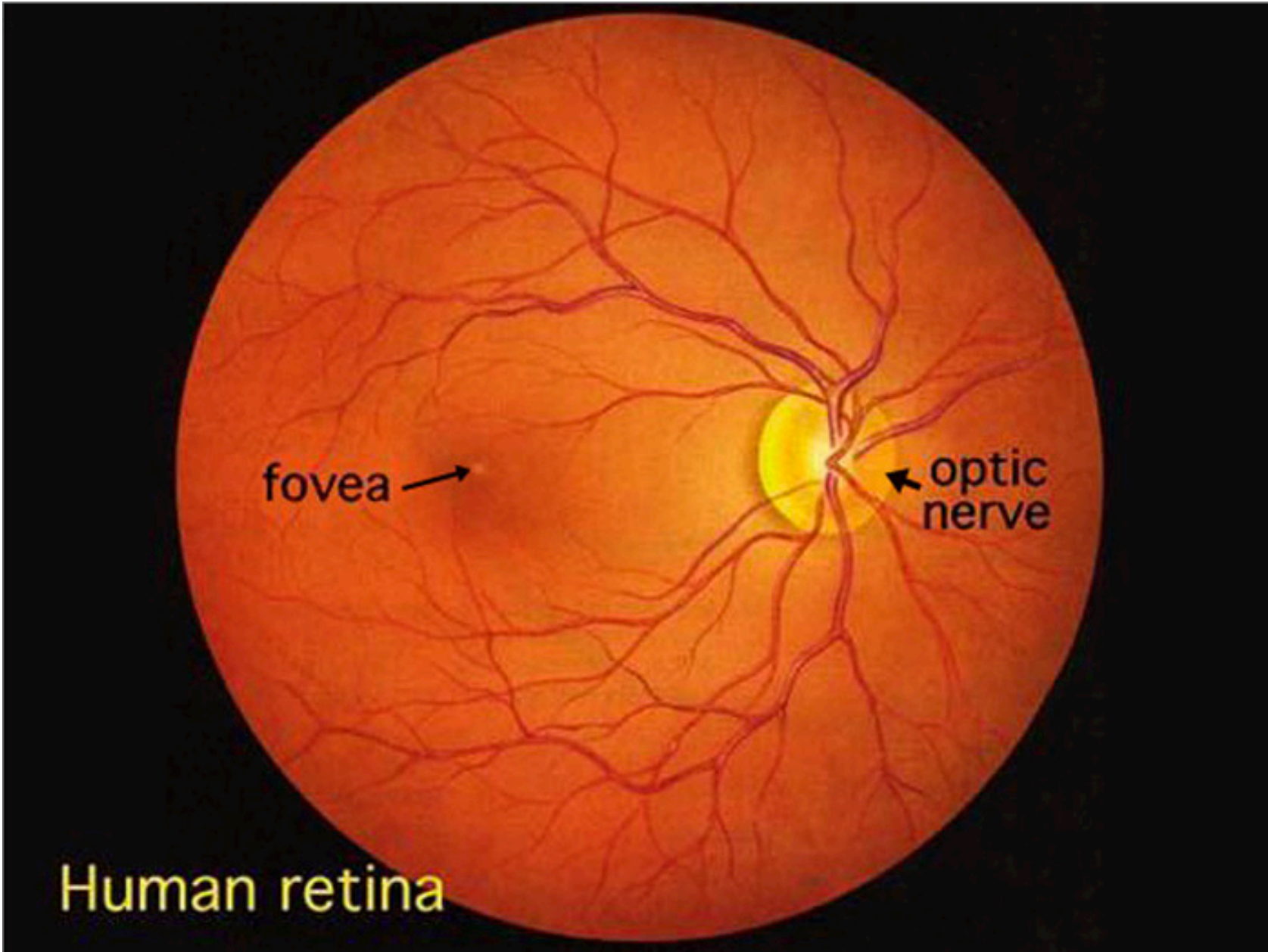


VEGF-receptor signaling









fovea →

← optic
nerve

Human retina

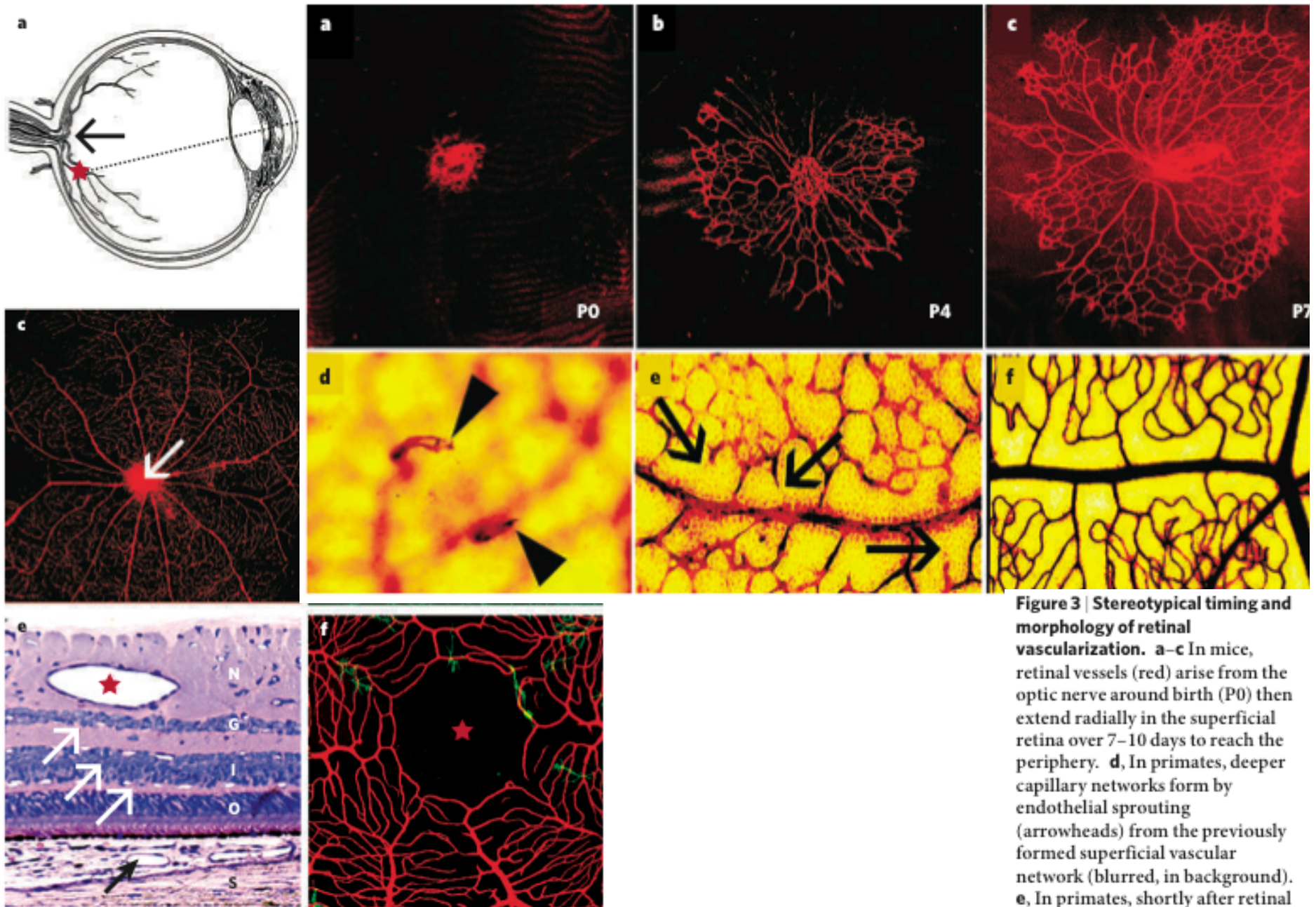
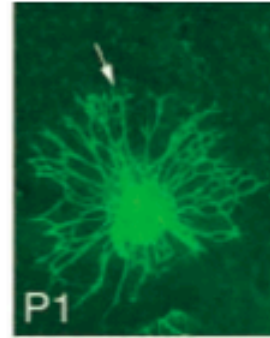
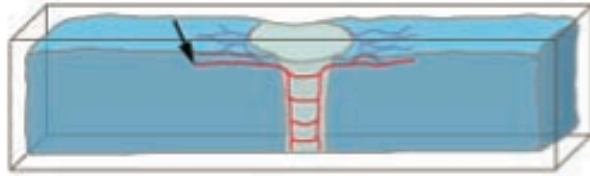


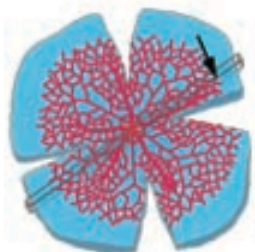
Figure 3 | Stereotypical timing and morphology of retinal vascularization. **a–c** In mice, retinal vessels (red) arise from the optic nerve around birth (P0) then extend radially in the superficial retina over 7–10 days to reach the periphery. **d**, In primates, deeper capillary networks form by endothelial sprouting (arrowheads) from the previously formed superficial vascular network (blurred, in background). **e**, In primates, shortly after retinal vessels form, capillary segments adjacent to nascent arteries (arrows) retract, to yield a periarterial capillary-free zone.



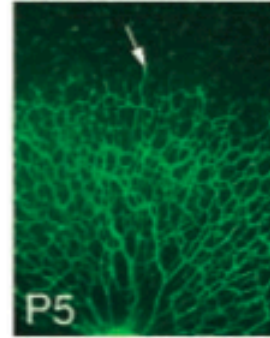
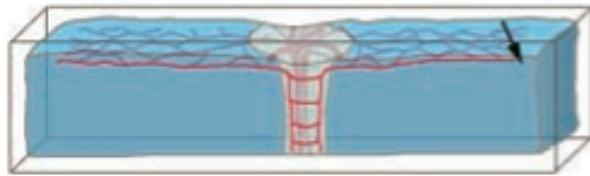
P1



P1



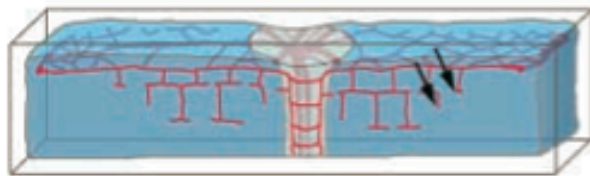
P5



P5



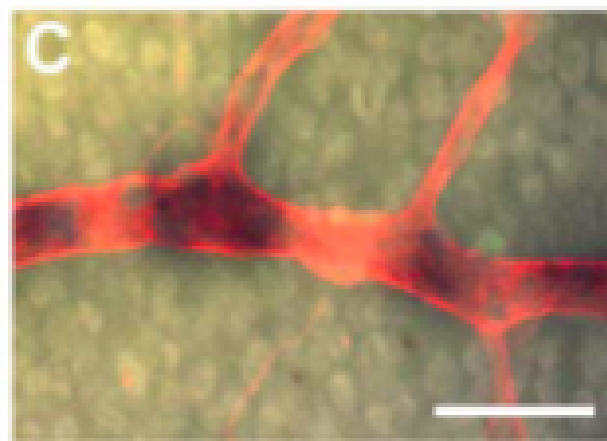
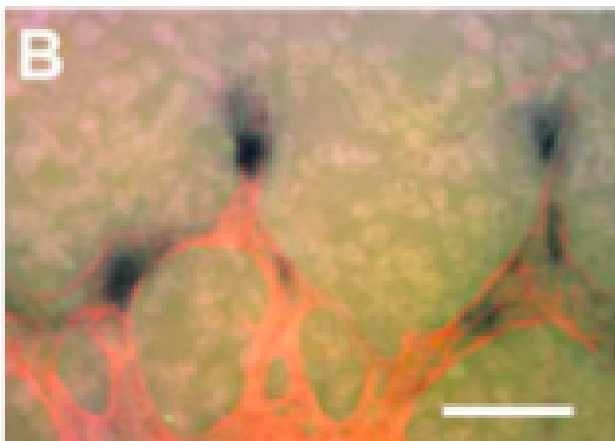
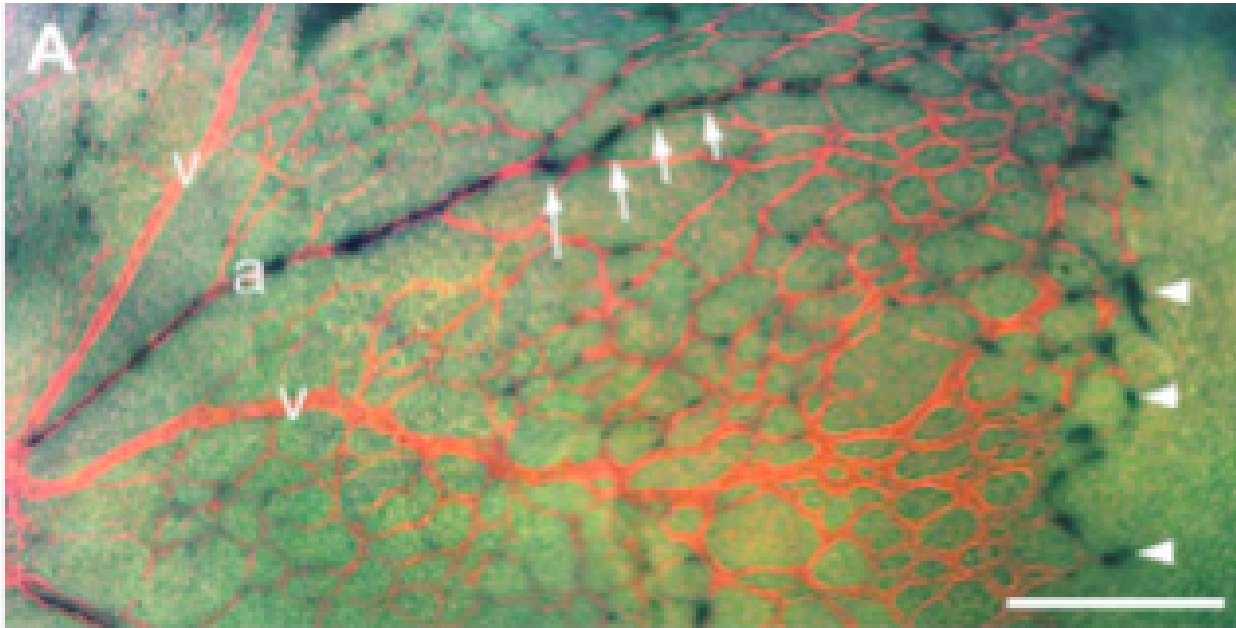
P8



P8

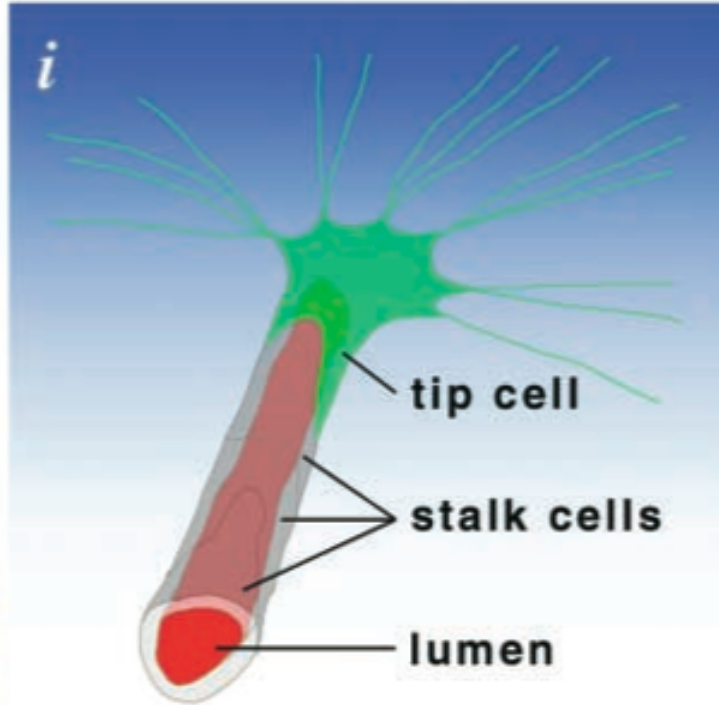
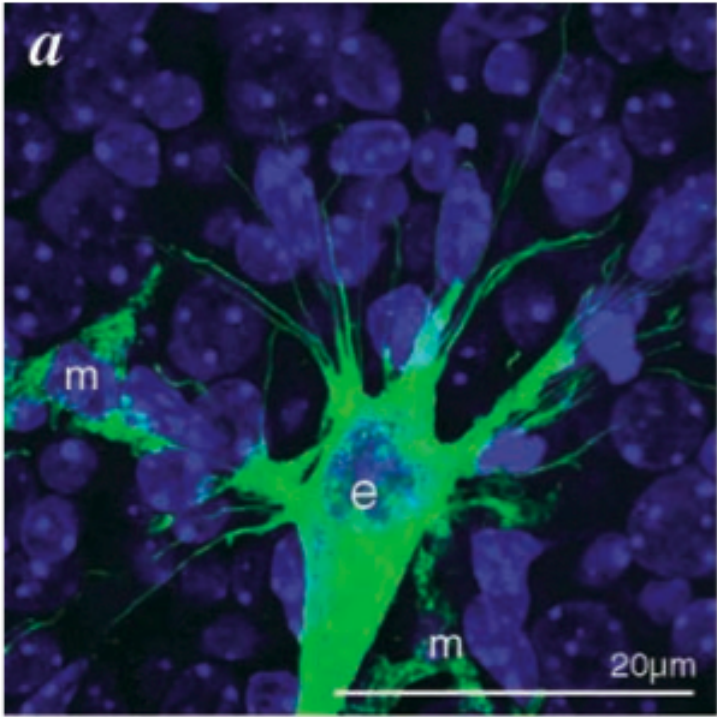
Delta4 expressed in retinal vasculature

arterial expression *tip cell expression*



in situ hybridization

Fruttinger, 2004



Normal intraretinal vasculature

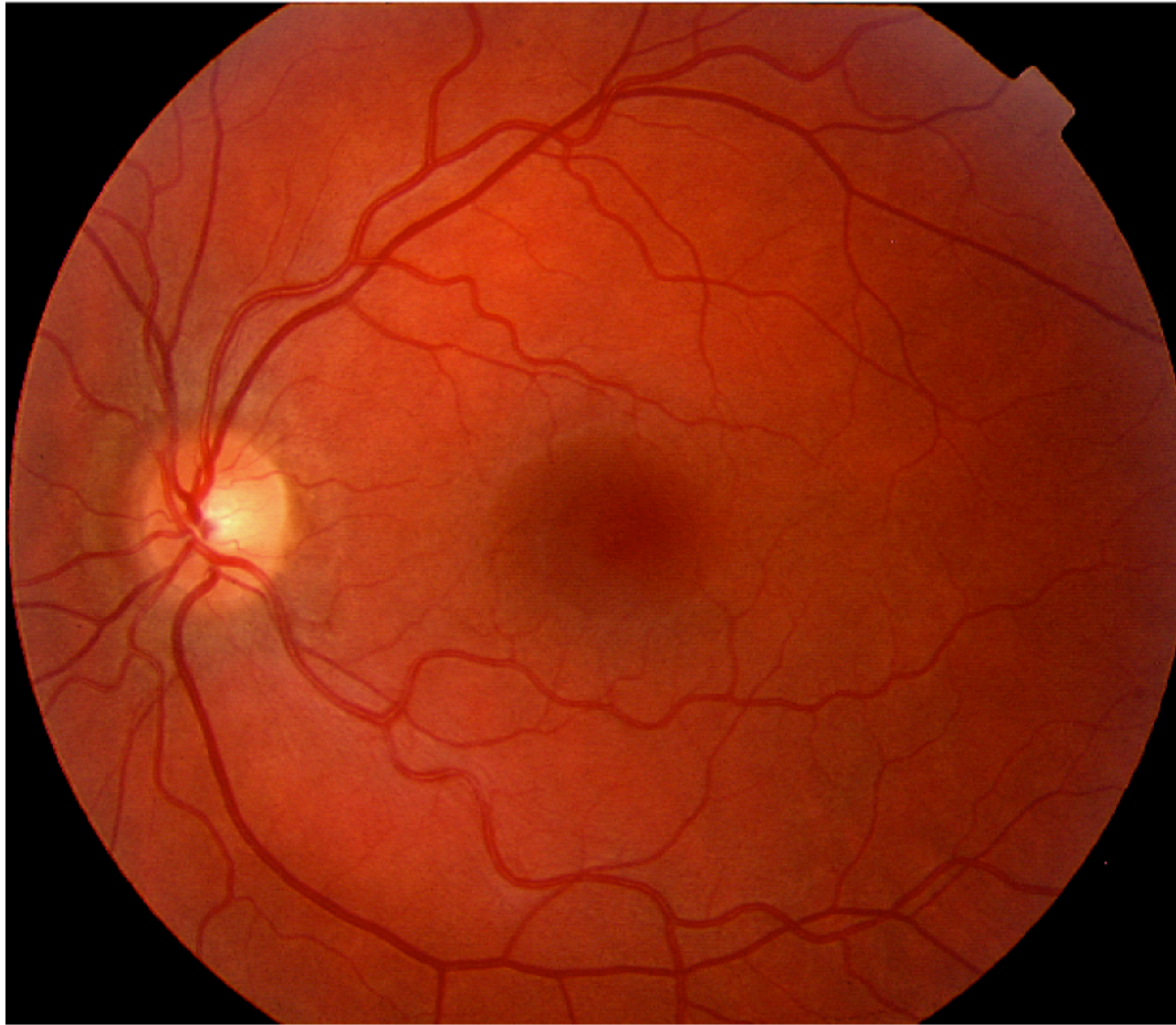
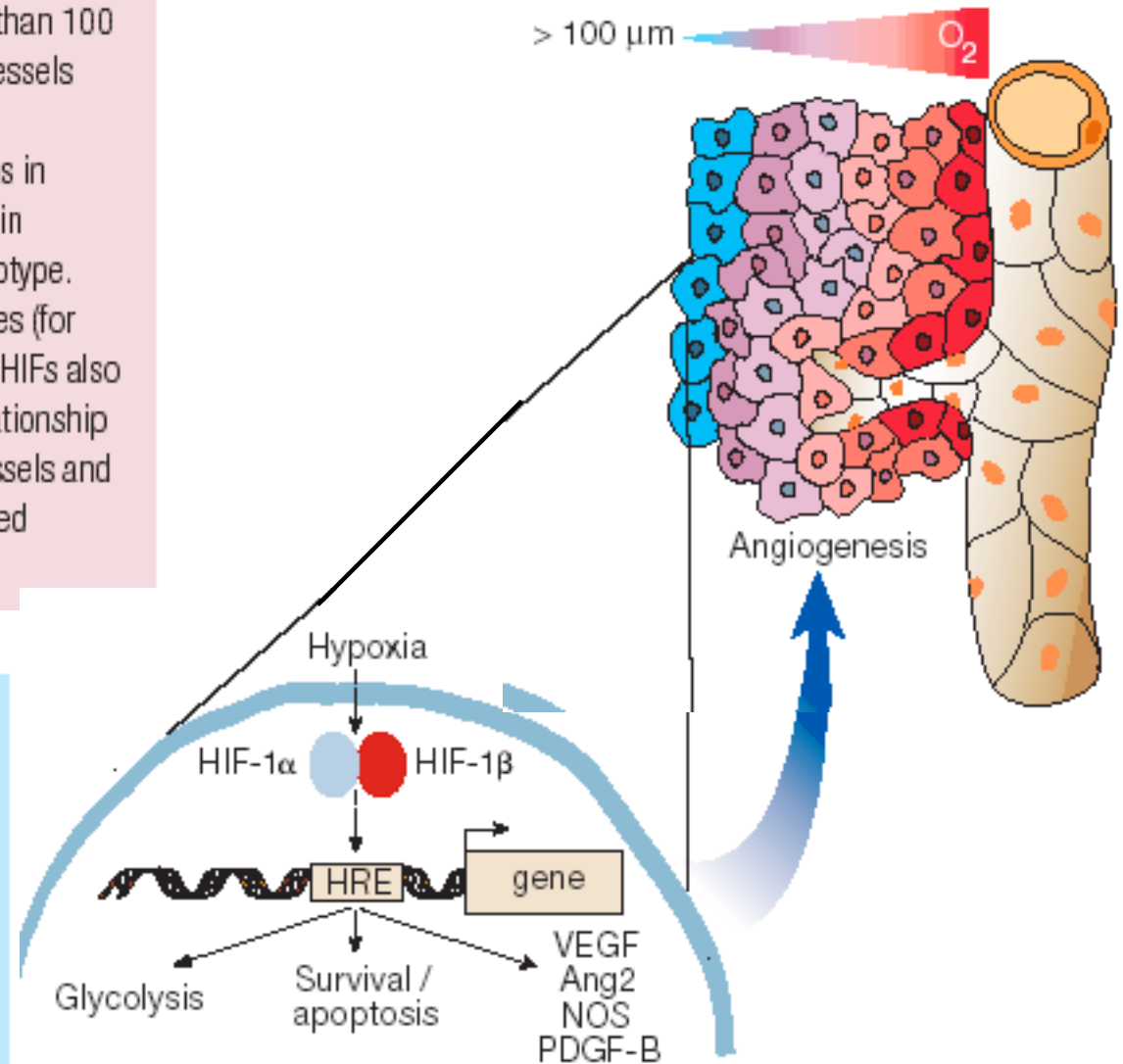
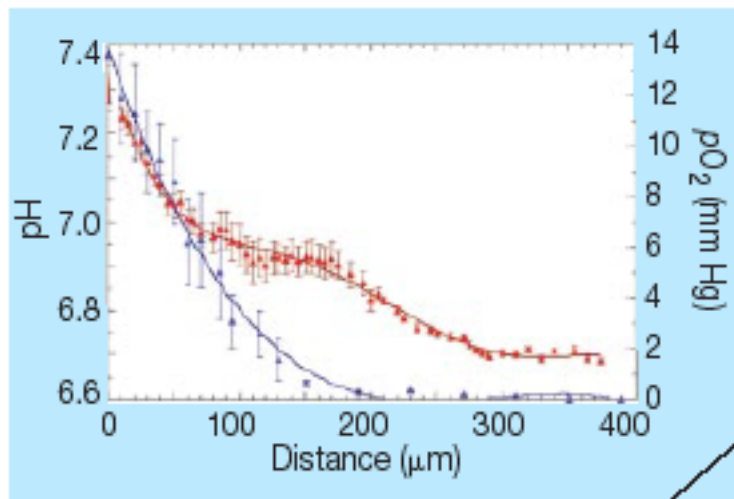


Figure 2 Role of hypoxia in tumour angiogenesis. Because of the irregular pattern and organization of the tumour vasculature, some cells in tumours are located more than 100 μm (the diffusion limit for oxygen) away from blood vessels and become hypoxic (red-to-blue gradient indicates progressive hypoxia). Tumour cells survive fluctuations in oxygen tensions, in part because clones are selected in hypoxic tumours that switch to a proangiogenic phenotype. HIFs increase transcription of several angiogenic genes (for example, genes encoding VEGF, PDGF-BB and NOS). HIFs also affect cellular survival/apoptosis pathways. Inset: relationship between the distance of tumour cells from nearby vessels and their degree of hypoxia (blue symbols) and acidosis (red symbols)²⁴.



Retinopathy of Prematurity

L.E.H. Smith / *Growth Hormone & IGF Research* 14 (2004) S140–S144

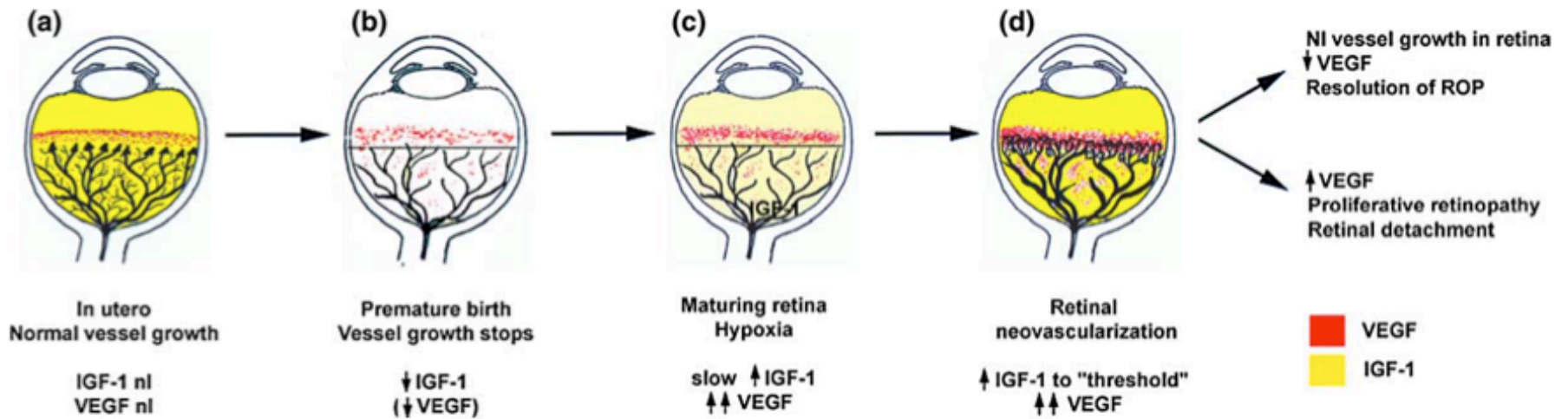
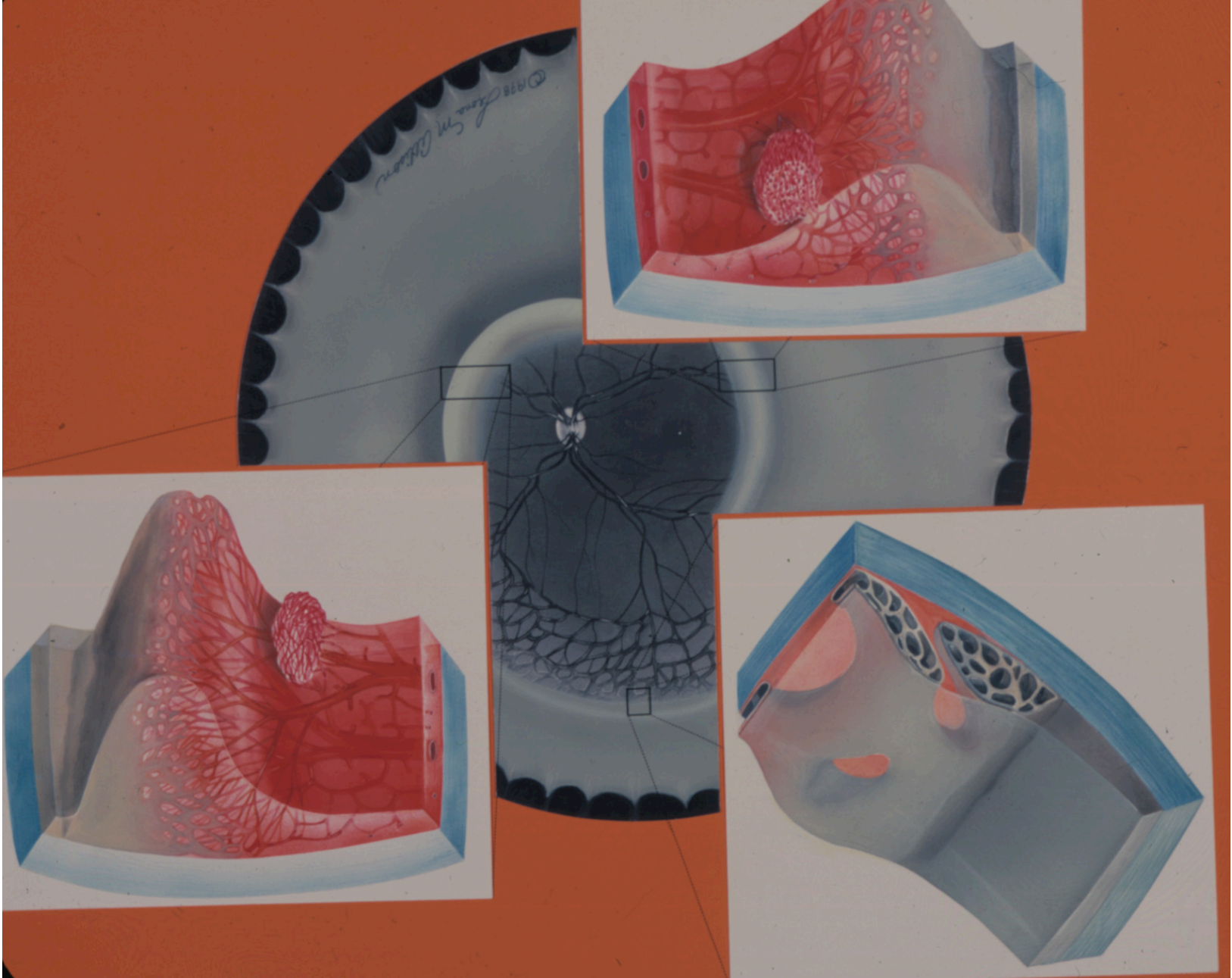


Fig. 1. Mechanism for retinopathy of prematurity (ROP) (Reprinted, with permission, from [37]).



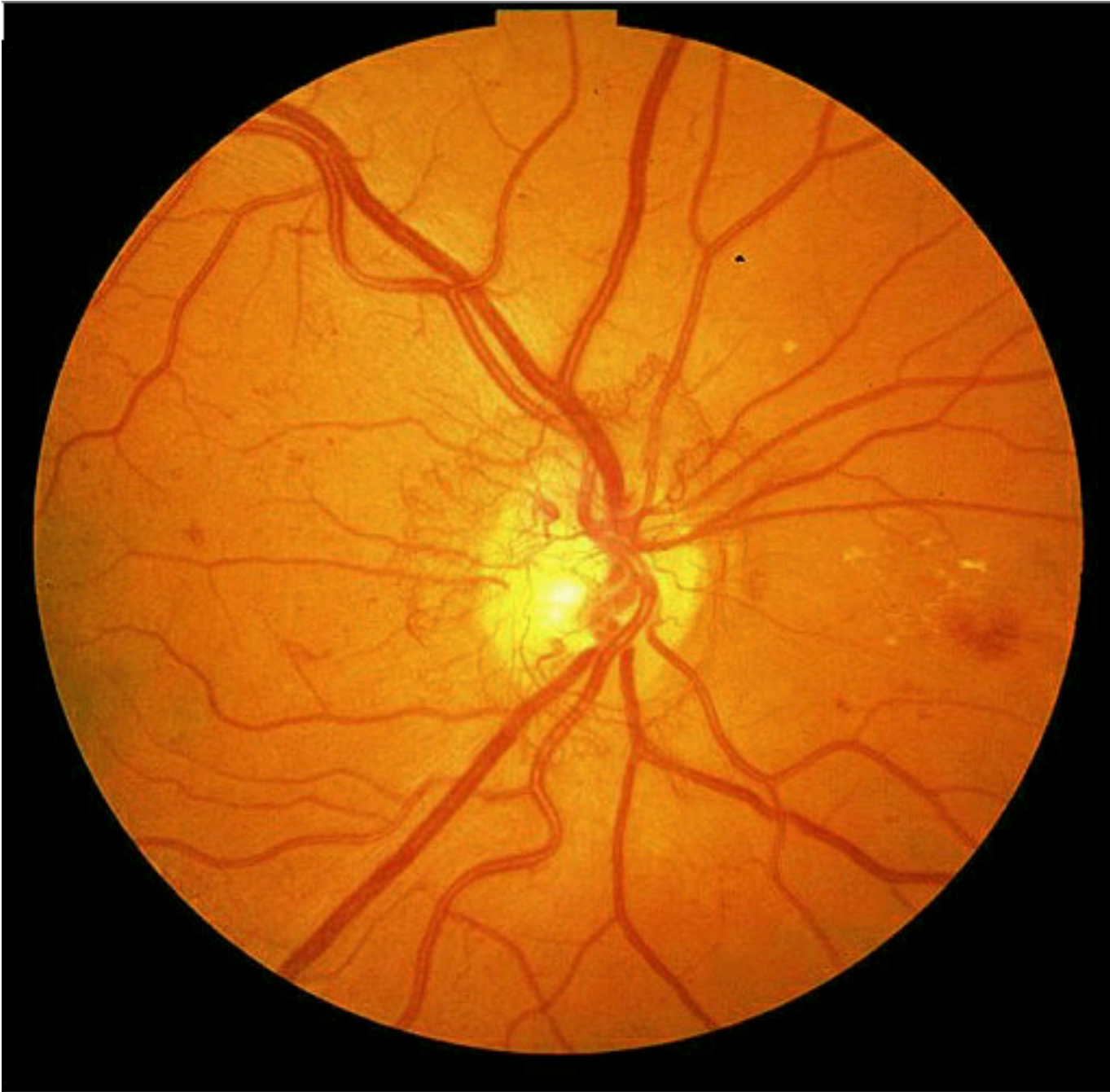
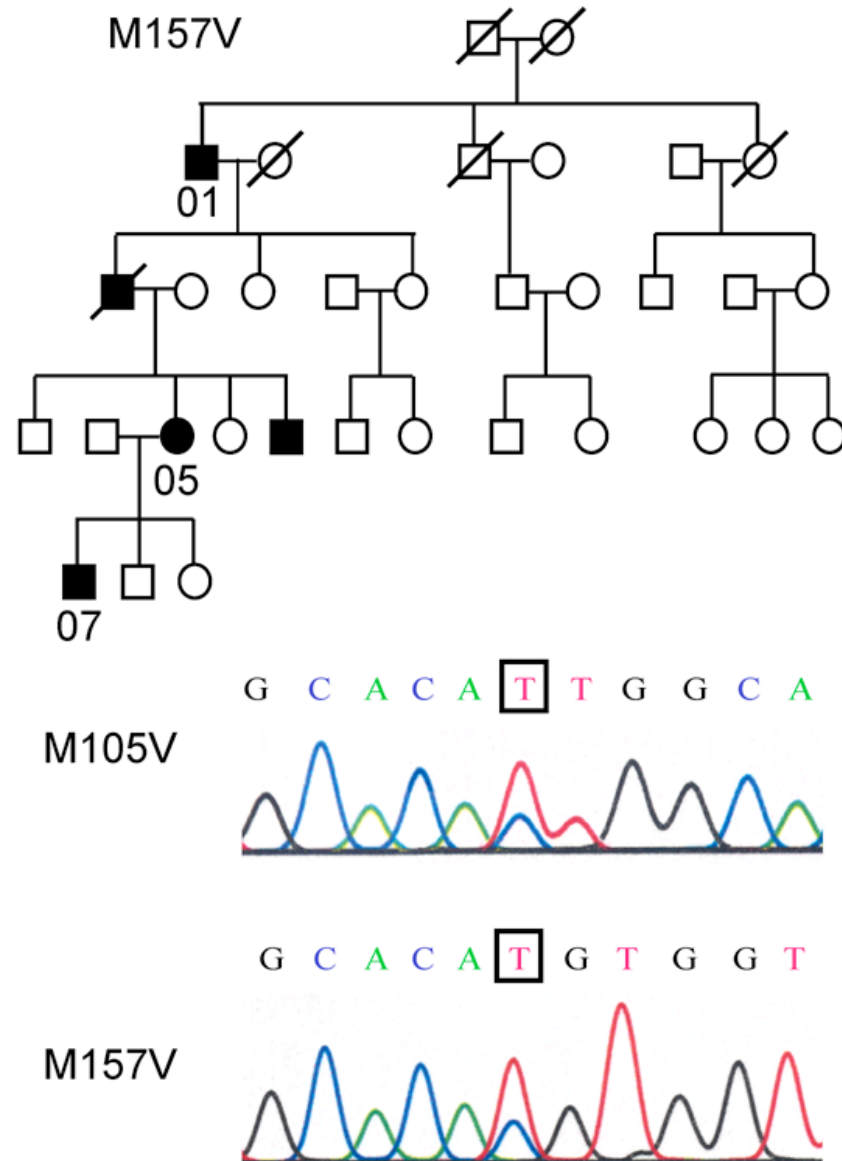


Fig. 25. A view of the fundus of the eye and of the retina in a patient who has advanced diabetic retinopathy.

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

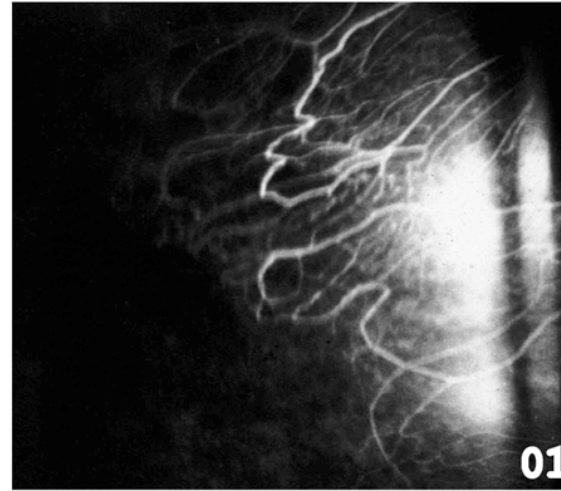
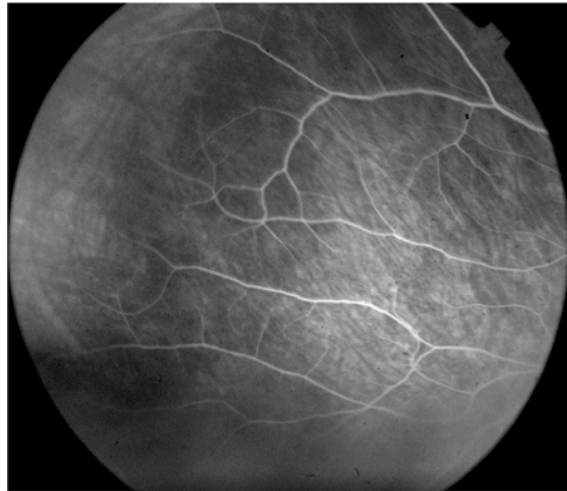
Autosomal dominant
FEVR mutations
In the cysteine-rich
domain (CRD) of Fz4



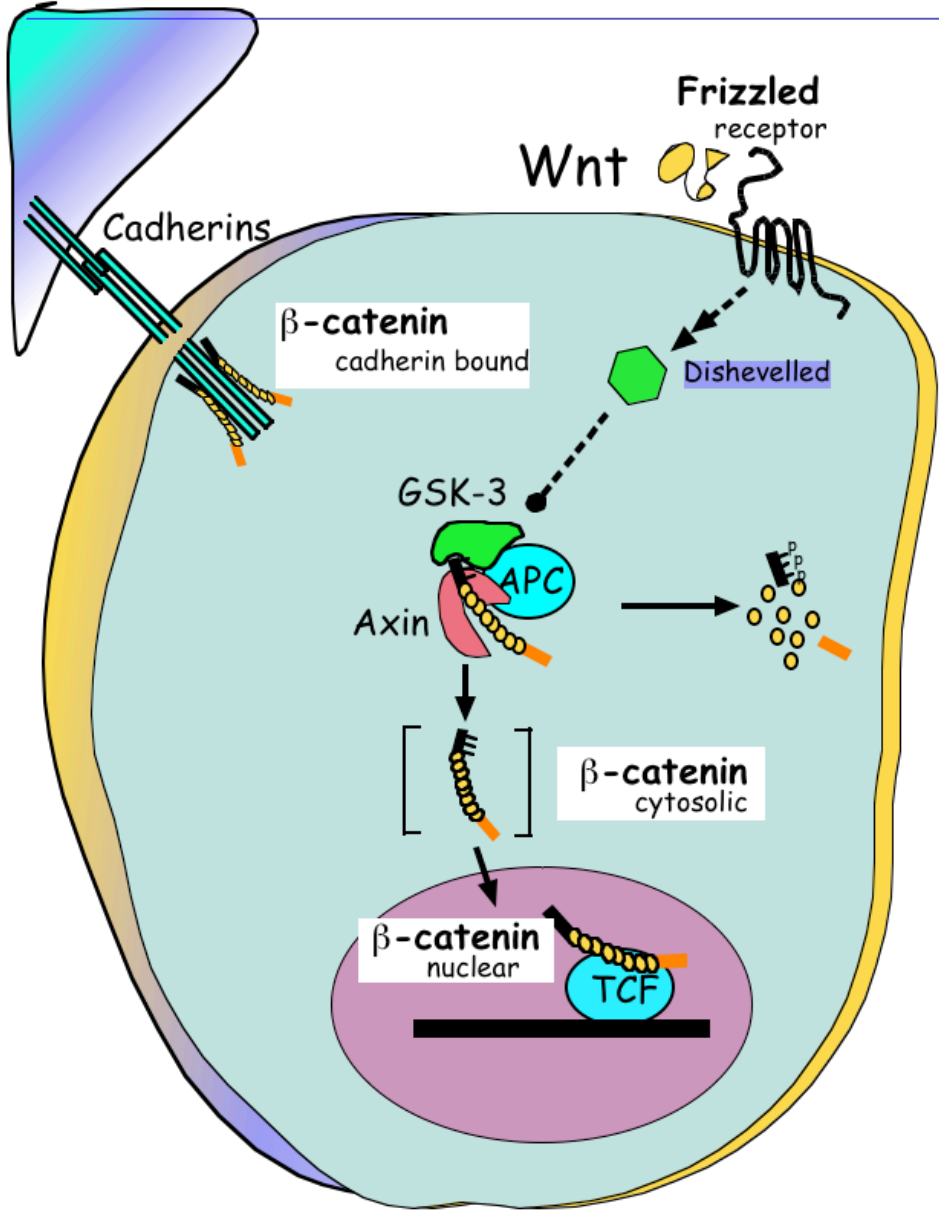
Retinal defects in FEVR patients heterozygous for Fz4 M157V

Normal

hFz4(+/-)



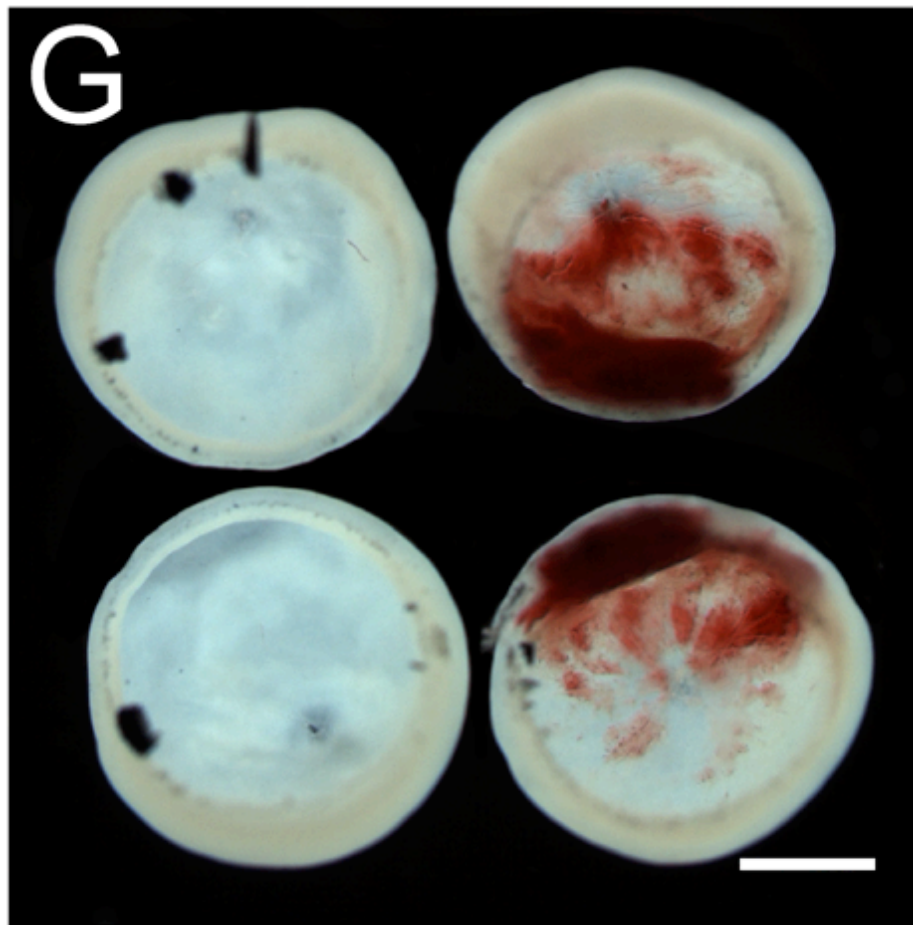
Frizzled-4 is a Wnt receptor



Intraocular hemorrhage in Fz4(-/-) mice

WT

-/-

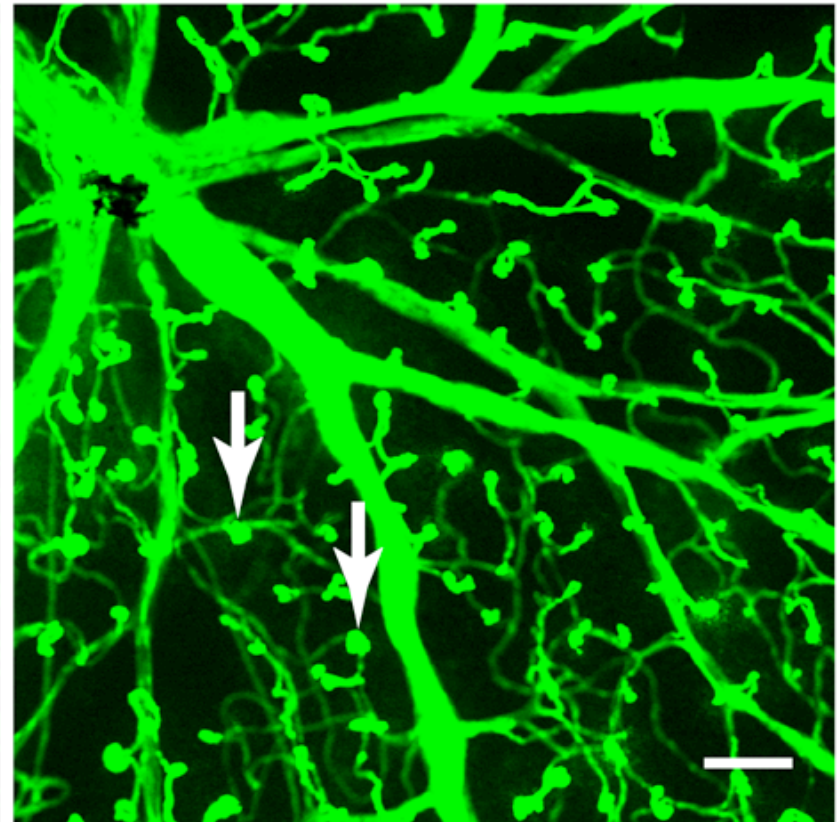
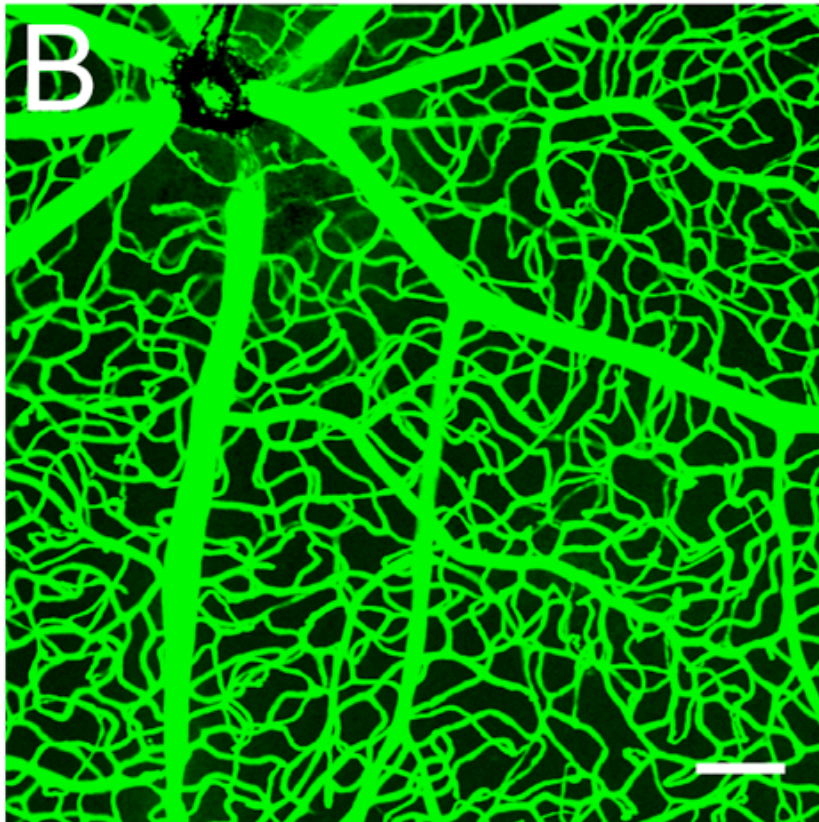


Absence of intra-retinal capillaries in Fz4(-/-) mice

WT

-/-

Outer IPL

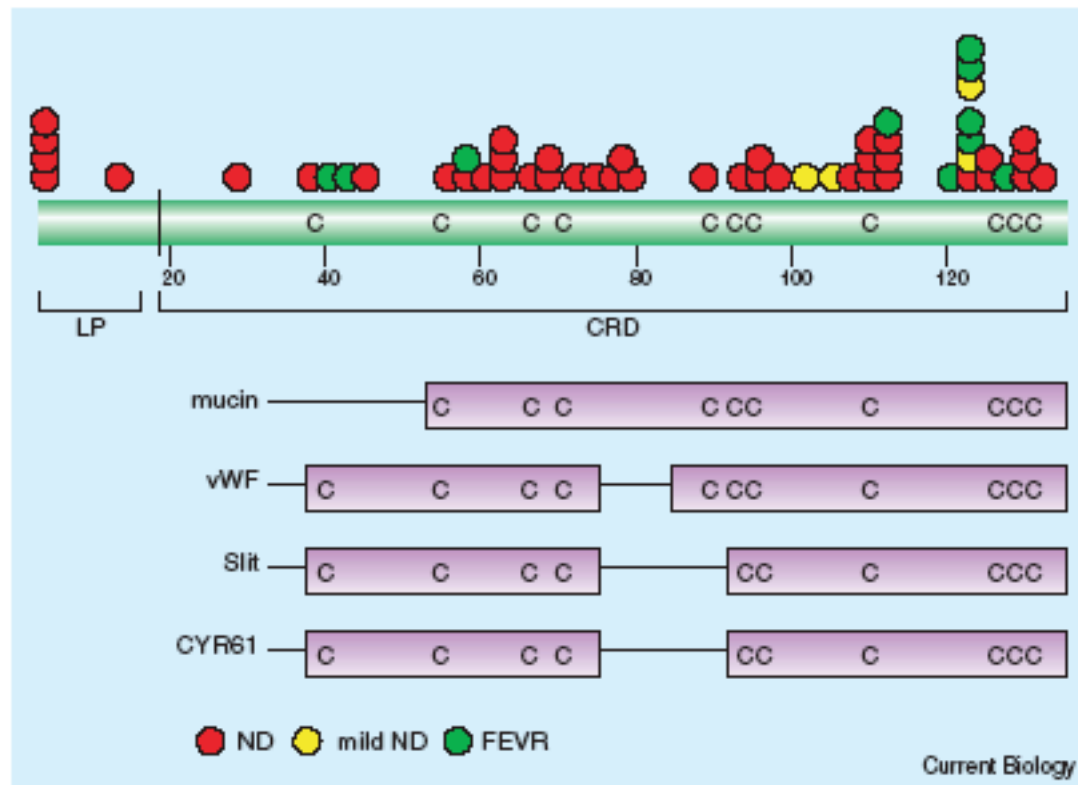


Norrie Disease

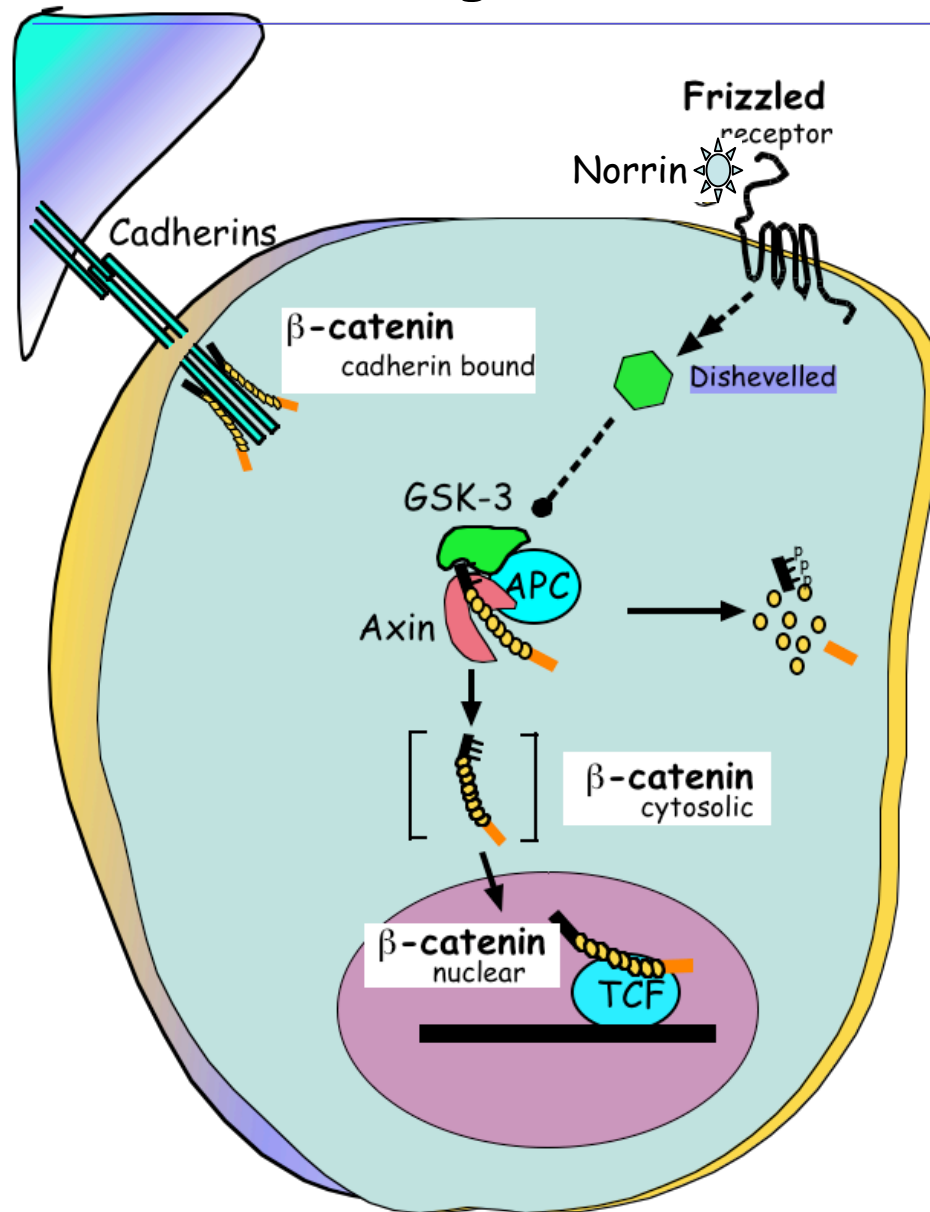
- First described by Norrie (1927) and analyzed systematically by Mette Warburg [Acta Ophthalmologica 39: 757-772 (1961); 41: 134-146 (1963); 89: 1-147 (1966)]
- X-linked recessive with variable phenotype
- Clinical characteristics
 - moderate vision loss to congenital blindness
 - retina: retinal folding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

Figure 1. The Norrin protein.

Missense and nonsense mutations in Norrin leading to classic or mild Norrie disease (ND) and to FEVR. Amino acid numbering is given on the scale below the protein. LP, leader peptide; CRD, cysteine-rich domain. The CRD is homologous to domains in the proteins indicated below (adapted from [1]).



Norrin is a ligand for Frizzled-4



Molecular genetics of Norrie Disease and FEVR

- FEVR

One autosomal dominant FEVR gene identified by Robitaille 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 disease

- Tumor angiogenesis
- Diabetic vascular complication
 - Diabetic retinopathy
 - Stroke
 - Ischemia
 - Wound repair
- Heart disease
- Obesity
- Blindness
 - Wet Macular Degeneration
 - Retinopathy of Prematurity

