
Angiogenesis
colon cancer
Alzheimer's disease
obesity
leukemia
alopecia
breast cancer
prostatic hypertrophy
Cancer
pancreatic cancer
peptic ulcers
lymphoma
peripheral neuropathy
brain cancer
diabetic retinopathy
age-related macular degeneration
melanoma
endometriosis
myocardial infarction
ovarian cancer
pterygium
trachoma
psoriasis
rosacea
warts
bone fractures
prostate cancer
lung cancer
claudication
multiple myeloma
kidney cancer
liver cancer
head and neck cancer
chronic limb ischemia
venous stasis ulcers
trypanosomiasis
malaria
burns
ischemic stroke
basal cell cancer
angina
testicular cancer
AIDS

WHAT IS ANGIOGENESIS

The formation of new blood vessels out of pre-existing capillaries.

INVOLVES : Sprouting

Splitting

Remodeling of the existing vessels

Intususeption

WHY IT IS IMPORTANT?

- Supply of oxygen and nutrients
- Removal of waste products

WHAT IS ANGIOGENESIS
WHY IT IS IMPORTANT

- Common denominator in most common diseases.
- New capillary blood vessel growth in the body.
- Natural process for healing and reproduction.
- Precise growth factors and inhibitors are needed to promote the angiogenesis process.
- Too little or too much can be fatal to the body.

DEFINITIONS

Vasculogenesis	*Formation of new vessels from EC precursors (angioblasts)*
Angiogenesis	*Formation of new vessels from pre-existing BV*
Arteriogenesis	*Subsequent stabilisation and maturation*
Collateralisation	*Enlarging existing vessels as bridges between networks*
(Myogenesis)	

ANGIOGENESIS *VS* VASCULOGENESIS

VASCULOGENESIS : the generation of blood vessels from **hemangioblasts** (endothelial cell precursors).

ANGIOGENESIS	VASCULOGENESIS
❑ New blood vessels mainly emerge from pre-existing ones.	❑ New endothelial cells differentiate from stem cells.
❑ Can be seen in adult life also.	❑ Seen during embryonic development(for primary vasculature).
❑ Physiologic stimuli during wound healing and the reproductive cycle in women lead to angiogenesis.	❑ Vasculogenesis is absent even in presence of physiologic stimuli.

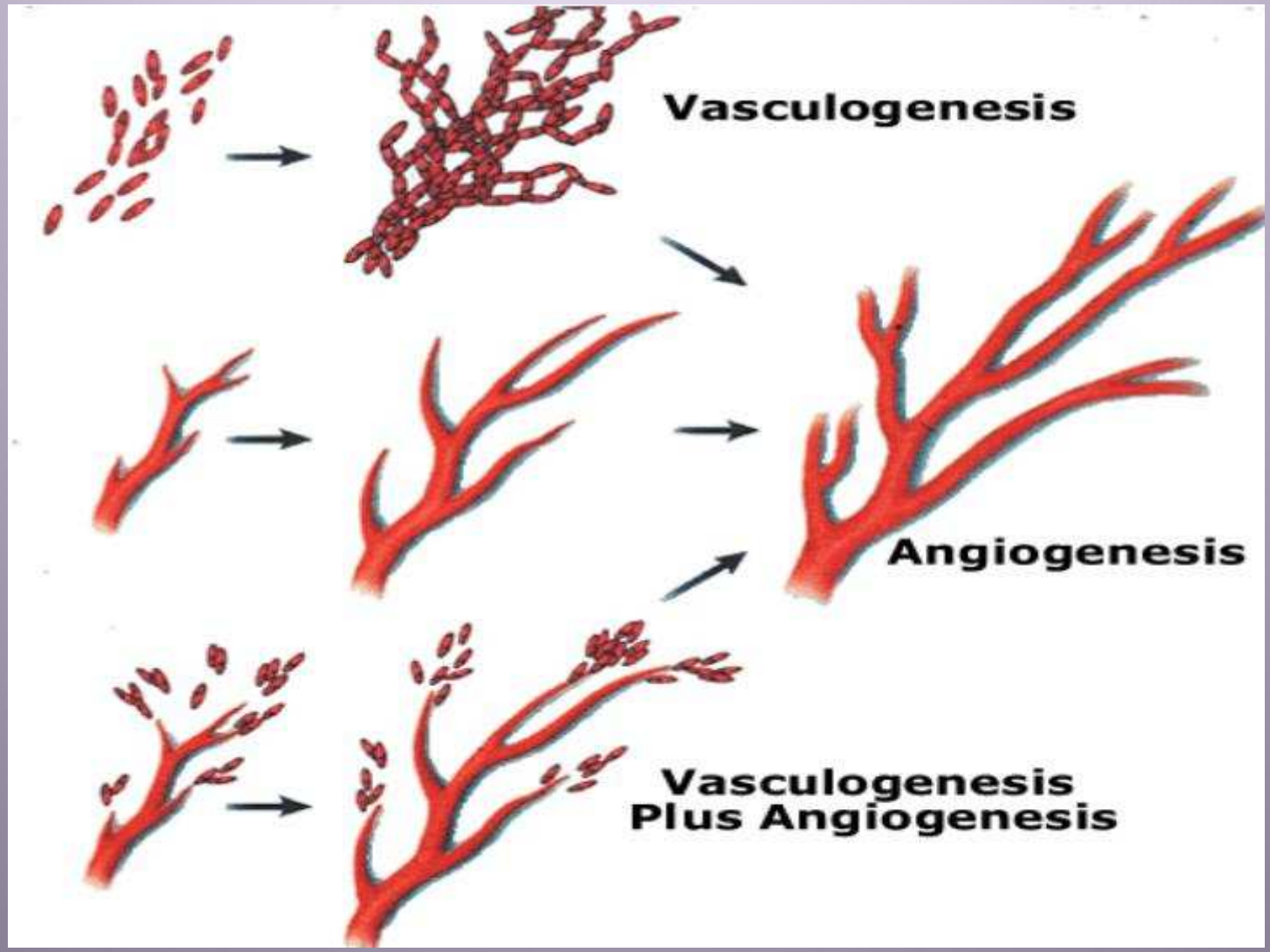
MODERN TERMINOLOGY OF ANGIOGENESIS

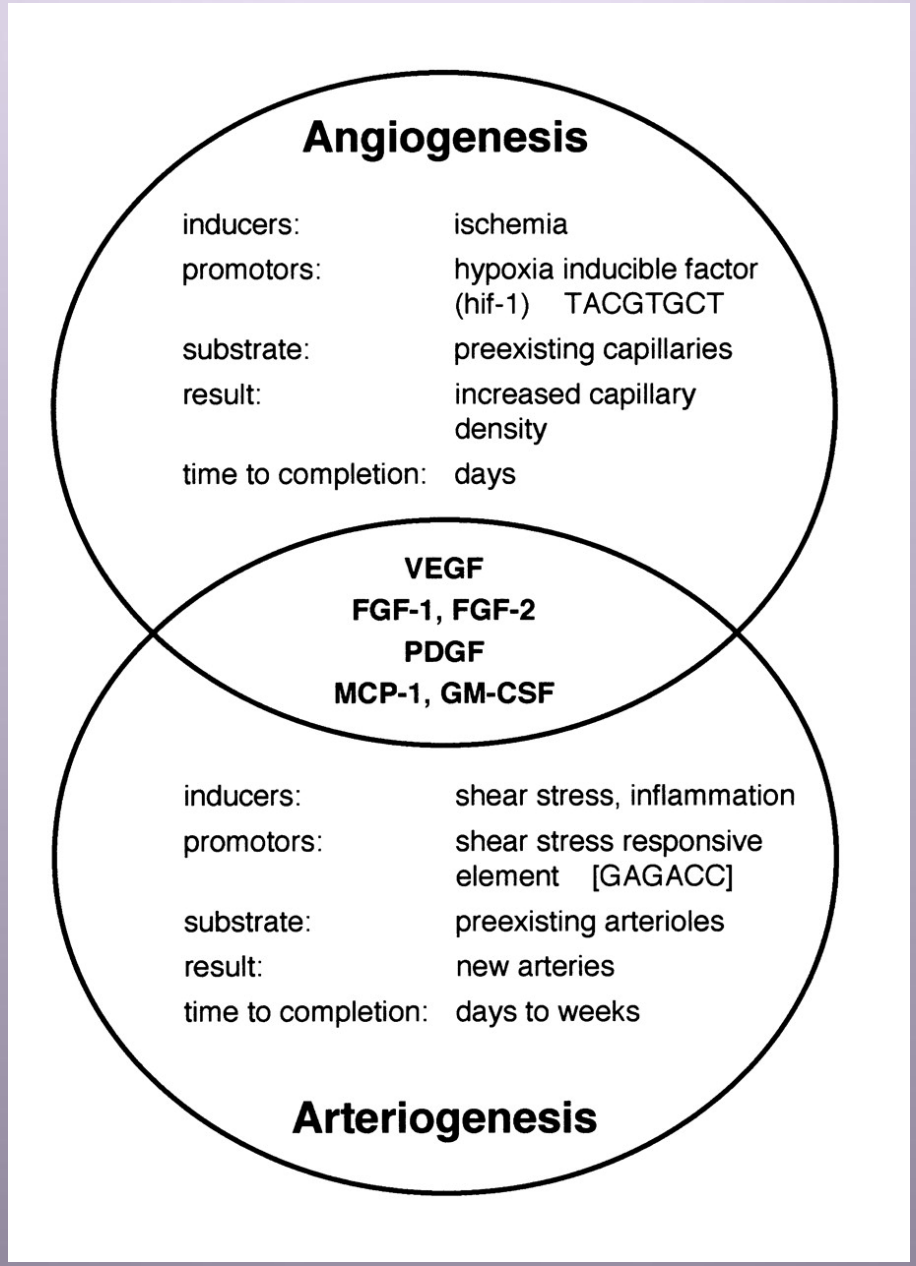
Vasculogenesis – Formation of vascular structures from circulating or tissue-resident endothelial stem cells(angioblasts), which proliferate into de novo endothelial cells. This form particularly relates to the embryonal development of the vascular system.

Angiogenesis – Formation of thin-walled endothelium-lined structures with /without muscular smooth muscle wall and pericytes (fibrocytes). This form plays an important role during the adult life span, also as "repair mechanism" of damaged tissues.

Arteriogenesis – Formation of medium-sized blood vessels possessing tunica media plus adventitia.

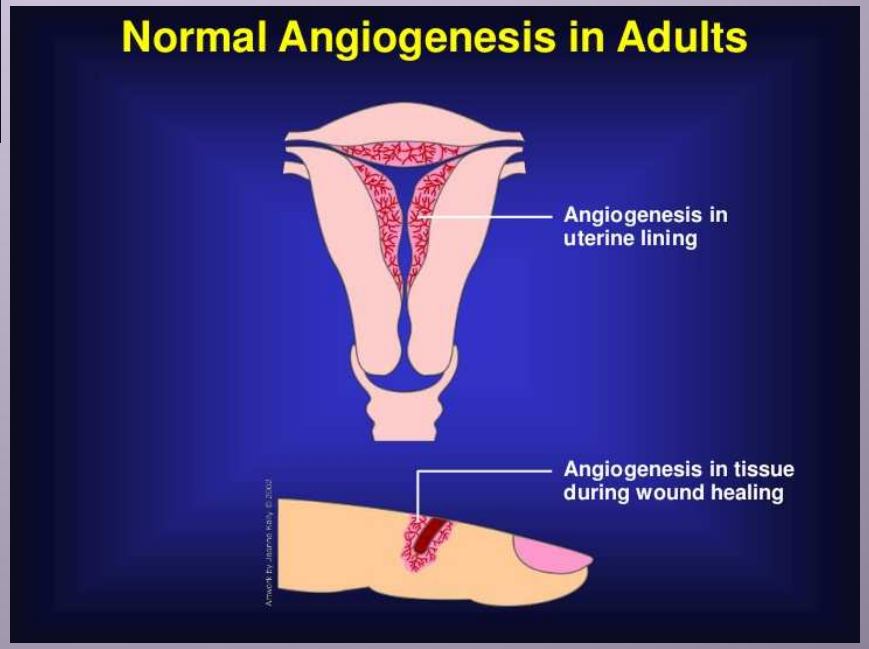
Because it turned out that even this differentiation is not a sharp one, today quite often the term "**Angiogenesis**" is used summarizing all different types and modifications of arterial vessel growth.

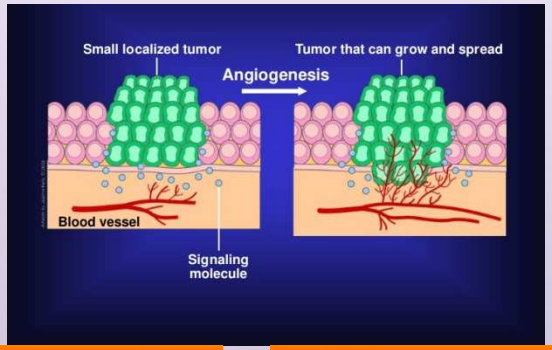

Vasculogenesis
Angiogenesis
Vasculogenesis
Plus Angiogenesis


Angiogenesis
inducers: ischemia
promotors: hypoxia inducible factor (hif-1) TACGTGCT
substrate: preexisting capillaries
result: increased capillary density
time to completion: days
VEGF
FGF-1, FGF-2
PDGF
MCP-1, GM-CSF
inducers: shear stress, inflammation
promotors: shear stress responsive element [GAGACC]
substrate: preexisting arterioles
result: new arteries
time to completion: days to weeks
Arteriogenesis

Normal Angiogenesis in Children

Normal Angiogenesis in Adults





INSUFFICIENT ANGIOGENESIS :

1. Ischemic tissue injury e.g. critical limb ischemia in diabetes
2. Cardiac failure
3. Delayed healing of gastric ulcers
4. Recurrent aphthous ulcerations
5. Organ dysfunction occurring in pre-eclampsia
6. Age-related diseases e.g. nephropathy and osteoporosis
7. Purpura, Telangiectasia
8. Pulmonary fibrosis & Emphysema
9. Amyotrophic Lateral Sclerosis
10. Alzheimer's disease

So PROMOTING ANGIOGENESIS is helpful here

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EXCESS ANGIOGENESIS :

- Cancer
- Arthritis
- Psoriasis
- Blinding retinopathy
- Atherosclerosis
- Restenosis
- Transplant arteriopathy
- Warts
- Scar keloids
- Synovitis
- Osteomyelitis
- Asthma
- Nasal polyps
- Choroideal and intraocular disorders
- Retinopathy of prematurity
- Diabetic retinopathy
- AIDS
- Endometriosis

So HALTING ANGIOGENESIS is helpful here

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HISTORY

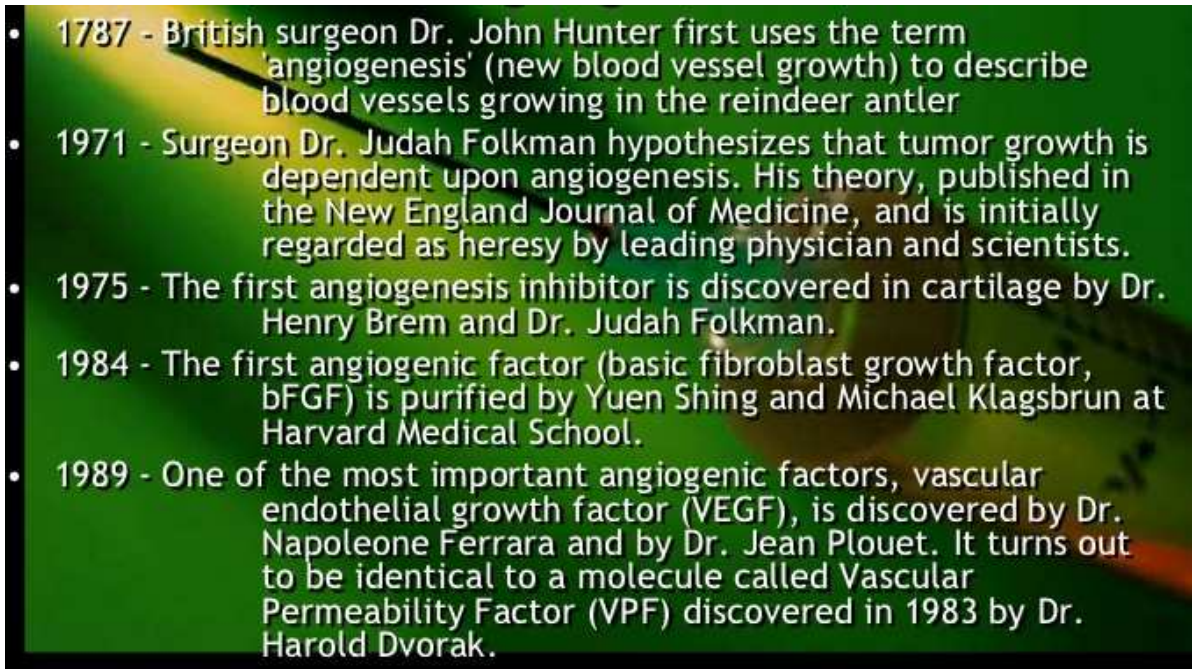
- The Scottish anatomist and surgeon **John Hunter** (1794) provided the first recorded scientific insights into the field of angiogenesis. His observations suggested that proportionality between vascularity and metabolic requirements occurs in both health and disease .

- The modern history of angiogenesis began with the work of **Judah Folkman**, who hypothesized (and published in 1971) that tumor growth is angiogenesis-dependent.

FACTS & FIGURES

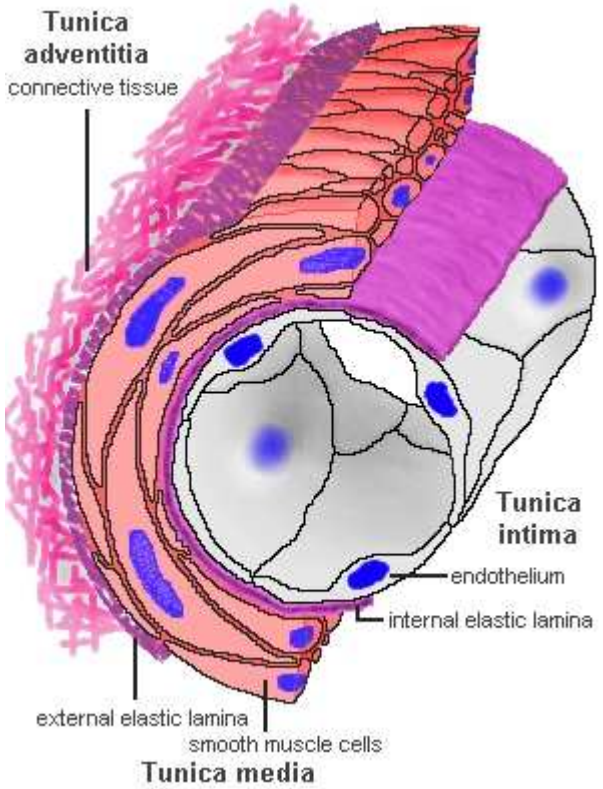
- 1787 – the term “angiogenesis” first used by British surgeon Dr. Hunter.
- 1975- basic fibroblast (1st angiogenesis inhibitor) was discovered by Dr. Folkman and Dr. Brem.
- 1989- Vascular endothelial growth factor (VEGF) was discovered.
- 1998- 1st FDA approved device for stimulating vessels. (TMR)
- 2003- Avastiv was the 1st anti-angiogenesis drug used in large scales for experimentation.
- $4 billion invested in further research.

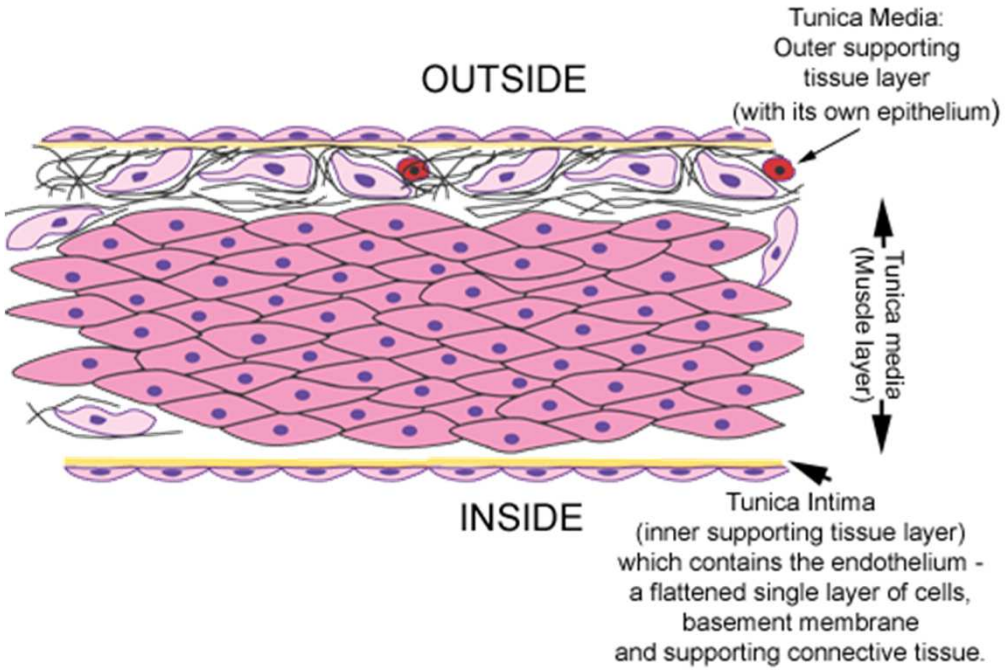
HYSTORICAL HIGHLIGHTS



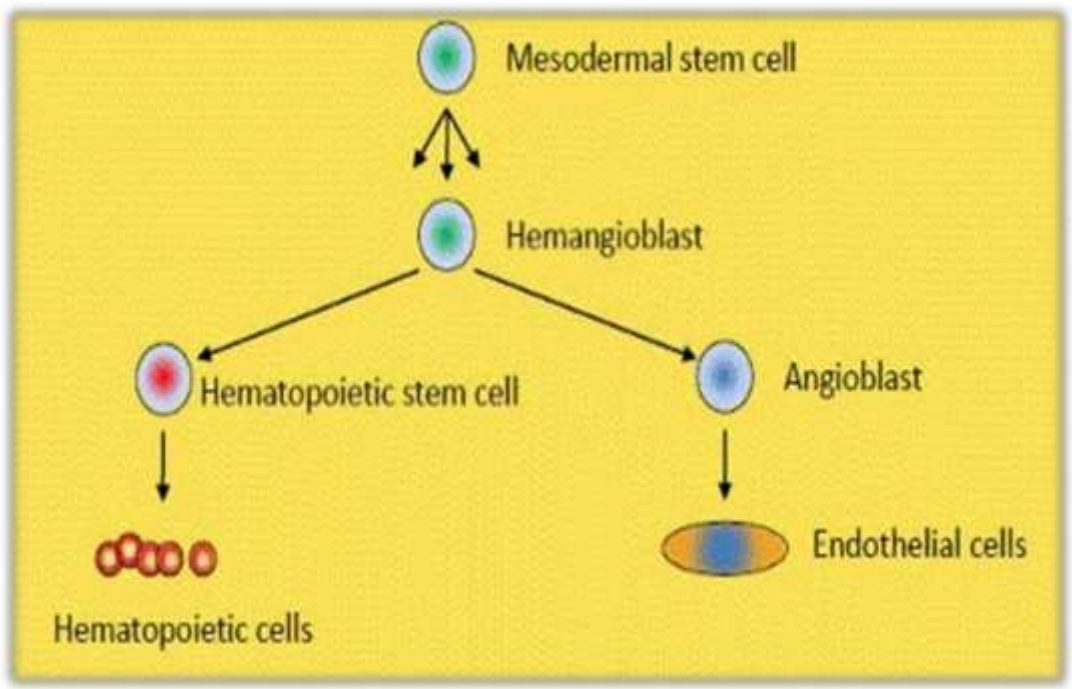
HYSTORICAL HIGHLIGHTS

BLOOD VESSELS

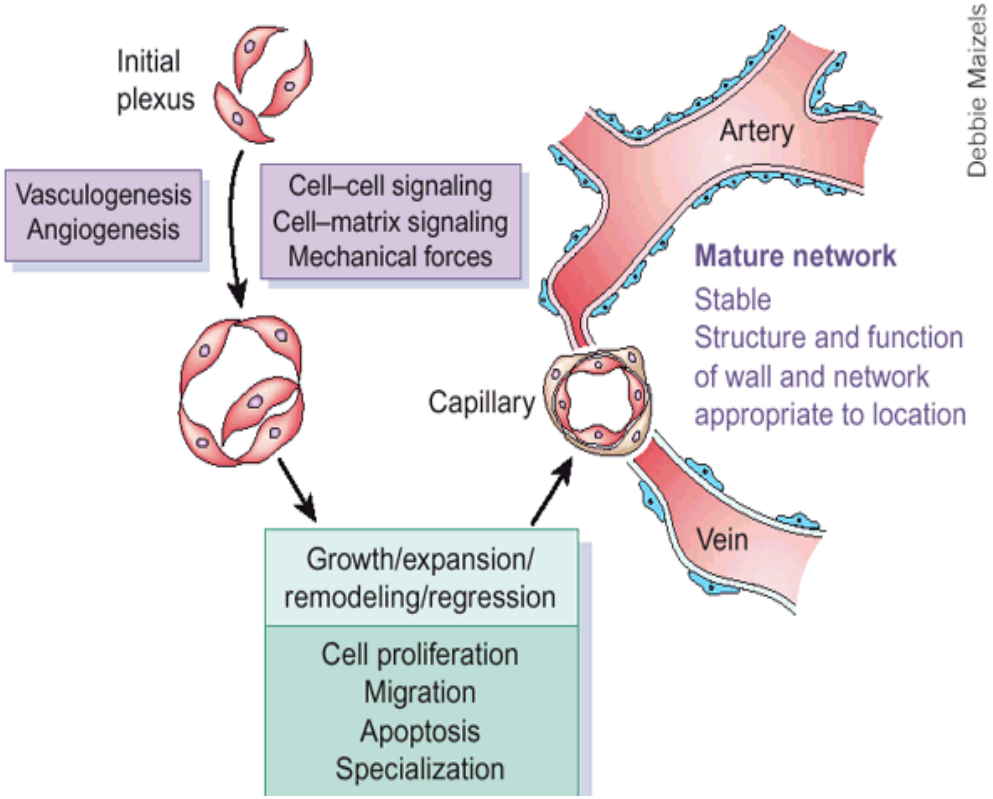




BLOOD VESSELS: ORIGIN



STEPS IN NETWORK FORMATION AND MATURATION DURING EMBRYONIC (PHYSIOLOGICAL) ANGIOGENESIS



- Stages

A: Vasculogenesis

B: Angiogenic remodeling

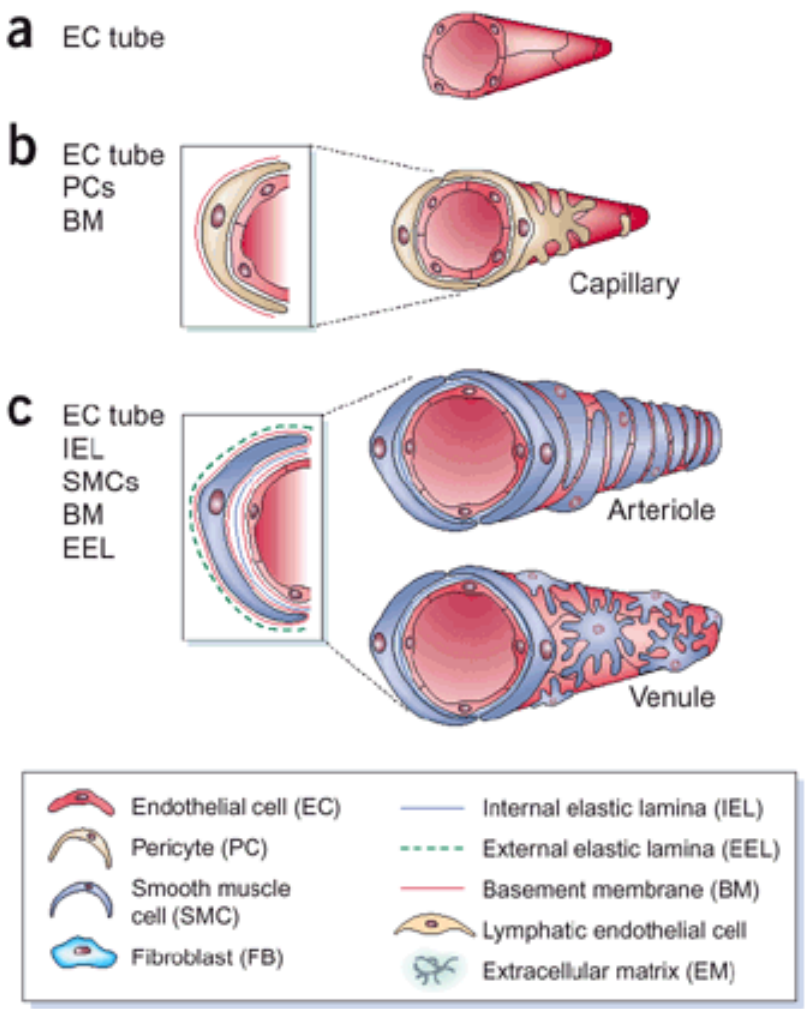
C: Stabilization and maturation

D: Destabilization

E: Regression

F: Sprouting

BLOOD VESSEL WALLS GROWTH



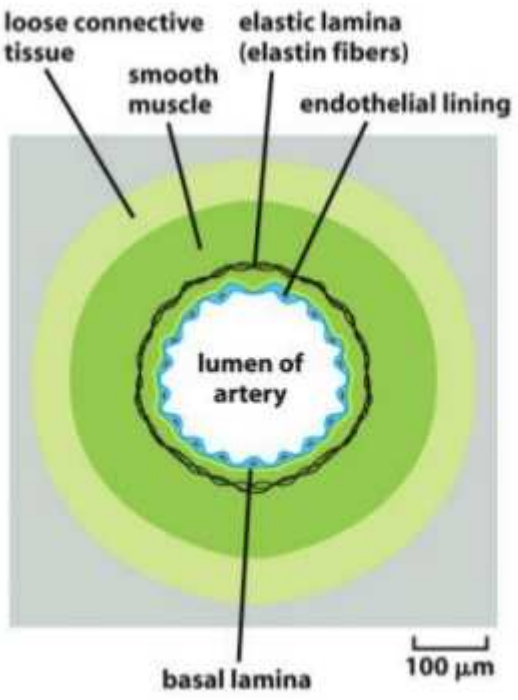
(a) Nascent vessels consist of a tube of ECs, which mature into specialized capillaries, arteries and veins.

(**b**) Capillaries consist of ECs surrounded by basement membrane and a sparse layer of pericytes embedded within the EC basement membrane. Capillary endothelial layer can be continuous (muscle), fenestrated (kidney/ endocrine glands) or discontinuous (liver sinusoids). The endothelia of the blood-brain barrier or blood-retina barrier are further specialized to include tight junctions, and are thus impermeable to various molecules.

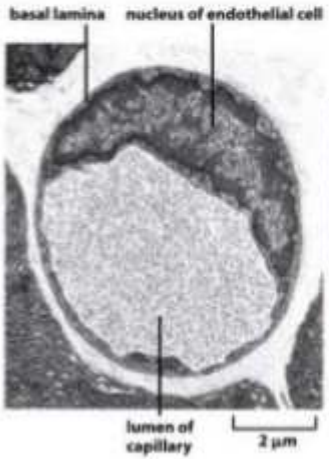
(**c**) Arterioles and venules have an increased coverage of mural cells compared with capillaries.

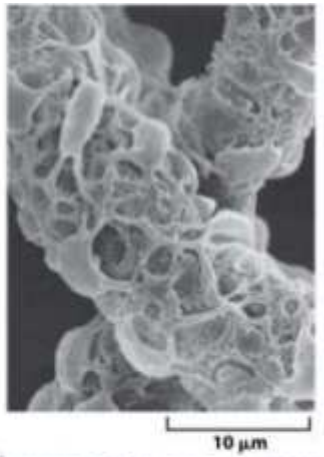
STRUCTURE OF VESSELS AND CAPILLARIES

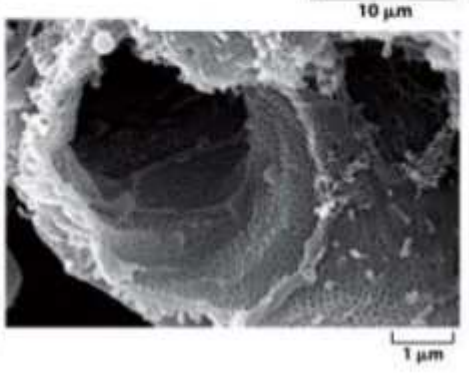
Small artery: Monocellular layer of endothelial cells



Capillary: endothelial cell, basal lamina, pericytes

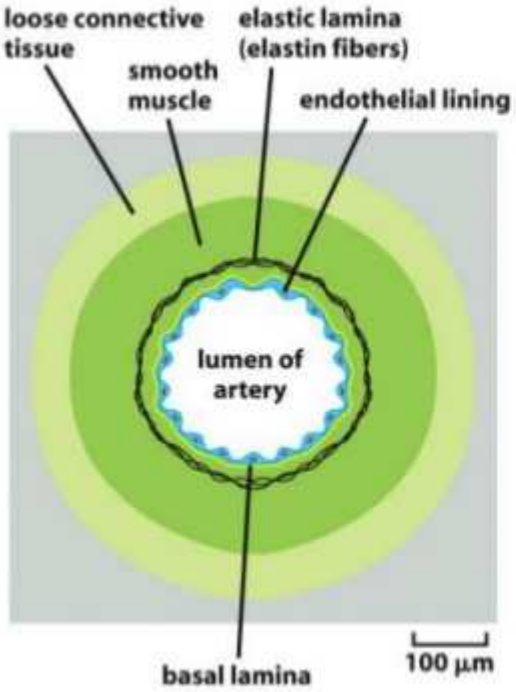




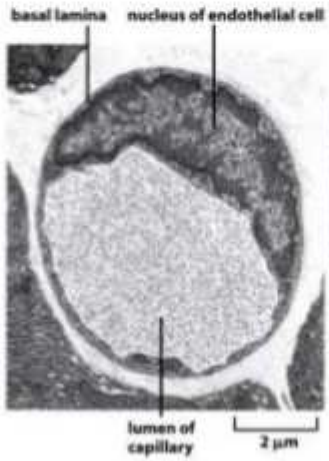


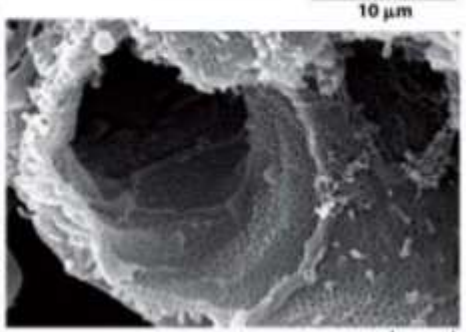
Structure of vessels and capillaries

Small artery: Monocellular layer of endothelial cells



Capillary: endothelial cell, basal lamina, pericytes





REGOLATION OF ANGIOGENESIS

A. Metabolic Factors

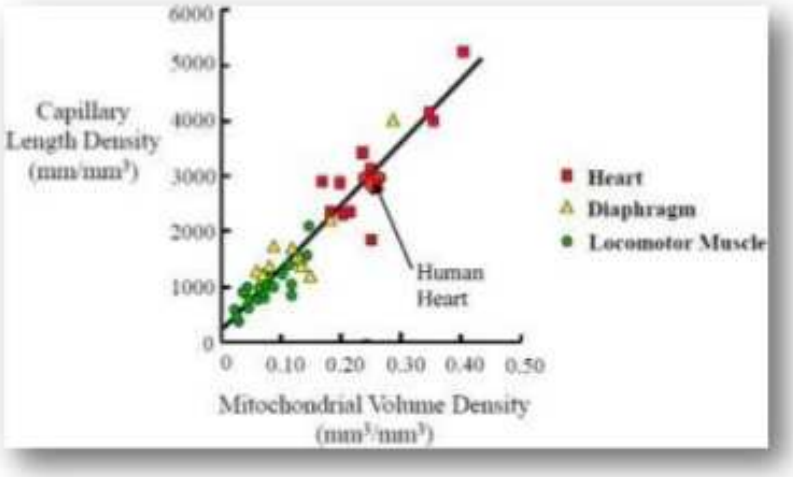
- Capillary growth is proportional to metabolic activity.
- Increasing metabolic activity stimulates blood vessel growth.
- Decreasing metabolic activity causes vascular regression.
- Long-term increases in blood pressure lead to vascular rarefaction.
- Oxygen is a master signal in growth regulation of the vascular system.
- Role of adenosine in metabolic regulation of vascular growth

B. Mechanical Factors

- Regardless of the growth factor(s) that stimulate angiogenesis, the fundamental steps required to build new capillaries are essentially the same.
- A better understanding of the mechanosensory mechanisms could therefore provide the basis for unique therapeutic interventions to control angiogenesis.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

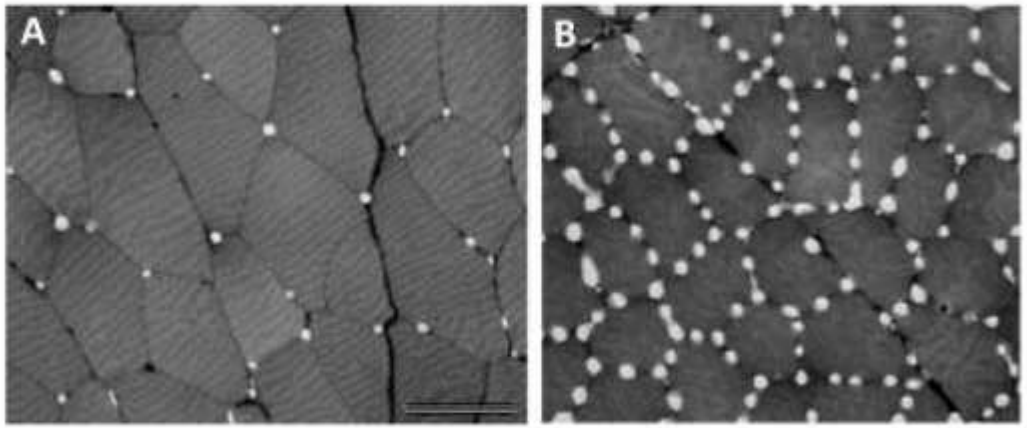
CAPILLARY GROWTH IS PROPORTIONAL TO METABOLIC ACTIVITY



Capillary length density and mitochondrial volume density are shown.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

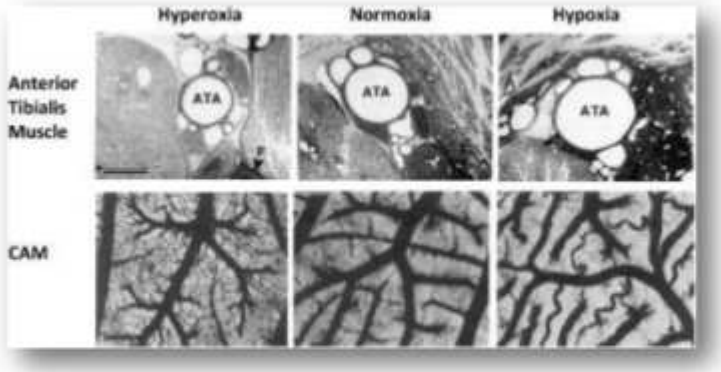
INCREASING METABOLIC ACTIVITY STIMULATES BLOOD VESSEL GROWTH



Chronic increases in muscular activity stimulate angiogenesis in rat skeletal muscle.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

INCREASING METABOLIC ACTIVITY STIMULATES BLOOD VESSEL GROWTH



Chronic exposure to a hypoxic environment (12% oxygen) stimulates diameter growth of the anterior tibialis artery (ATA) as well as blood vessel growth in the chorioallantoic membrane (CAM)

Exposure to a hyperoxic environment (70% oxygen) decreases growth of the CAM vasculature and ATA, compared with growth in a normoxic environment (21% oxygen). (lower right) Tortuous vessels in the CAM are often observed following incubation in 12% oxygen.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

DECREASING METABOLIC ACTIVITY CAUSES VASCULAR REGRESSION

- Overoxygenation (hyperoxia) of muscle tissues is a likely cause of capillary rarefaction in sedentary muscles.
- Muscles use less oxygen when muscular activity decreases, which causes the muscles to be overperfused and hence overoxygenated.
- This overperfusion is expected to cause an autoregulatory vasoconstriction of muscle arterioles, which lowers blood flow to the muscle and thus decreases oxygen delivery.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

LONG-TERM INCREASES IN BLOOD PRESSURE LEAD TO VASCULAR RAREFACTION

- When the blood pressure is too high, excessive amounts of blood are literally pushed through the microcirculation.
- This overperfusion of existing microvessels leads to a loss of microvessels (microvascular rarefaction).
- Microvascular rarefaction is well-documented in the skeletal muscles of various rat models of hypertension.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

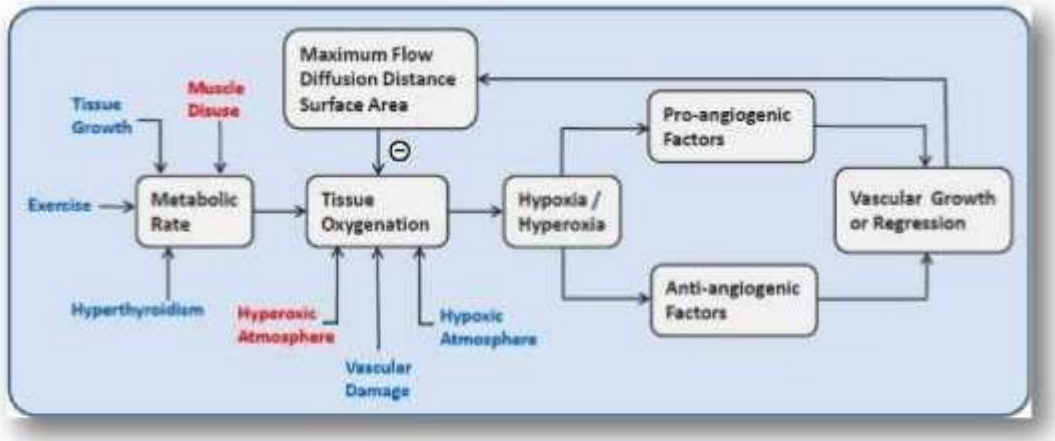
OXYGEN IS A MASTER SIGNAL IN GROWTH REGULATION OF THE VASCULAR SYSTEM

Why?

- Oxygen is especially critical because cells have limited stores compared with metabolic substrates such as glucose, fatty acids, and amino acids.

- This relative inability of tissues to store oxygen can explain why oxygen is a master signal in growth regulation and why oxygen falls to low levels in skeletal muscle within a few seconds following an increase in metabolic rate.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS



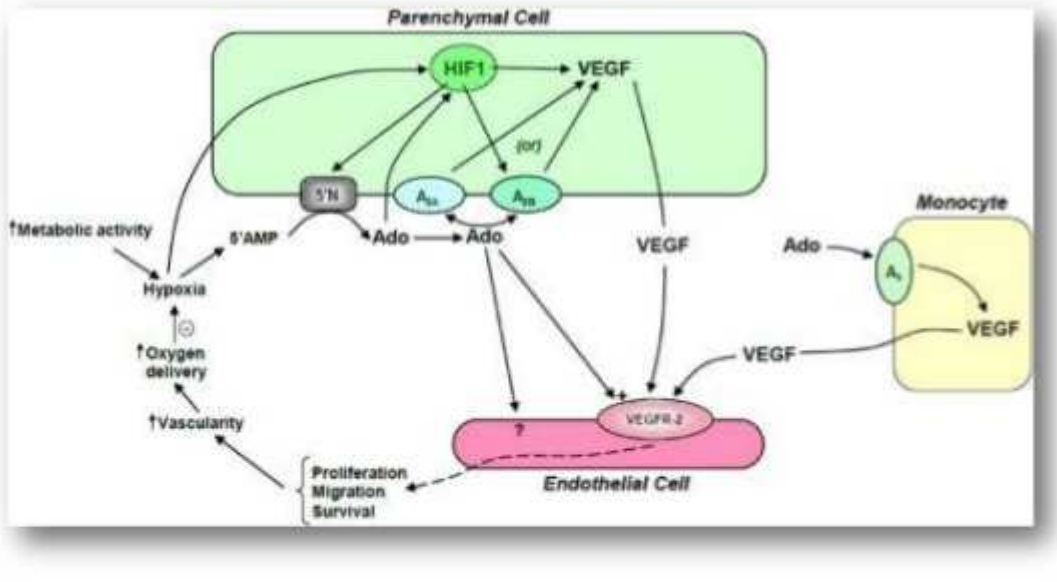
- Central role of oxygen in metabolic regulation of vascular growth and regression.
- Factors listed in **blue** are thought to **decrease** tissue oxygenation causing hypoxia, which leads to vascular growth.
- Factors listed in **red** are thought to **increase** tissue oxygenation causing hyperoxia, which leads to vascular regression.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS

ROLE OF ADENOSINE IN METABOLIC REGULATION OF VASCULAR GROWTH

- Adenosine is a nucleoside produced in all cells of the body by stepwise dephosphorylation of ATP. Hypoxic tissues produce adenosine from ATP, and the adenosine in turn functions to restore balance between oxygen demand and oxygen supply.
- Adenosine increases oxygen supply acutely by causing vasodilation and increased blood flow in the heart, skeletal muscle, brain, and other tissues.
- Adenosine can decrease oxygen demand in the heart by multiple mechanisms.
- For these reasons, adenosine is thought to serve as a negative feedback signal to maintain tissue oxygenation within a normal range.

REGOLATION OF ANGIOGENESIS
A. METABOLIC FACTORS



Mechanism of adenosine-induced angiogenesis.

Ado, adenosine; HIF1, hypoxia inducible factor-1; VEGFR2, VEGF receptor-2; A_1, A_{2A}, and A_{2B}, adenosine receptors; 5'N, ecto-5-nucleotidase; 5'AMP, 5'adenosine monophosphate.

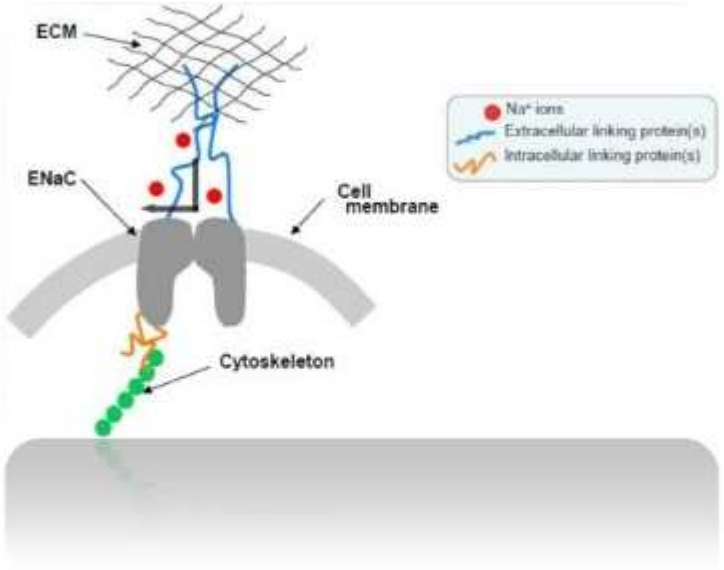
REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Epithelial Sodium Channel Protein Biology

- One possible candidate for mediating mechanosensory events in angiogenesis is the epithelial sodium channel (ENaC), which is thought to form a mechanosensory complex.
- ENaC proteins have been localized in vascular smooth muscle cells and endothelial cells: both cell types express α-, β-, and γ-subunit proteins

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Epithelial Sodium Channels Can Form a Mechanosensory Complex



Model of mechanosensor with pore of epithelial sodium channel (ENaC)

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Epithelial Sodium Channels Can Mediate Mechanotransduction in Mammals

- ENaC family members have been shown by immunocytochemistry to be expressed in mechanoreceptor structures in the rat foot pad , baroreceptors, sensory nerve endings in rat larynx , sensory nerve endings of vibrissae , the muscle spindle , and vascular tissues.

- Stretch-induced vasoconstriction (i.e., the myogenic response), the baroreceptor reflex, blood flow autoregulation, and migration of vascular smooth muscle cells can be attenuated using pharmacologic and/or genetic suppression of DEG/ENaC proteins

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

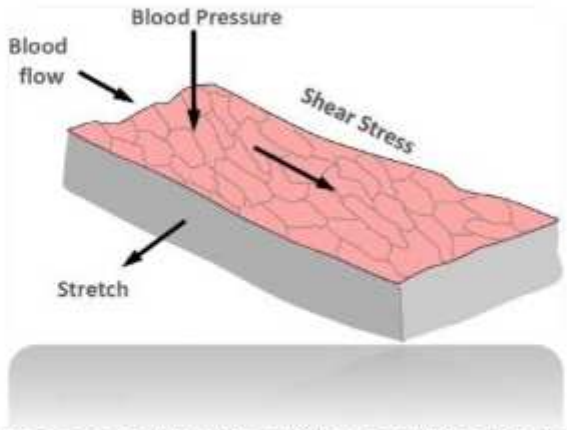
Do Epithelial Sodium Channels Mediate Angiogenesis?

- ENaCs play a critical role in the angiogenic process, possibly by acting as mechanosensors for migration of endothelial and vascular smooth muscle cells as well as endothelial tube formation.

- Recent studies suggest that ENaCs are required for angiogenesis . In these studies, a specific ENaC inhibitor (benzamil) abolished both VEGF-A and FGF2 stimulated microvessel growth in the rat aortic ring angiogenesis assay

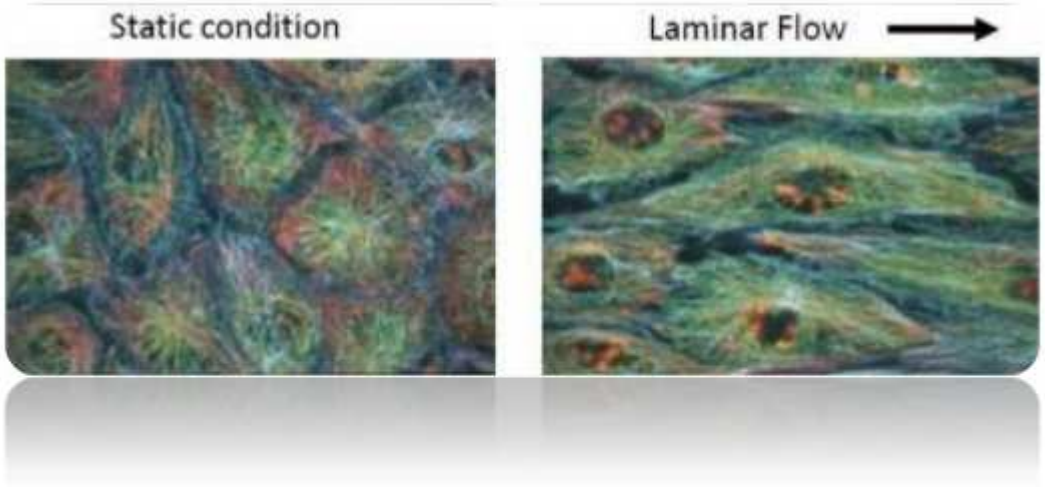
REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Physical Forces Acting on the Walls of Blood Vessels



- Physical forces caused by blood flow and blood pressure act on the walls of blood vessels.
- Flowing blood generates shear stress tangential to the endothelial cell surface.
- Circumferential stretch is caused by the action of blood pressure.

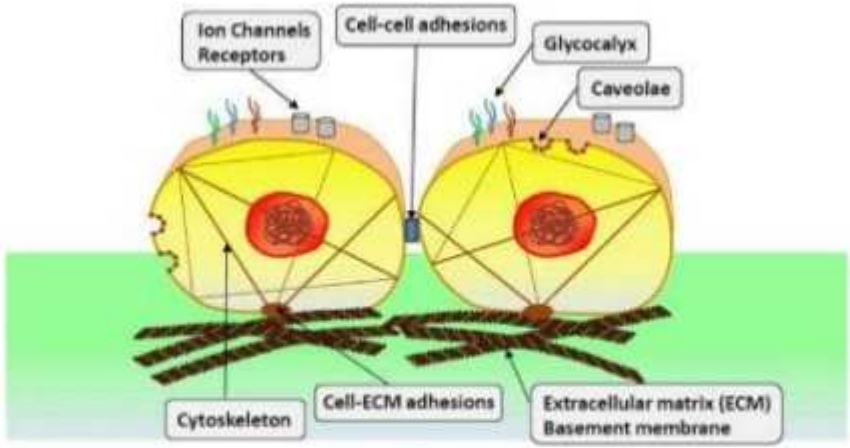
REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS



- Effect of laminar flow on cytoskeletal organization and orientation of endothelial cells.
- Cytoskeletal elements are triple stained for actin (pseudocolor blue), microtubules (green), and intermediate filaments (red).
- Photomicrographs were taken under (left) static conditions and (right) 24 h after laminar shear flow at 12 dyn/cm^2.

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

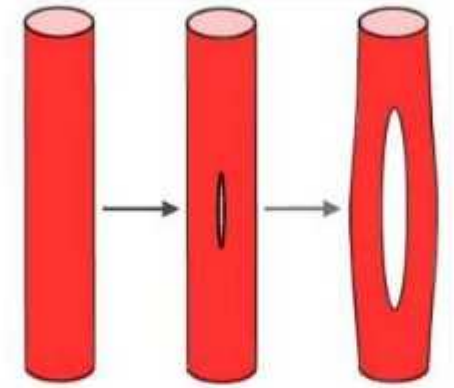
Shear Stress Is Sensed by the Endothelium



Elements of shear stress mechanosensing in endothelial cells.
ECM, extracellular matrix.

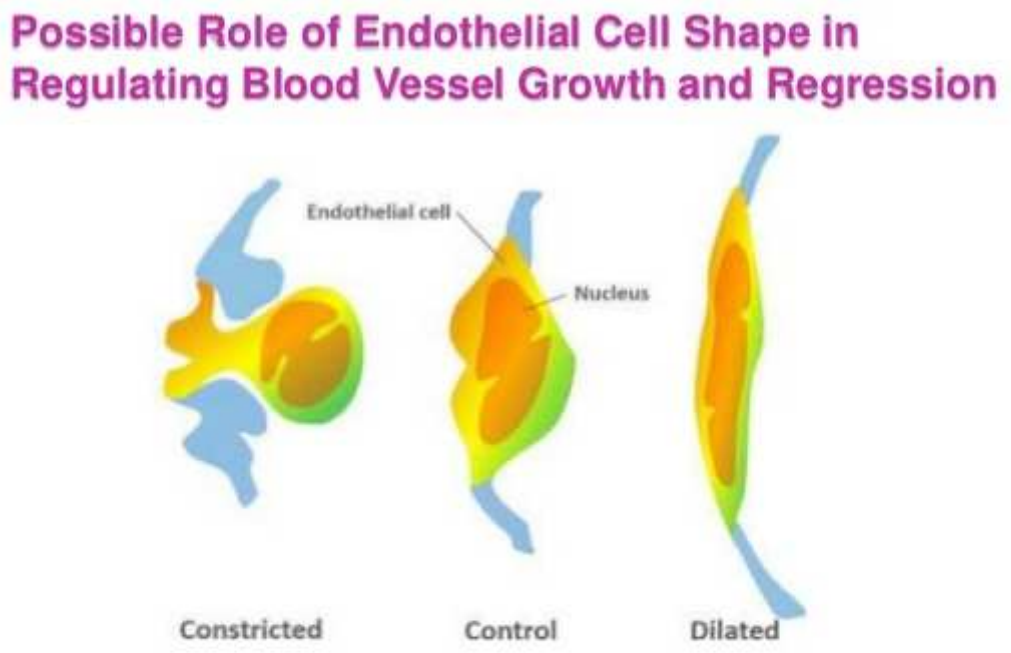
REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Increased Blood Flow (Shear Stress) Can Stimulate Angiogenesis



Shear stress-induced intussusceptive angiogenesis gives rise to longitudinal splitting of blood capillaries.

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS



Model of endothelial cell shape during relative dilation and constriction of an arteriole.

REGOLATION OF ANGIOGENESIS
B. MECHANICAL FACTORS

Mechanical Factors Have an Accessory Role in Angiogenesis

- Those steps in the angiogenic process that require mechanosensation of physical stimuli serve to implement angiogenesis under the umbrella of metabolic regulation.

- The proangiogenic actions of shear stress are thought to facilitate, but not regulate the angiogenesis.