Vascular Endothelial Growth Factor (VEGF)

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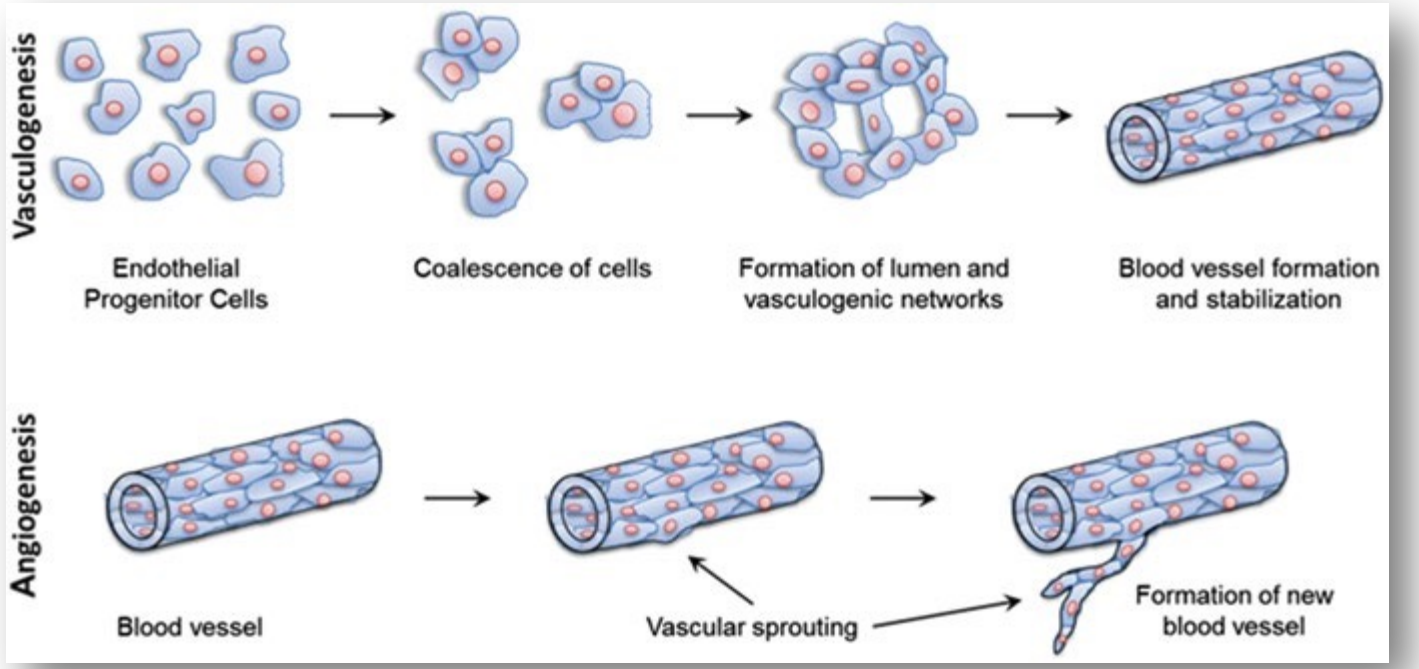
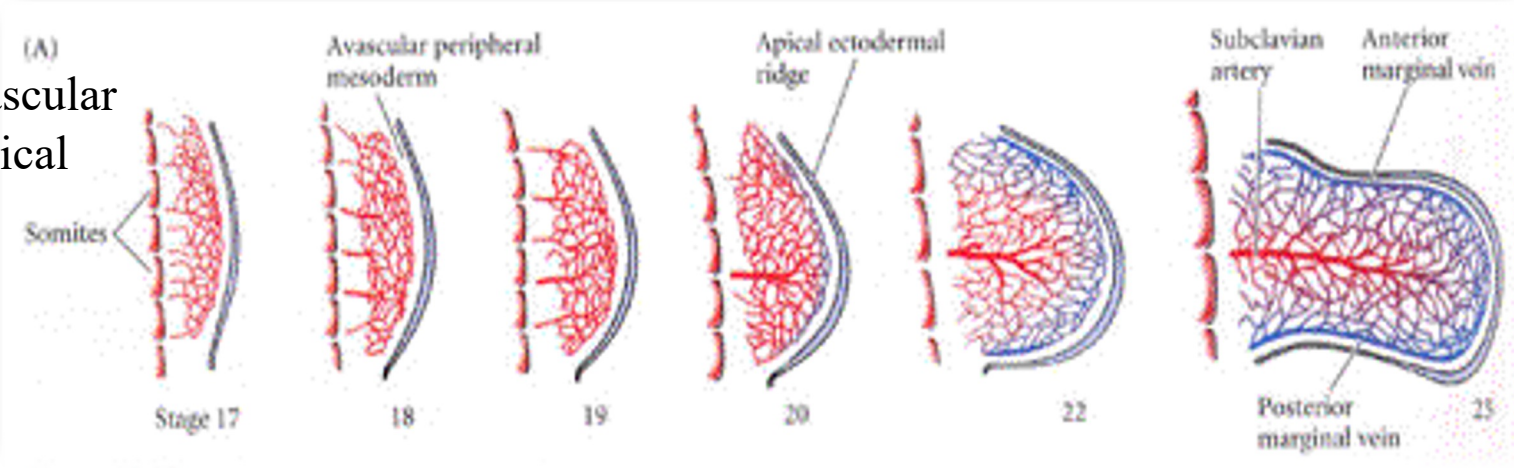
Introduction

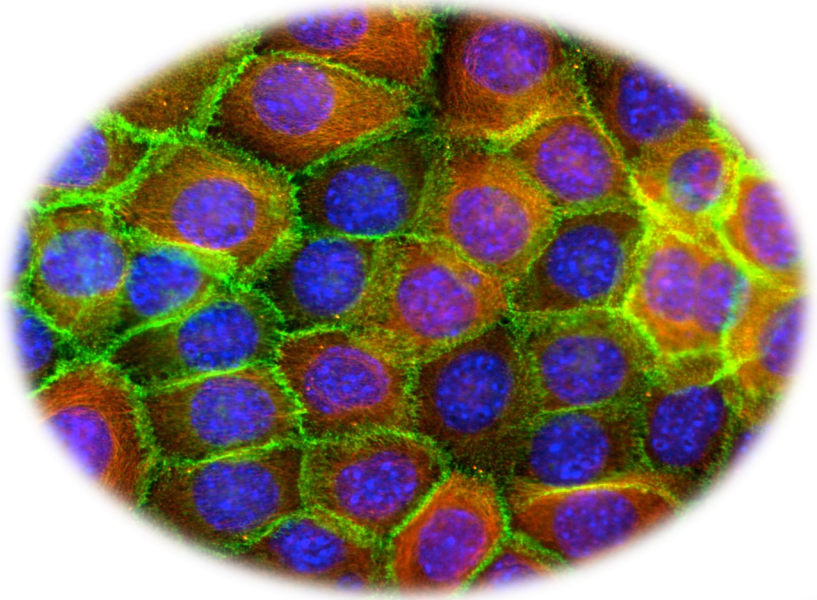
- Vascular endothelial growth factor (VEGF) vascular permeability factor (VPF)
- member of the PDGF/VEGF growth factor family.
- factor induces proliferation and migration of vascular endothelial cells
- is essential for both physiological and pathological angiogenesis.
- The activities of VEGF are not limited to the vascular system; VEGF plays a role in normal physiological functions such as:
  - bone formation
  - hematopoiesis
  - wound healing
  - development.

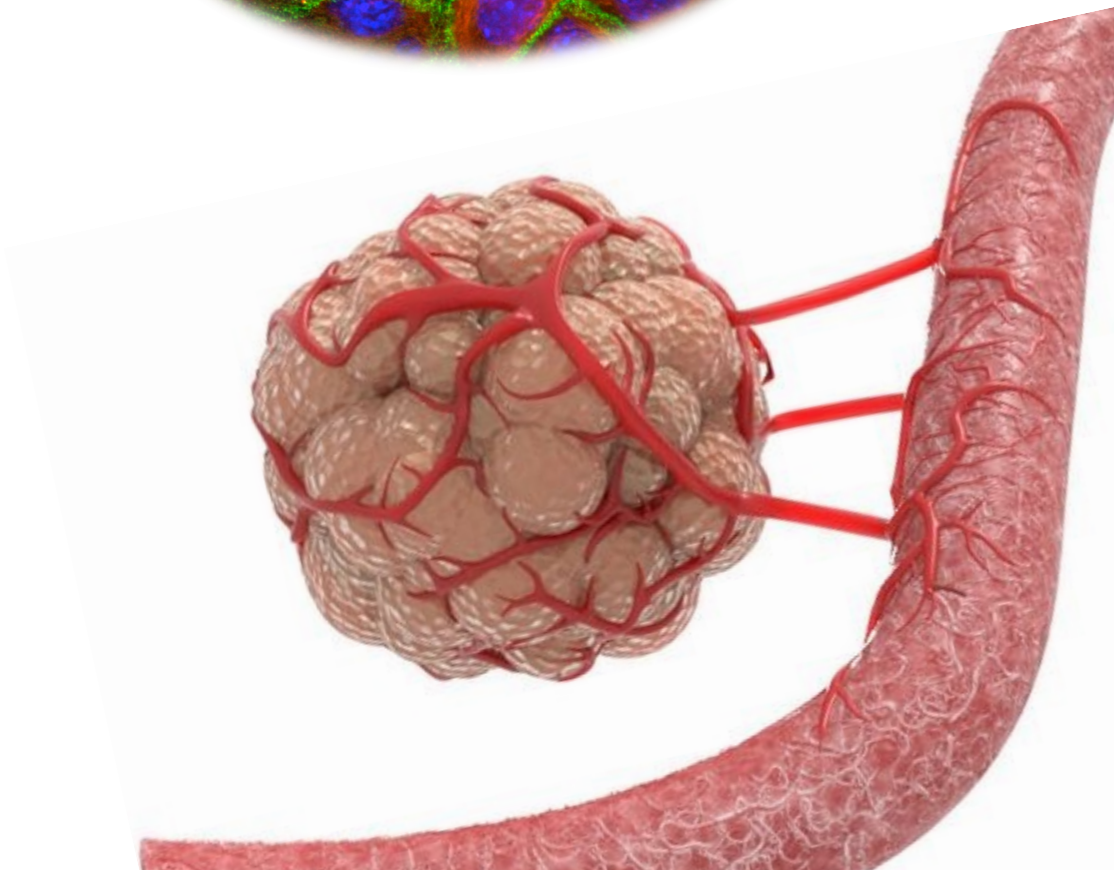




VEGF is produced by many cell types including:

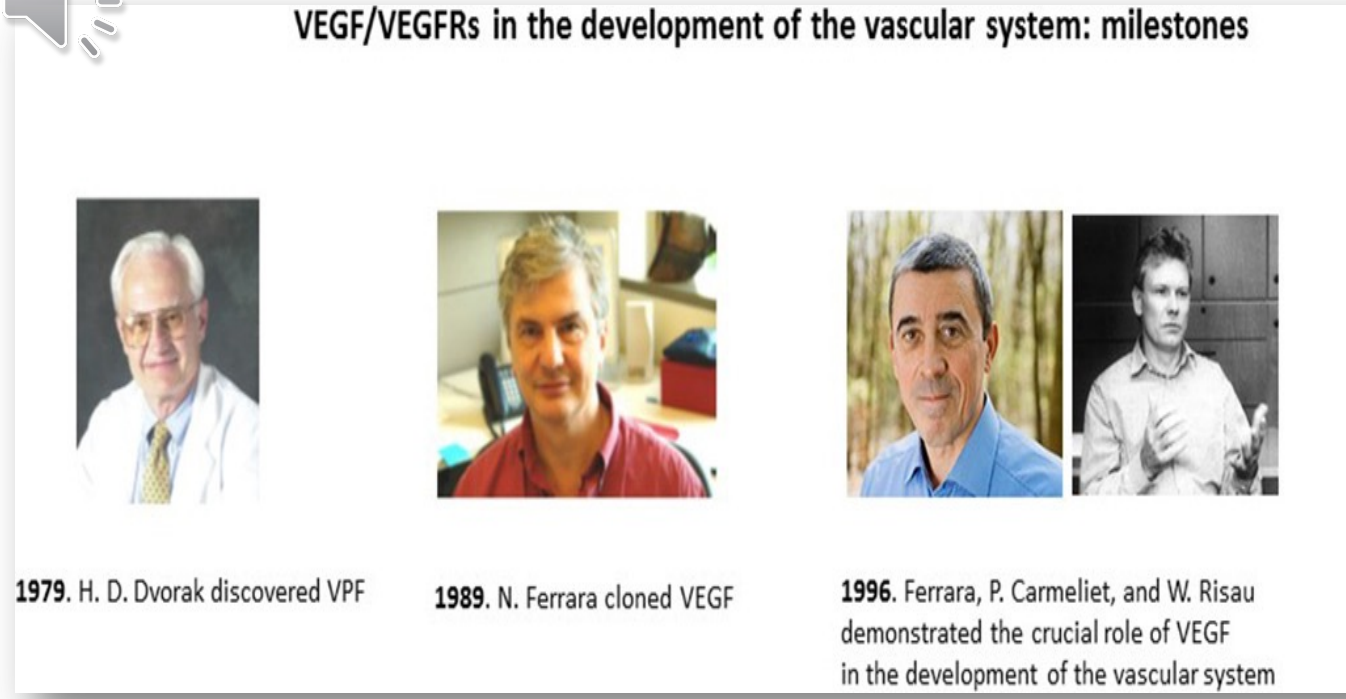
- tumor cells,
- macrophages,
- platelets,
- keratinocytes





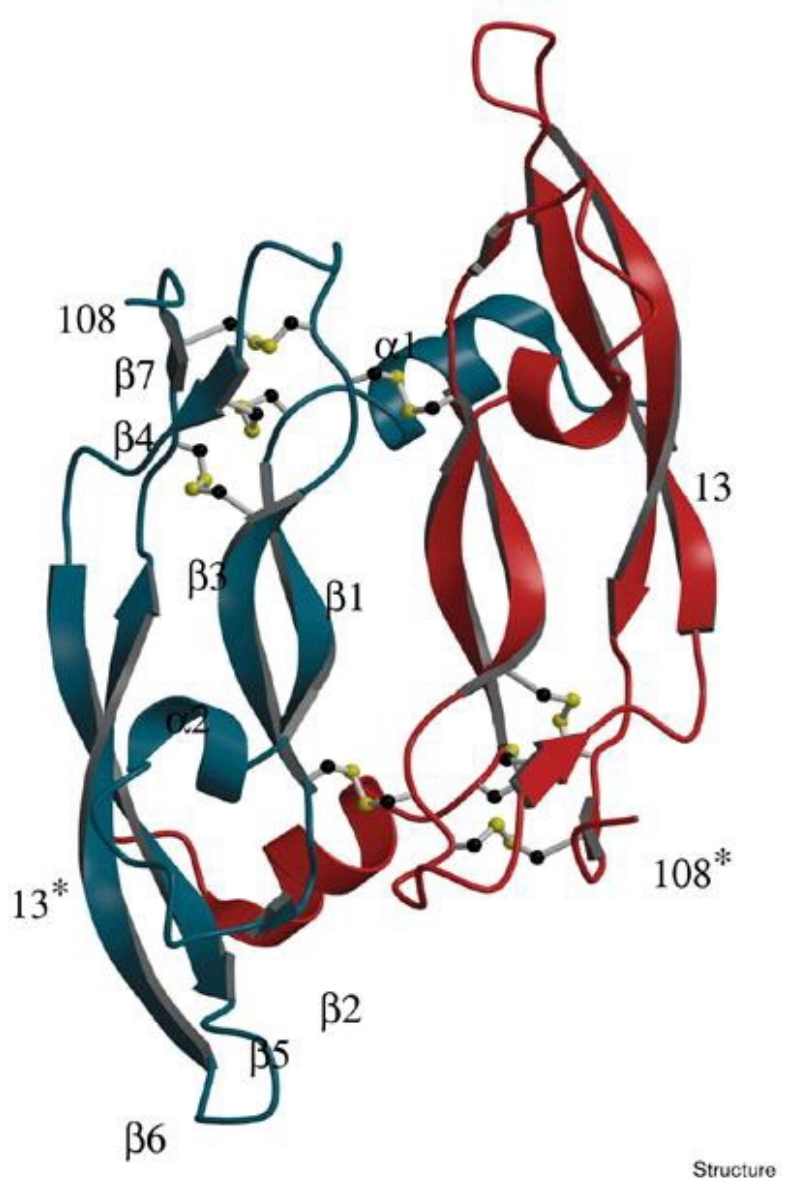
History

- In 1979, Harold D. Dvorak found that supernatants from cell-free supernatants of tumors generated an intense blue spot Dvorak called this tumor supernatant permeabilizing activity vascular permeability factor (VPF),
- In 1983 Senger et al. identified a vascular permeability factor secreted by tumors in guinea pigs and hamsters
- In 1989 Ferrara and Henzel described an identical factor in bovine pituitary follicular cells which they purified, cloned and named VEGF
- Between 1996 and 1997, Christinger and De Vos obtained the crystal structure of VEGF, first at 2.5 Å resolution and later at 1.9 Å



Protein structure

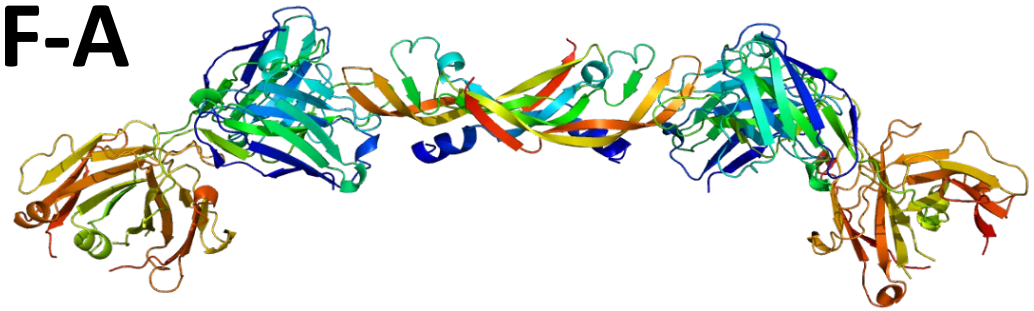
- Homodimeric member of the cystine knot family of growth factors
- antiparallel homodimer covalently linked by two disulfide bridges between Cys-51 and Cys-60.
- cystine knot motif is found in other growth factors:
  - eight-residue ring formed by the disulfide bridges Cys-57–Cys-102 and Cys-61–Cys-104,
  - with a third disulfide bond (Cys-26–Cys-68) passing through it.
  - From this motif extends a central four-stranded β-sheet
- In the VEGF dimer, the 2-fold axis is perpendicular to the sheet, resulting in an antiparallel orientation of the monomers with the two four-stranded sheets side by side

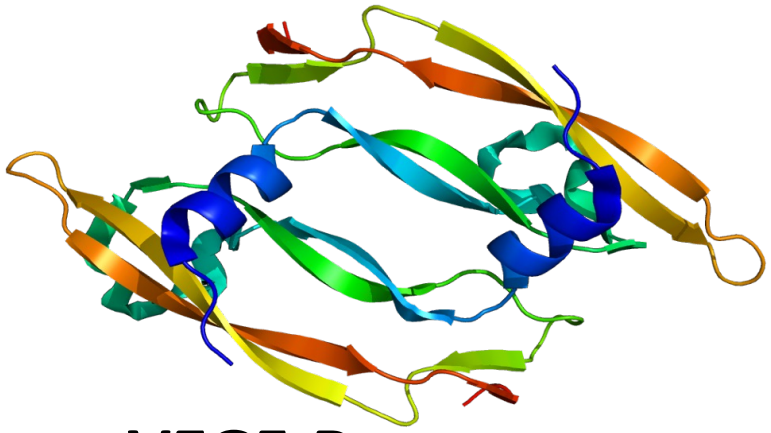


Structure

Classification

VEGF-A

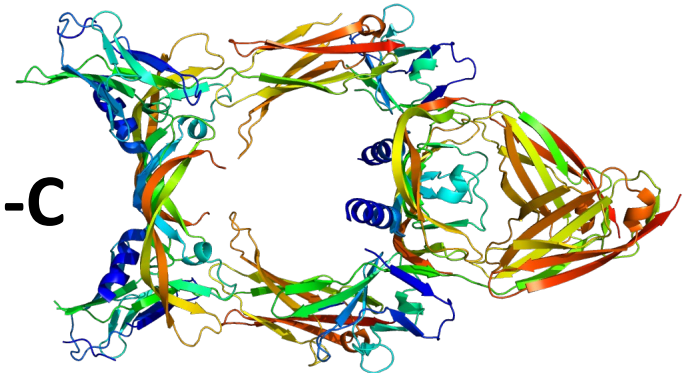




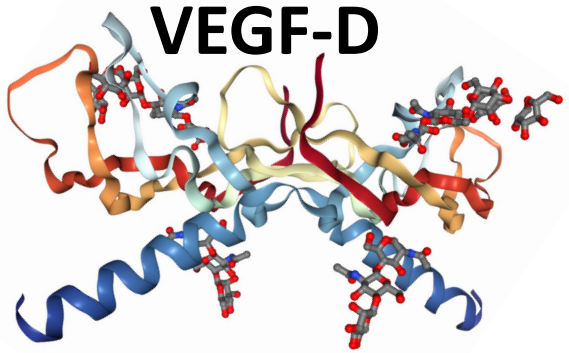
VEGF-B

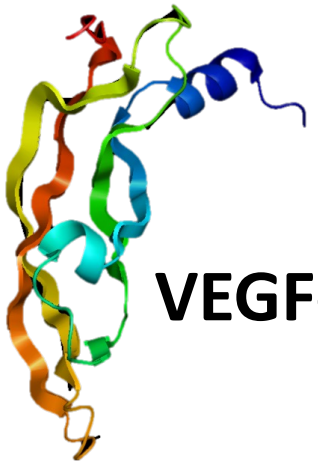
- In mammals, the VEGF family comprises five members:
  - VEGF-A
  - placenta growth factor (PGF),
  - VEGF-B
  - VEGF-C
  - VEGF-D
- A number of VEGF-related proteins encoded by viruses (VEGF-E) and in the venom of some snakes (VEGF-F) have also been discovered.

VEGF-C



VEGF-D

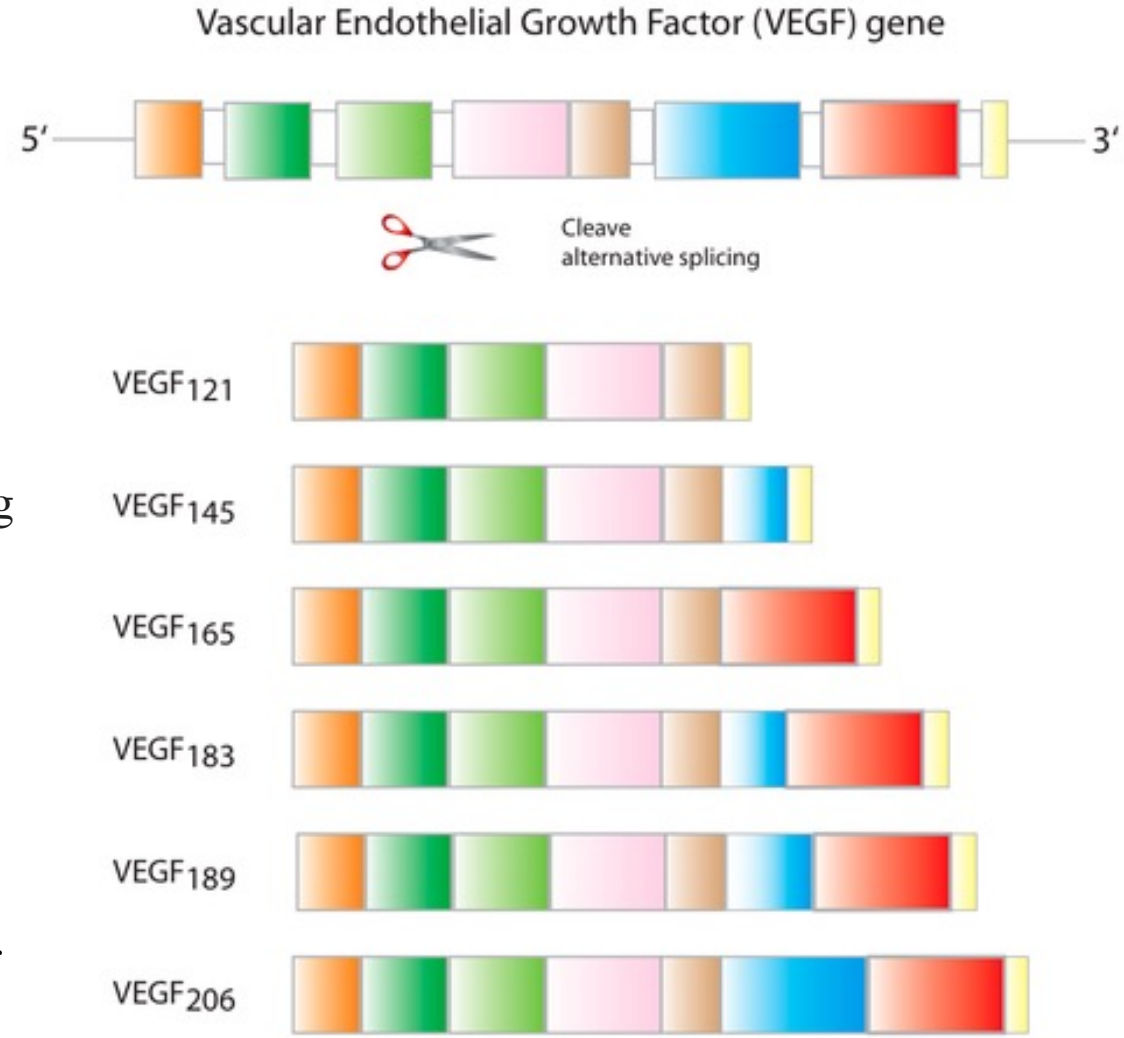




VEGF-F

Type	Function
VEGF-A	Angiogenesis ↑ Migration of endothelial cells ↑ mitosis of endothelial cells ↑ αvβ3 activity ↑ Matrix metalloproteinase activity creation of blood vessel lumen creates fenestrations Chemotactic for macrophages and granulocytes Vasodilation (indirectly by NO release) Lymphangiogenesis
VEGF-B	Embryonic angiogenesis (myocardial tissue, to be specific)
VEGF-C	Lymphangiogenesis
VEGF-D	Needed for the development of lymphatic vasculature surrounding lung bronchioles

Isoforms

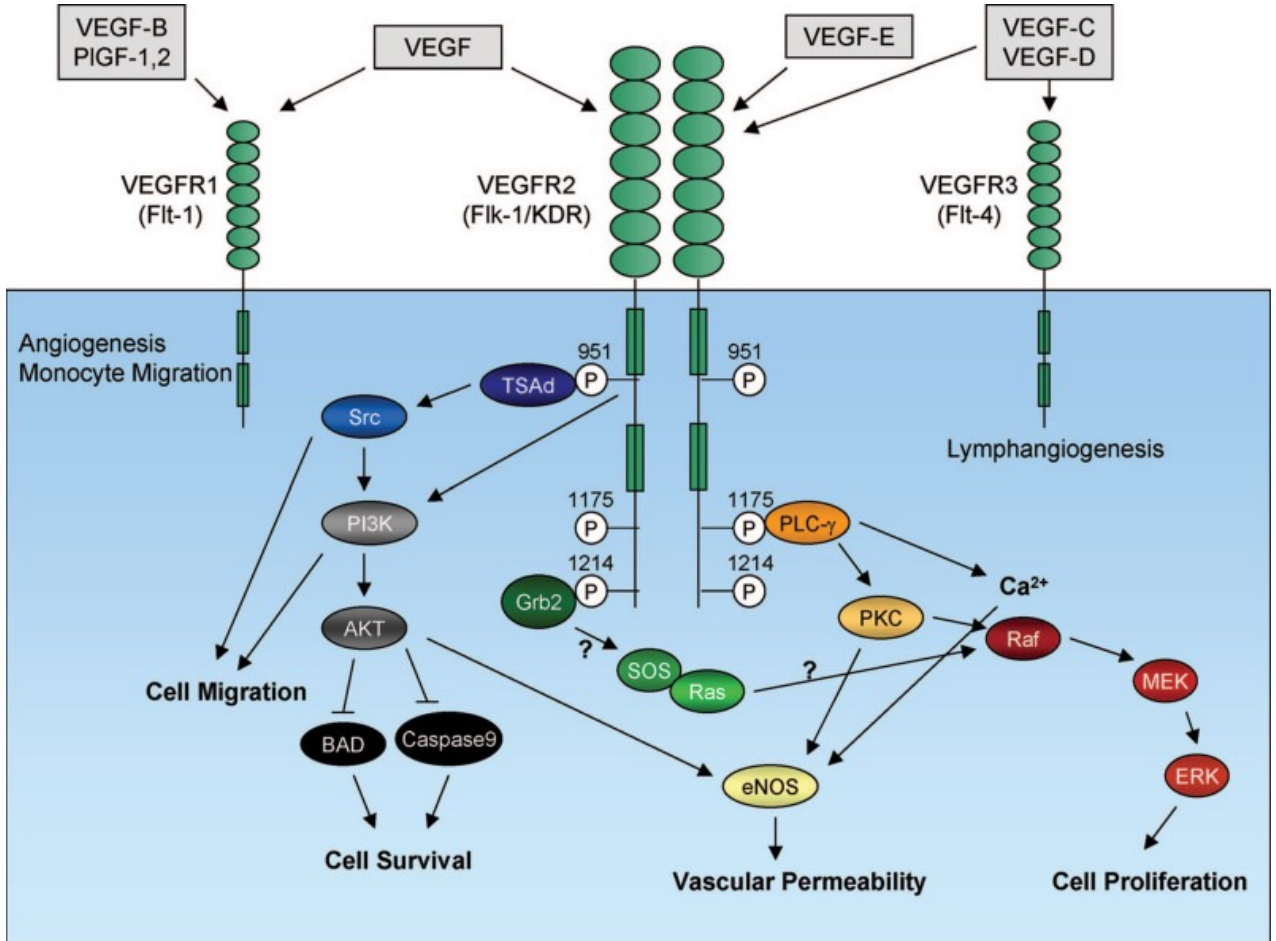


- There are multiple isoforms of VEGF-A that result from alternative splicing of mRNA from a single, 8-exon VEGFA gene.
- These are classified into two groups which are referred to according to their terminal exon (exon 8) splice site:
  - the proximal splice site (denoted $VEGF_{xxx}$)
  - distal splice site ($VEGF_{xxx}b$).
- In addition, alternate splicing of exon 6 and 7 alters their heparin-binding affinity and amino acid number (in humans: VEGF121, VEGF121b, VEGF145, VEGF165, VEGF165b, VEGF189, VEGF206; the rodent orthologs of these proteins contain one fewer amino acids).
- These domains have important functional consequences for the VEGF splice variants:
  - terminal (exon 8) splice site determines whether the proteins are pro-angiogenic (proximal splice site, expressed during angiogenesis) or anti-angiogenic (distal splice site, expressed in normal tissues).

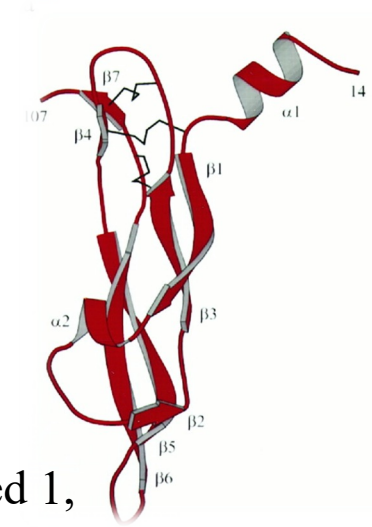
Function and Mechanism

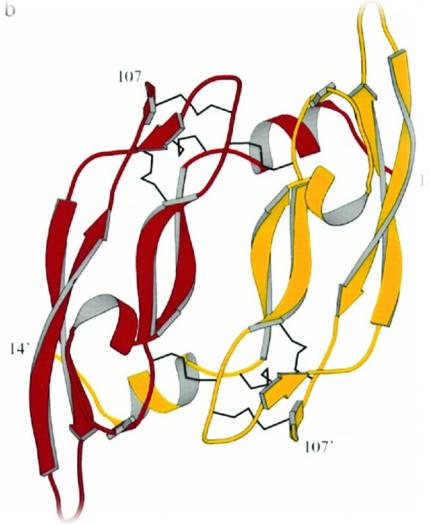
VEGF signaling protein → VEGF receptor → Stimulation of vasculogenesis and Angiogenesis

All members of the VEGF family stimulate cellular responses by binding **to tyrosine kinase receptors (the VEGFRs)** on the cell surface, causing them to **dimerize** and become **activated through transphosphorylation**, although to different sites, times, and extents.

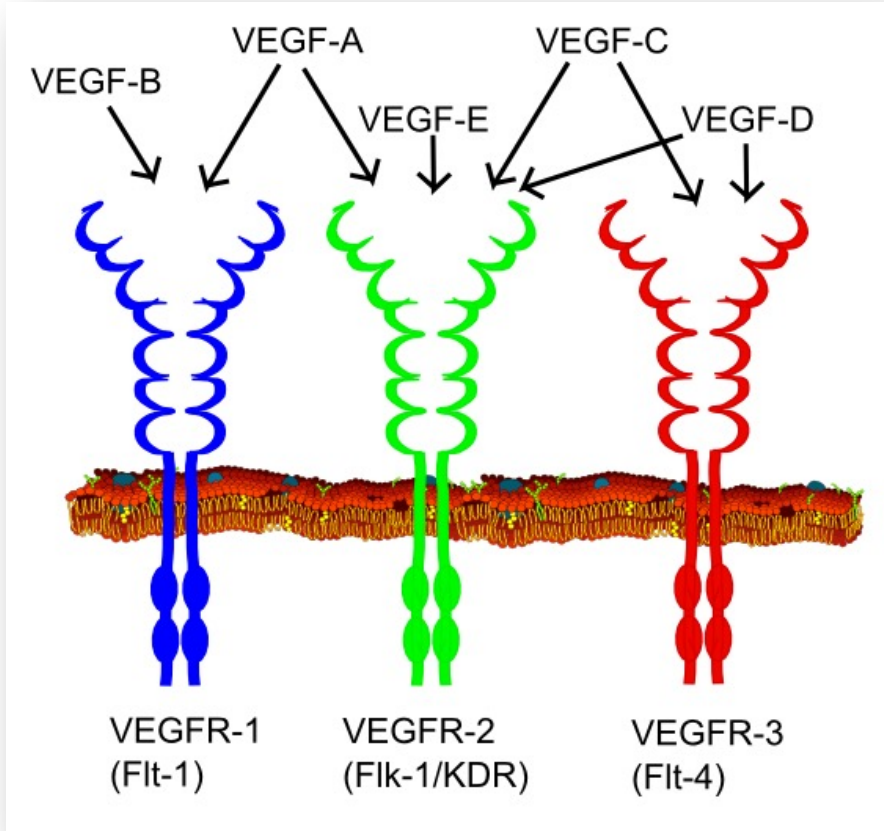


Receptor





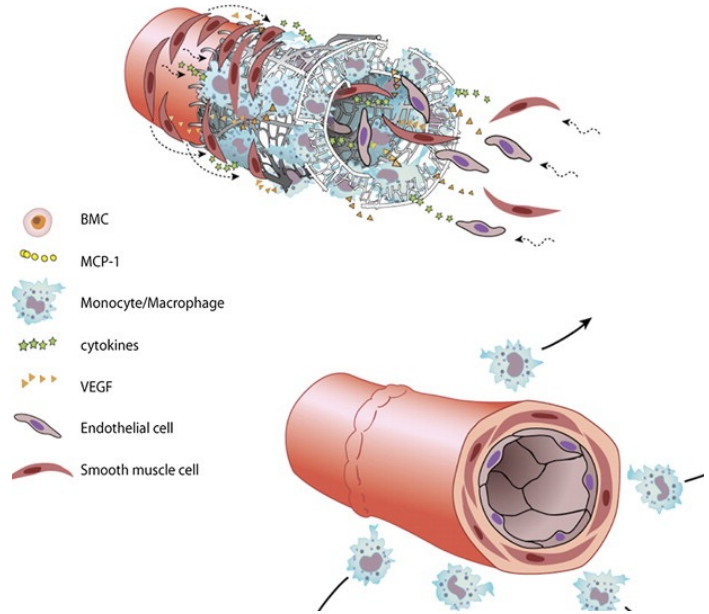
- There are three main subtypes of VEGFR, numbered 1, 2 and 3. Also, they may be membrane-bound (mbVEGFR) or soluble (sVEGFR), depending on alternative splicing.
- The VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain
- VEGF-A binds to VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1).
- VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF.
- VEGF-C and VEGF-D, but not VEGF-A, are ligands for a third receptor (VEGFR-3/Flt4), which mediates lymphangiogenesis.



Roles of VEGF

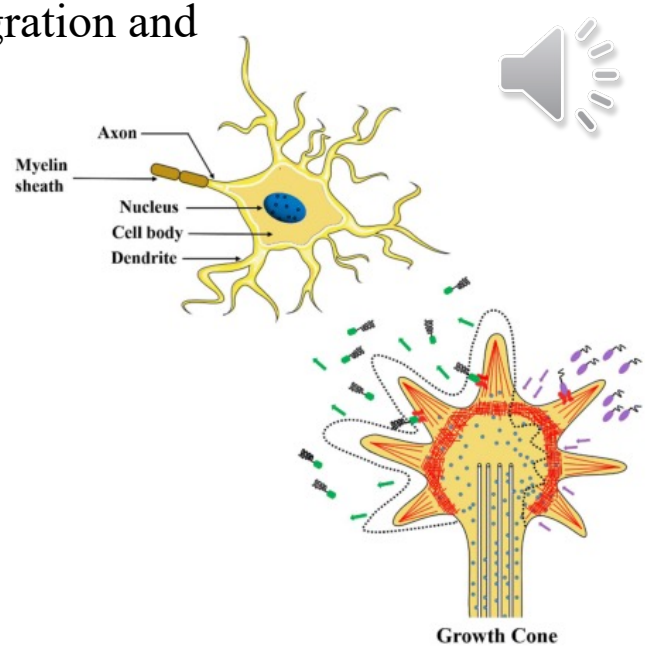
VEGF in the Cardiovascular System

- Myofibroblasts play a major role in the growth, development and repair of normal tissue and are found at the site of infarction
- VEGF contributes to tissue remodelling at the site of infarction in an autocrine manner



VEGF and the Central Nervous System (CNS)

- In the central nervous system (CNS) both positive (pro-migratory) and negative (anti-migratory) regulatory factors are essential for axonal guidance
- Sema3A, a member of the semaphorin family, acts as an inhibitor of neuronal migration and induces neuronal cell death through the neuropilin-1 receptor (NP-1)
- NP-1 also acts as an additional receptor for $VEGF_{165}$ isoform
- $VEGF_{165}$ or anti-NP-1 antibody blocked the effect of Sema3A on undifferentiated
- VEGF has a neurotrophic effect and enhances survival of Schwann cells



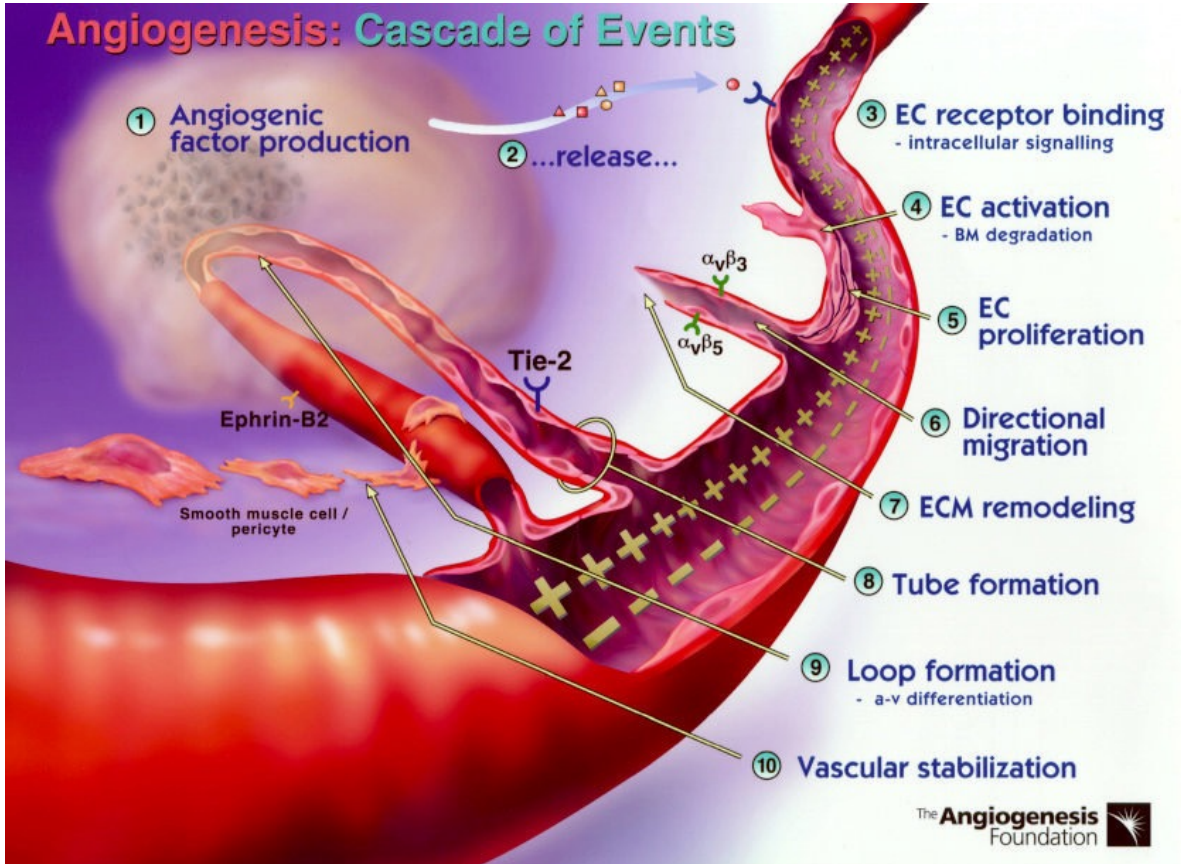
VEGF and Its Role in Bone

- VEGF is produced by hypertrophic chondrocytes in the growth plate where it co-ordinates extracellular matrix (ECM) remodelling, angiogenesis, and bone formation.

Oxygen sensing and expression of VEGF

- VEGF-A production can be induced in a cell that is not receiving enough oxygen.
  - When a cell is deficient in oxygen, it produces HIF, hypoxia-inducible factor, a transcription factor.
  - HIF stimulates the release of VEGF-A, among other functions (including modulation of erythropoiesis).
  - Circulating VEGF-A then binds to VEGF receptors on endothelial cells, triggering a tyrosine kinase pathway leading to angiogenesis.

- The expression of angiopoietin-2 in the absence of VEGF leads to endothelial cell death and vascular regression.



Role of VEGF in Disease

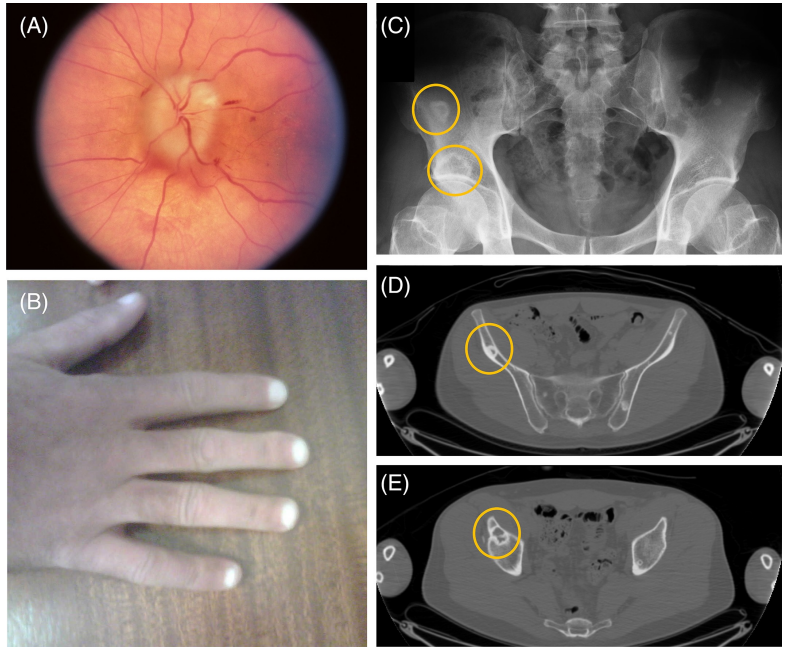
Cancer: Anti-VEGF strategies to treat cancers were designed to target the pro-angiogenic function of VEGF and thereby inhibit neovascularization.

POEMS syndrome:

- Elevated levels of this protein are found in patients with POEMS syndrome, also known as Crow-Fukase syndrome.
- Allelic variants of this gene have been associated with microvascular complications of diabetes 1 (MVCD1) and atherosclerosis

CNS: VEGF-A and the corresponding receptors are rapidly up-regulated after traumatic injury of the central nervous system (CNS).

- VEGF-A is also released **in rheumatoid arthritis** in response to TNF-α, increasing endothelial permeability and swelling and also stimulating angiogenesis (formation of capillaries



- VEGF-A is also important in **diabetic retinopathy (DR)**. The microcirculatory problems in the retina of people with diabetes can cause retinal ischaemia

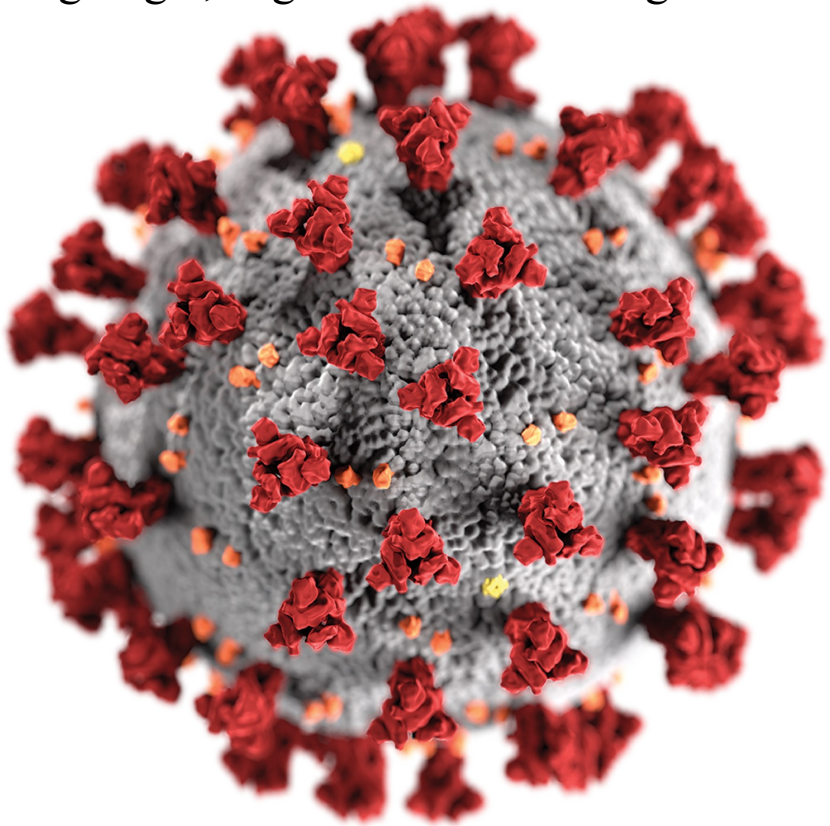
- In the kidney, increased expression of VEGF-A in glomeruli directly causes the **glomerular hypertrophy** that is associated with **proteinuria**

A special case of VEGF: Corona

The levels of VEGF are increased during infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

- promoting inflammation by facilitating recruitment of inflammatory cells, and by increasing the level of angiopoietin II (Ang II), one of two products of the SARS-CoV-2 binding target, angiotensin-converting enzyme 2 (ACE2).

- In turn, Ang II facilitates the elevation of VEGF, thus forming a vicious cycle in the release of inflammatory cytokines



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