The Role of Vascular Endothelial Growth Factor (VEGF) in Tumour Angiogenesis and Anti-Angiogenic Therapeutic Methods to Treat Cancer and Various Retinal Diseases

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In reference to: Research Paper on Anti-VEGF Treatments

What is VEGF?

- **V**ascular **E**ndothelial **G**rowth **F**actor

- Essential cytokine that binds to receptor tyrosine kinases on vascular endothelial cells to induce their growth and proliferation

- Promotes **angiogenesis** (the formation of new blood vessels from pre-existing ones) in response to hypoxia

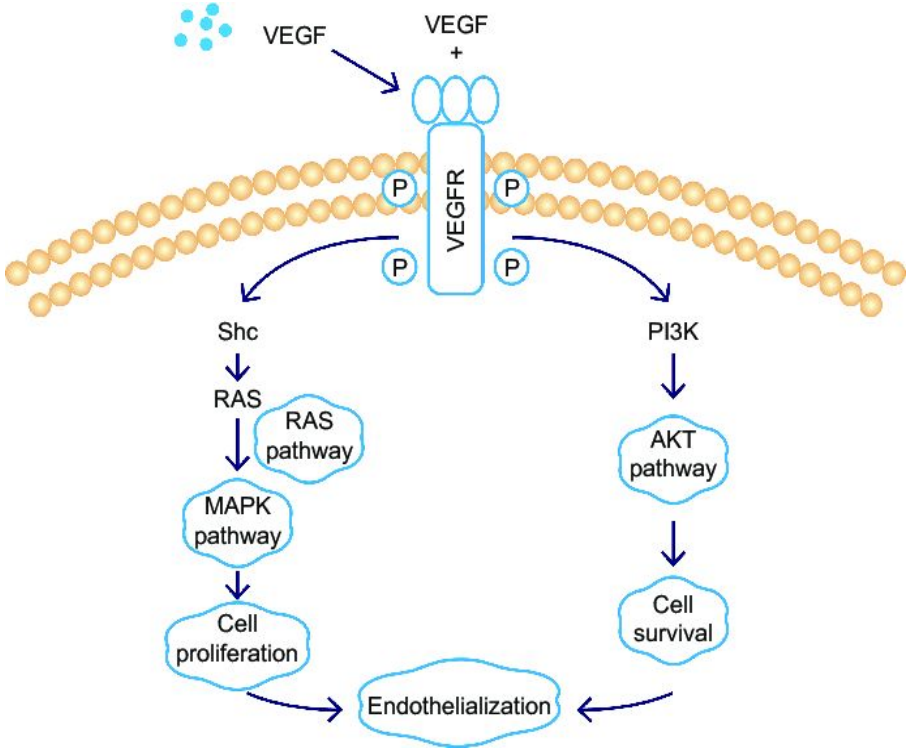

Figure 1: VEGF molecular signaling networks

VEGF Signaling Pathway

- A complex network of signaling pathways

- Focus on PLC-γ-PKC-MAPK Pathway

4 Main Steps:

1. VEGF-A binds to and dimerizes VEGFR1 and VEGFR2 (forming a homodimer)

2. Transphosphorylation of VEGFRs → activates second messengers

3. Intracellular signal transduction is carried out by second messengers

4. Genes promoting angiogenesis are activated

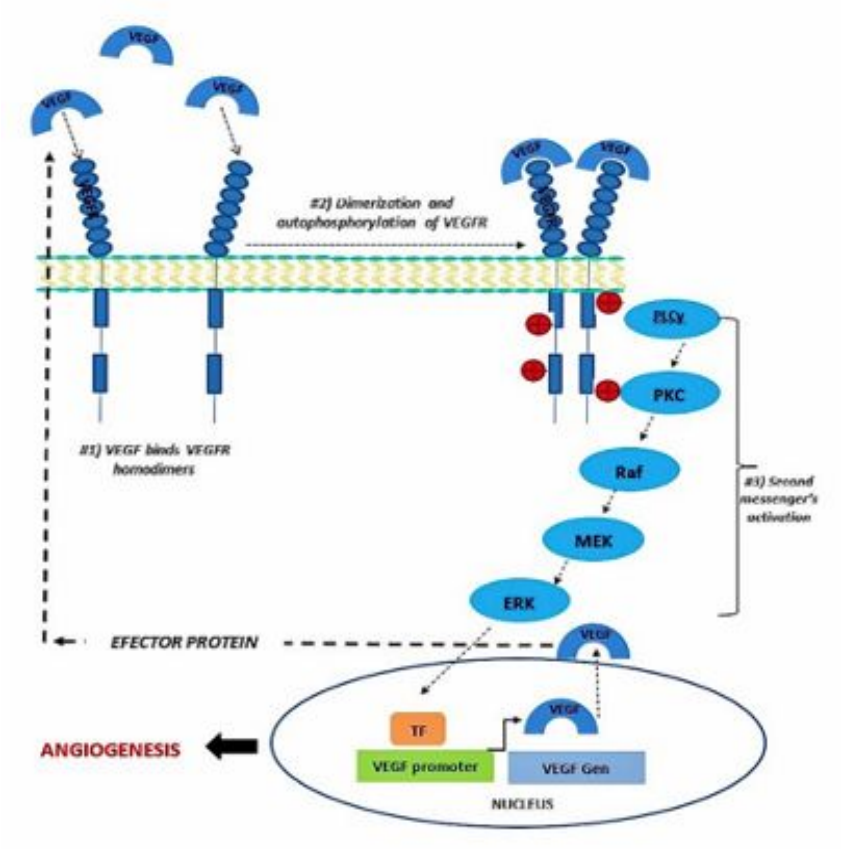

Figure 2: The PLC-γ-PKC-MAPK Pathway

Role of Angiogenesis in Tumour Growth

- Tumour cells require blood to survive

- Secrete abnormally high amounts of VEGF

- Vasculature around tumour allows for growth, expansion, and **metastasis** → the spread of a tumour through blood or lymph to other parts of the body

- Therapeutic goal is to deprive tumour cells of oxygen and nutrients

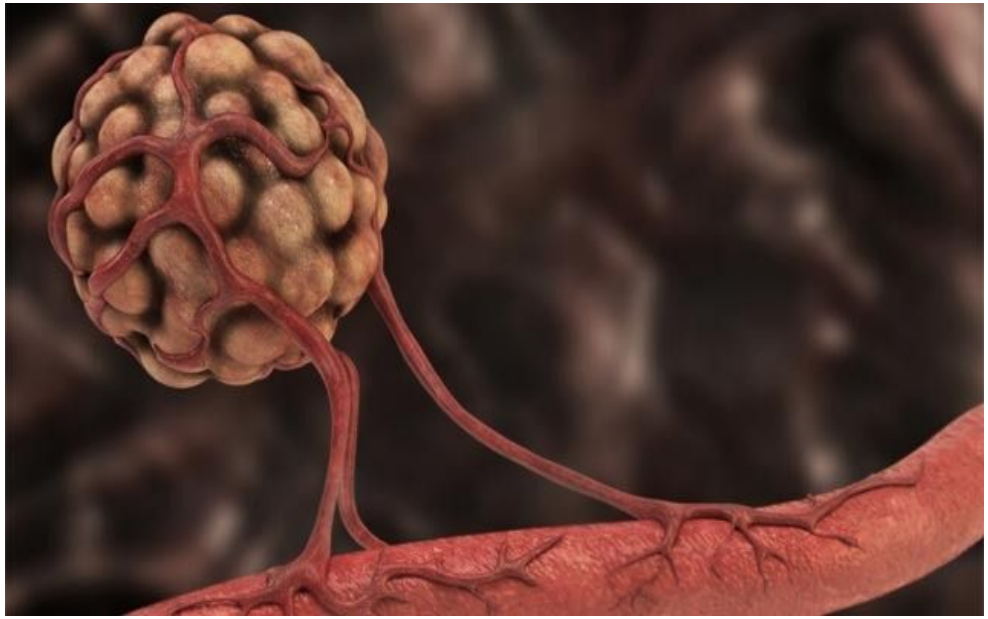

Figure 3: The formation of a tumour vasculature as a result of angiogenesis

VEGF Upregulation Factors in Tumours

- Oncogene expression, other growth factors, hypoxia, etc

- High vascular permeability causes leakage of blood

- Vasculature is suboptimal, resulting in hypoxia and an increase in HIF-1

- HIF-1 stimulates further production of VEGF, resulting in more angiogenesis

- Allows for significant growth and proliferation of tumour, and increases its metastatic potential

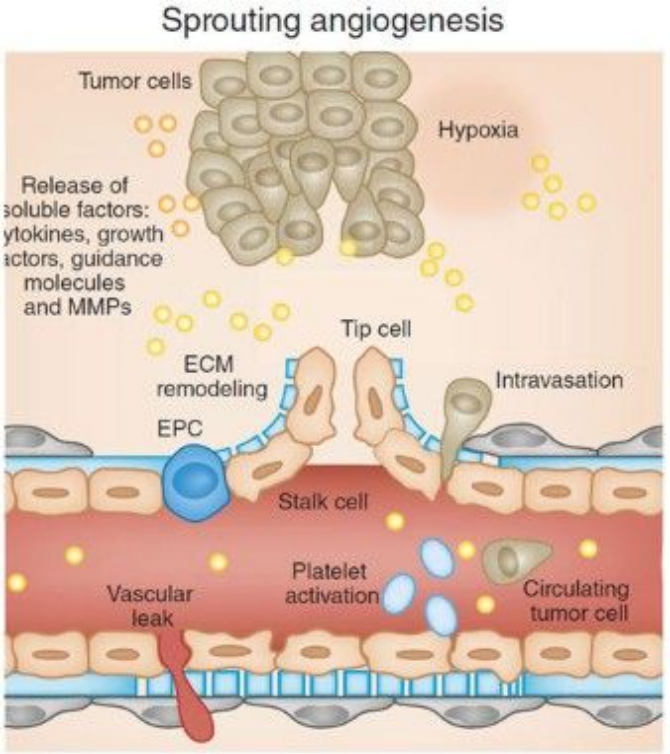

Figure 4: Factors that upregulate the secretion of VEGF

Role of VEGF in Retinal Diseases

- Hypoxia due to capillary nonperfusion (usually as a result of diabetic retinopathy) is the main cause of VEGF production in the eye

- VEGF upregulation can result in aberrant neovascularization and the breakdown of the blood-retinal barrier

- This can cause retinal diseases including:

1. Wet AMD due to CNV

2. Macular edema

- Therapeutic goal is to normalize blood flow

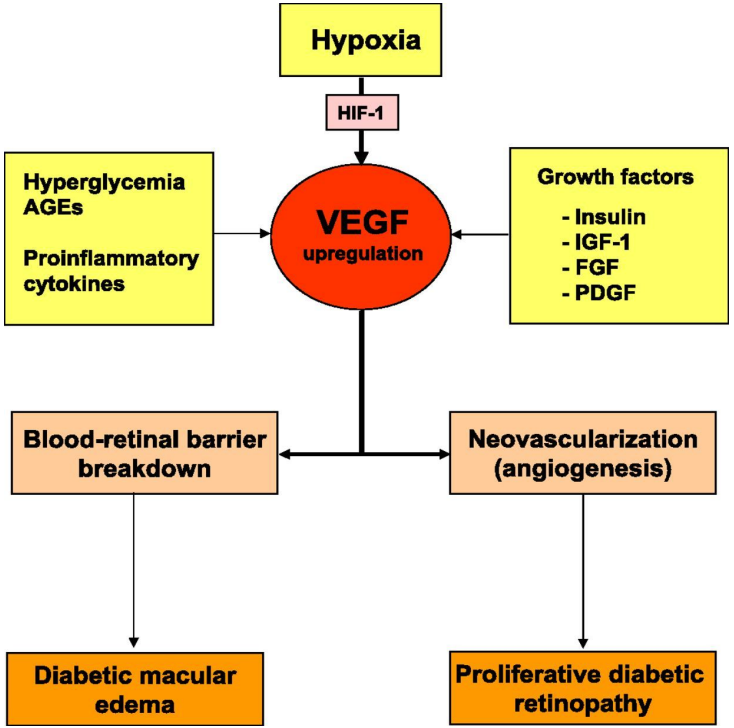

Figure 5: Involvement of VEGF in retinal diseases

Anti-Angiogenic Therapeutic Techniques & Pharmacologic Agents

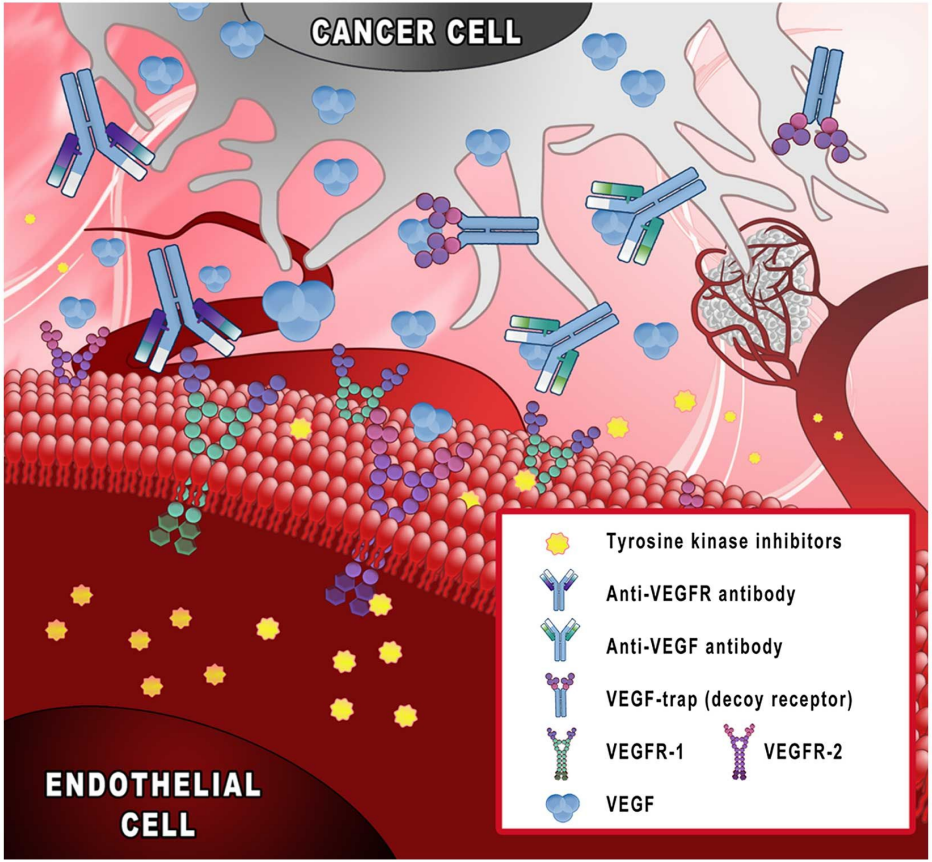

Figure 6: Anti-angiogenic therapeutic methods

1) Anti-VEGF monoclonal antibody treatment

Bevacizumab

- Full-length humanized monoclonal antibody

- Binds to circulating VEGF-A and inhibits the cytokine from binding to its receptors

- Limits and normalizes blood flow to the tumour

- Can treat metastatic colorectal cancer when combined with chemotherapeutic methods

- Sold under the brand name, Avastin®

Figure 7: Avastin medication

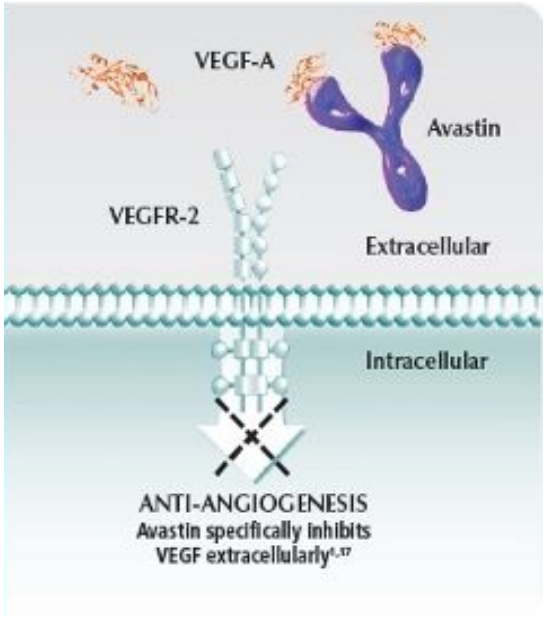

Figure 8: Bevacizumab structure and mechanism of action

Ranibizumab

- Recombinant humanized monoclonal antibod fragment

- Binds to all active isoforms of VEGF-A with high affinity

- Goal is to prevent neovascularization and vascular leakage

- Used to suppress the progression of retinal diseases

- Sold under the brand name, Lucentis®

Figure 9: Molecular structure of Ranibizumab

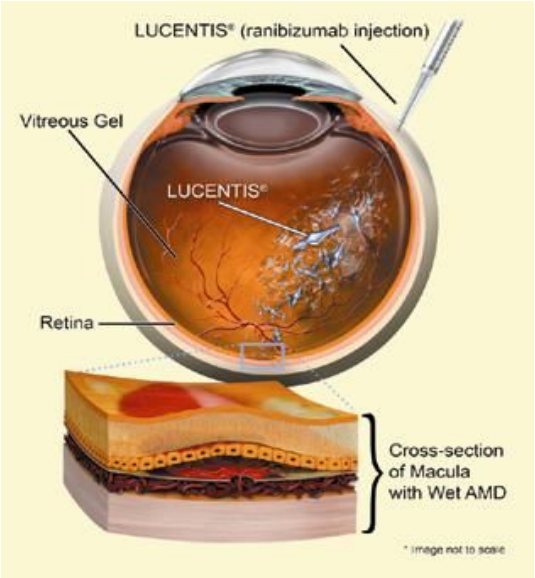

Figure 10: Intravitreal injection of Ranibizumab (Lucentis®) to treat wet AMD

Aflibercept

- Soluble decoy receptor

- Binds to VEGF-A, VEGF-B and PlGF with higher affinity than the cytokines' natural receptors

- Prevents highly permeable blood vessels from forming under retina

- Also effective against metastatic colorectal cancer when combined with chemotherapy

- Sold under the brand names, Eylea® & Zaltrap®

Figure 11: Eylea® medication (for intravitreal injection)

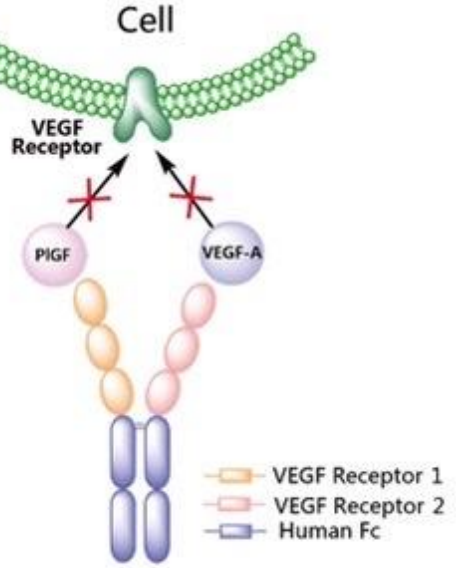

Figure 12: Aflibercept structure and mechanism of action

2) Tyrosine Kinase Inhibitors

- Suppress the signal transduction networks of protein kinases

- Sunitinib, Sorafenib and Pazopanib → TKIs approved for the treatment of patients with advanced cancer

<u>All follow the same mechanism of action:</u>

Competitively bind to catalytic binding sites of TKs → inhibition of autophosphorylation → no activation of intracellular signal transduction pathway → no angiogenic factors transcribed → suppression of angiogenesis

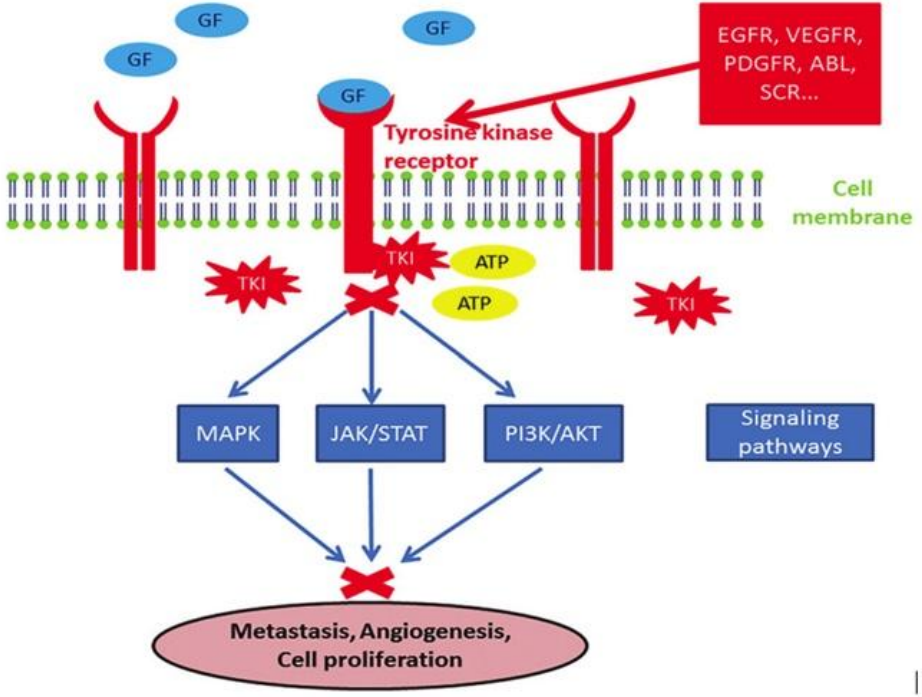

Figure 13: Tyrosine kinase inhibitor mechanism of action

Other Potential Therapeutics

- Anti-VEGFR antibodies ⟶ antibodies that block VEGF Receptors on vascular endothelial cells

- Second messenger inhibitors ⟶ molecules that inhibit the phosphorylation of second messengers and thus suppress intracellular signal transduction

- VEGF gene inhibitors ⟶ molecules that inhibit the expression of the VEGF gene in tumour cells and thus prevent the synthesis and secretion of VEGF

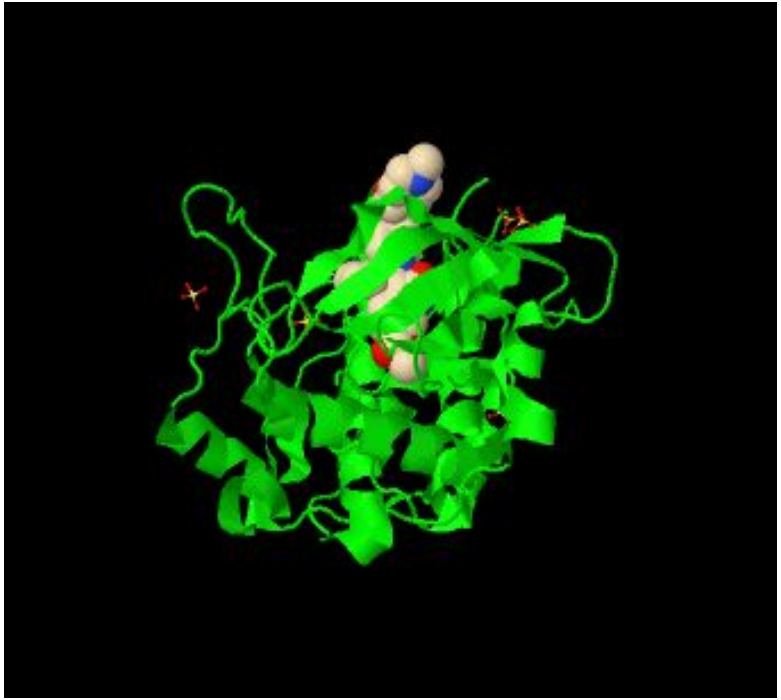

Figure 14: VEGF-VEGFR Complex in 3D