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VEGFR1 signaling in retinal angiogenesis and microinflammation

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VEGFR, vascular endothelial growth factor receptor.

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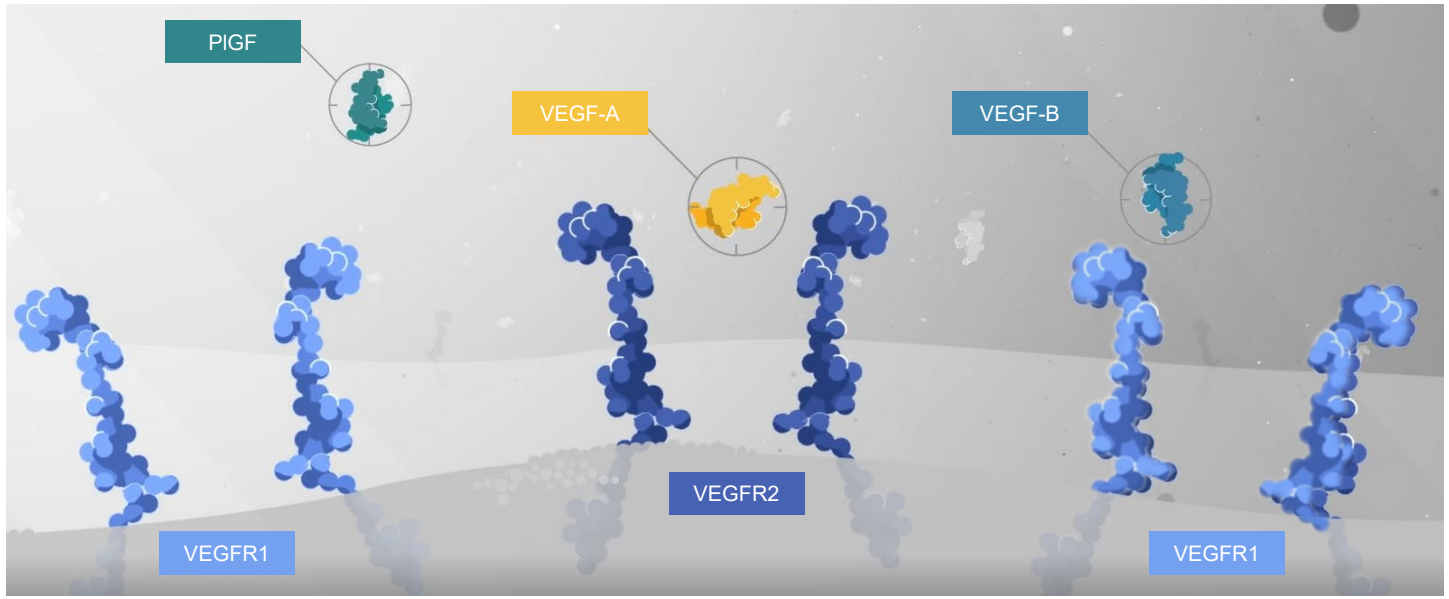
Background

VEGF and their receptors in retinal diseases

- AMD, DR, and RVO lead to the overactivation of VEGFRs, resulting in abnormal growth of blood vessels in the retina[1]
- Intravitreal anti-VEGF therapy is the gold-standard treatment, providing fast and sustained improvements in visual acuity[2]
- Anti-VEGF treatments target VEGF ligands, preventing them from binding to and activating VEGFRs[2]
  - The varying molecular features of these drugs contribute to their unique safety and efficacy profiles[1]



AMD, age-related macular degeneration; DR, diabetic retinopathy; PIGF, placental growth factor; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Lanzetta P *et al. Graefes Arch Clin Exp Ophthalmol* 2017; 255 (7): 1259–1273.

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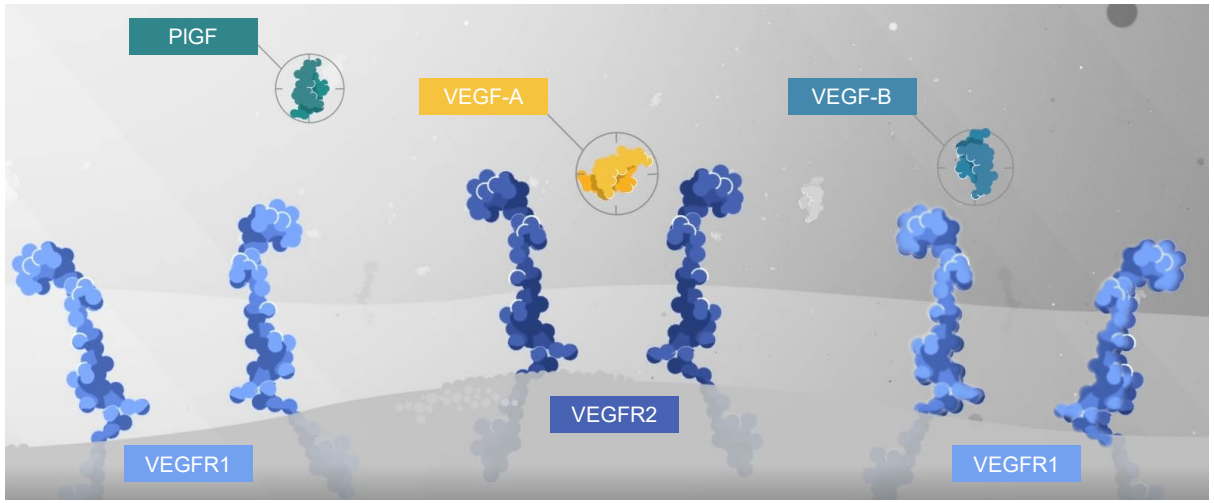
VEGFRs and VEGF ligands

- 3 VEGFRs and 5 VEGF ligands exist in humans and have different functions and ligand-binding properties[1,2]
  - Receptors: VEGFR1, VEGFR2, VEGFR3
  - Ligands: VEGF-A, -B, -C, -D, PlGF
- VEGF-B and PlGF bind and activate VEGFR1, whereas VEGF-A binds and activates both VEGFR1 and VEGFR2[1]
  - Competition among VEGF-A, -B, and PlGF for VEGFR1 binding sites can result in an increased proportion of free VEGF-A which can then activate VEGFR2[1]
  - Although VEGF-A, VEGF-B and PlGF bind VEGFR1, each activates the receptor in a unique manner[3] and the ligands may also have the ability to interact as heterodimers and propagate an increased response[4]
  - VEGFR3 and its ligands VEGF-C and VEGF-D regulate the formation of lymphatic vessels which are absent in the retina.[1] This presentation therefore focuses on VEGFR1 and its ligands



PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Peach CJ *et al. Int J Mol Sci* 2018; 19 (4): 1264; 3. Autiero M *et al. Nat Med* 2003; 9 (7): 936–943; 4. Crespo-Garcia S *et al. Invest Ophthalmol Vis Sci* 2017; 58 (12): 4997–5006.

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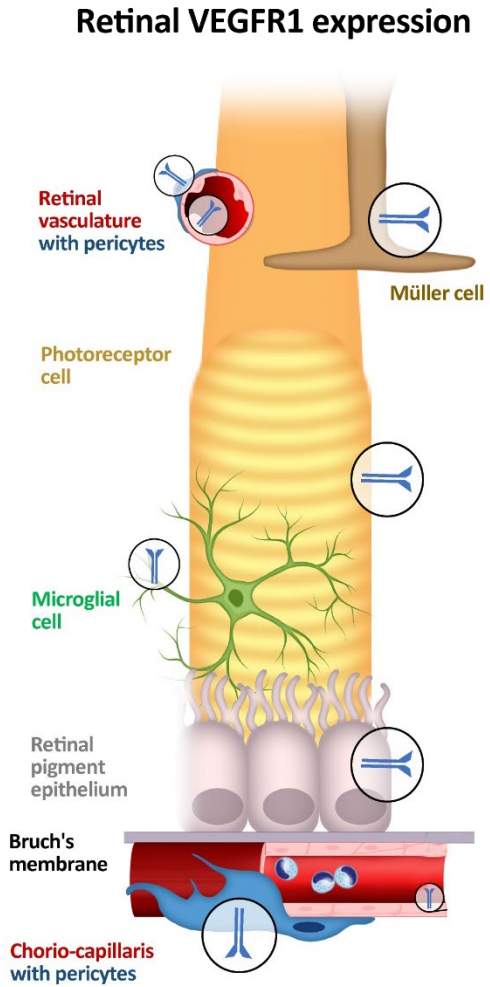
Retinal VEGFRs

- Most research has focused on VEGFR2,[1] shown to induce angiogenesis and increase vascular permeability when activated by VEGF-A in endothelial cells[2]
  - However, both VEGFR1 and VEGFR2 have a role in retinal disease
- VEGFR1 expression has been detected in retinal and choroidal endothelial cells, pericytes, retinal and choroidal mononuclear phagocytes, Müller cells, photoreceptor cells, and RPE cells[1]
- VEGFR1 activation by any of its ligands increases vascular permeability and induces macrophage and microglia production and pro-inflammatory and pro-angiogenic mediators[1] leading to angiogenesis
- Consequences of excess VEGFR1 signaling differ between cell types[1]



RPE, retinal pigment epithelial; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Peach CJ *et al. Int J Mol Sci* 2018; 19 (4): 1264.

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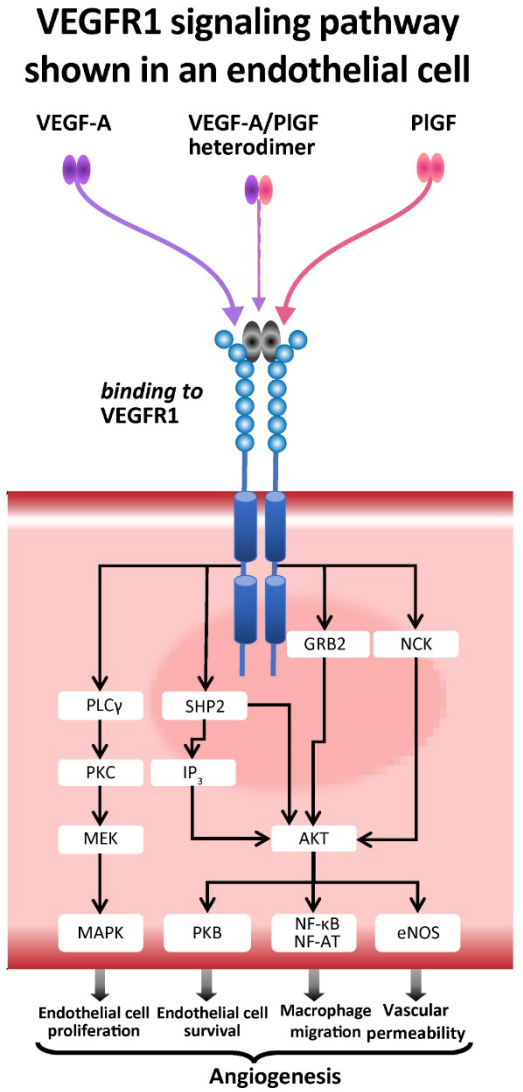
Signaling via VEGFR1

VEGFR, vascular endothelial growth factor receptor.

Signaling via VEGFR1

- Activation of VEGFR1 by VEGF-A or PlGF alone or as a heterodimer induces:
  - Signaling cascades that lead to gene transcription
  - The promotion of pathologic processes involved in angiogenesis in endothelial cells and pericytes in the choroid and retina
- This process is kept under control in healthy eyes, but excess VEGFR signaling can lead to increased:
  - Endothelial cell proliferation
  - Endothelial cell survival
  - Macrophage migration
  - Vascular permeability
- Ultimately leading to pathologic angiogenesis



PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954.

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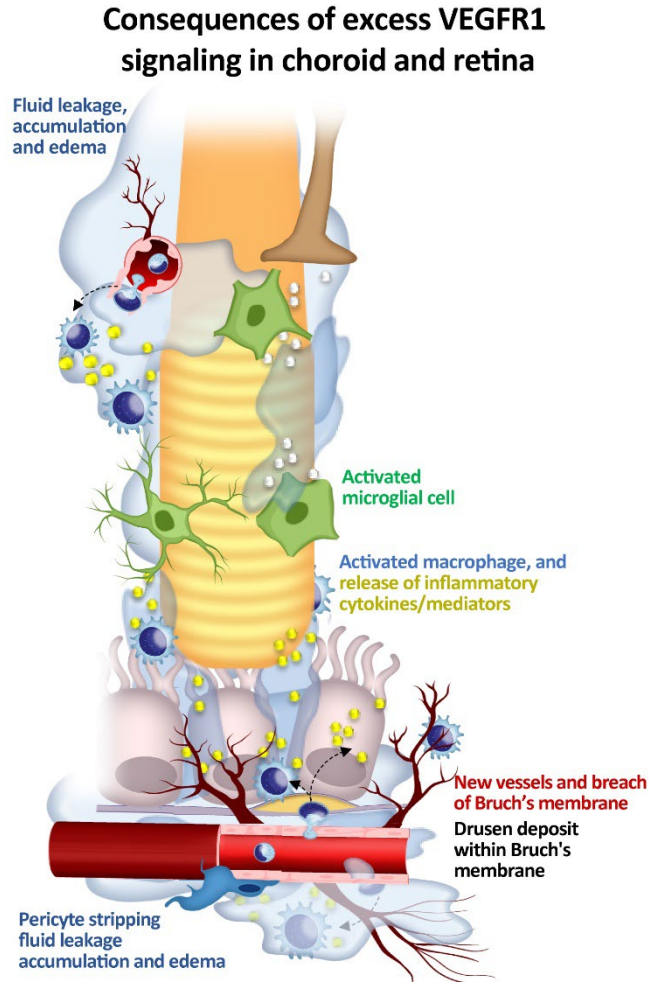
Consequences of excess VEGFR1 signaling in the choroid and retina

- **RPE cells:** neoangiogenesis of vessels through Bruch's membrane into the RPE and loss of RPE cells
- **Photoreceptor cells:** rod death, cone segment loss, and a reduction in photoreceptor integrity
- **Müller cells:** activation, promoting angiogenesis
- **Microglial cells:** recruitment, accumulation, and activation of microglial cells and other retinal macrophages. This results in the release of pro-inflammatory cytokines and the subsequent development of hyper-reflective foci



RPE, retinal pigment epithelium / epithelial; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954.

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Biological functions of VEGFR1

VEGFR, vascular endothelial growth factor receptor.

Biological functions of VEGFR1

- The impacts of activation of VEGFR1's signaling cascades depend on the cell type and the presence of VEGFR1 ligands, other growth factors, and cytokines[1]
- VEGFR1 activation by its ligands can cause retinal disease processes, including increased:[1]
  - Angiogenesis
  - Vascular permeability
  - Inflammation

VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al*. *Prog Retin Eye Res* 2021; 84: 100954.

Biological functions of VEGFR1: angiogenesis

Angiogenesis in the retina
Click the video to play[a]

- Loss of vision in retinal disease is due to pathologic retinal angiogenesis[1]
- VEGFR1 and VEGFR2 are expressed on the cell surface of most blood endothelial cells, and retinal angiogenesis depends on both the gradient of VEGF-A and its concentration[2]
- The direct role of VEGFR1 signaling in angiogenesis has not been fully characterized, and although higher levels of VEGFR1 ligands can increase angiogenesis, results often depend on context due to the complex nature of VEGFR1 signaling[3]

[a]If viewing in browser, please download the PDF in order to play the video.
VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
1. Pierce EA *et al. Proc Natl Acad Sci U S A* 1995; 92 (3): 905–909; 2. Gerhardt H *et al. J Cell Biol* 2003; 161 (6): 1163–1177;
3. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954.

Biological functions of VEGFR1: vascular permeability

- The inner retina is dependent on the retinal vasculature and inner BRB, while the outer retina is maintained by the highly permeable choroidal vasculature and outer BRB[1]
- Although largely attributed to the actions of VEGF-A / VEGFR2, vascular permeability is also controlled by VEGFR1 via activation of endothelial nitric oxide synthase,[1] as stimulated by VEGF-A[2]
- Excess signaling can result in increased vascular permeability, as well as edema and hemorrhage[1]

Increased vascular permeability in the retina
Click the video to play[a]

[a]If viewing in browser, please download the PDF in order to play the video.
BRB, blood–retina barrier; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Bussolati B *et al. Am J Pathol* 2001; 159 (3): 993–1008.

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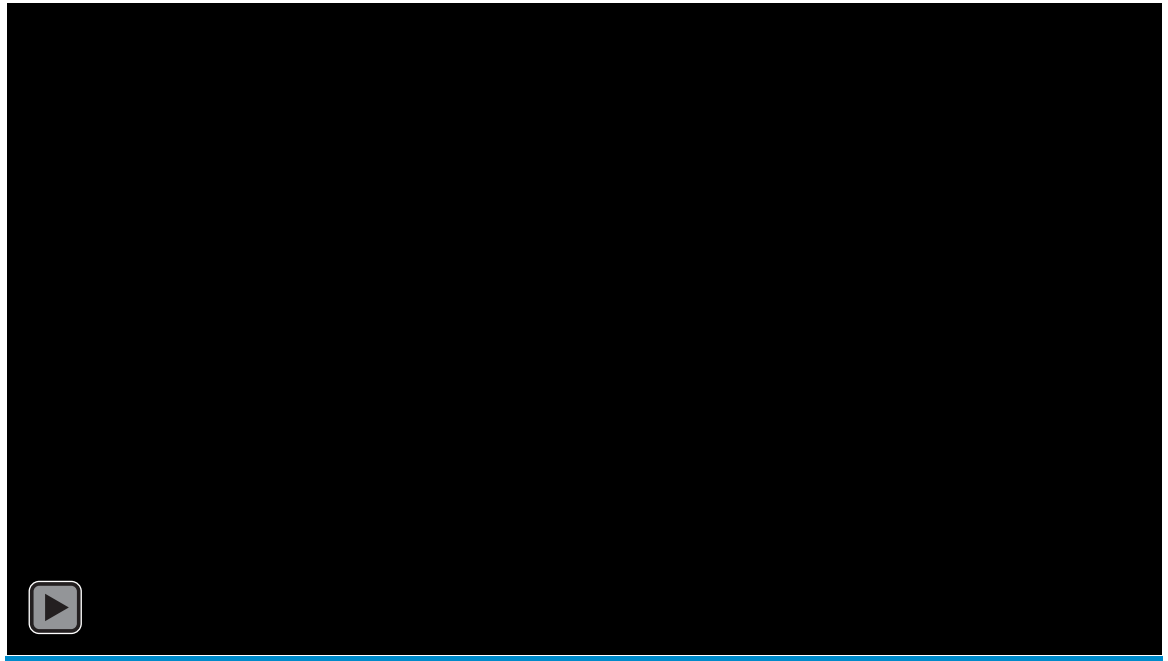
Biological functions of VEGFR1: inflammation



Increased inflammation in the retina
Click the video to play[a]

- VEGFR1 is expressed by mononuclear phagocytes such as microglia and macrophages,[1] which play important immunologic roles in the retina[2]
- Chronic inflammation can be associated with mononuclear phagocytes[3] and can contribute to various retinal pathologies[2]
- In retinal disease, VEGFR1 activation causes macrophages and microglia to produce pro-inflammatory and pro-angiogenic mediators, including certain cytokines and VEGF-A[3]
- It is thought that macrophage-derived VEGF and/or PlGF activate VEGFR1,[4] although further clarity is needed on the ways in which VEGF ligands affect the VEGFR1 signal in macrophages

[a]If viewing in browser, please download the PDF in order to play the video.
PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
1. Crespo-Garcia S *et al. Invest Ophthalmol Vis Sci* 2017; 58 (12): 4997–5006; 2. Rashid K *et al. Front Immunol* 2019; 10: 1975;
3. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 4. Ogura S *et al. JCI Insight* 2017; 2 (3): e90905.

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The role of VEGFR1 in retinal diseases

VEGFR, vascular endothelial growth factor receptor.

The role of VEGFR1 in retinal diseases

- Increased VEGF levels in ocular fluids of patients with retinal eye disease led to the introduction of anti-VEGF therapies in diseases such as neovascular AMD, DR / DME, retinal vein occlusions, and others[1]
- Although our understanding of the molecular and cellular aspects of VEGFRs and their ligands has increased, we are only recently beginning to unravel the relationship between these molecules and the specific pathophysiology of retinal diseases

AMD, age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954.

The role of VEGFR1 in retinal diseases: AMD

- In AMD, unregulated angiogenesis from the subretinal space into the retina results in the formation of leaky vessels[1]
- Growing evidence suggests that the expression of VEGFR1 is greater than VEGFR2 in cells associated with AMD[2]
  - Blocking VEGFR1 can inhibit the development of CNV in murine models[3]
  - PlGF inhibition decreases the volume of activated subretinal mononuclear phagocytes and reduces vessel leakage associated with CNV[4]
- PlGF and VEGF-A are thought to interact via VEGFR1[4]
  - Blocking both VEGF-A and PlGF has an increased inhibitory effect versus blocking PlGF alone, suggesting both ligands mediate monocyte recruitment and mononuclear phagocyte activation[4]
- It is expected that any anti-VEGF therapy inhibiting VEGFR1 could control retinal inflammation in AMD caused by VEGFR1 signaling[2]

AMD, age-related macular degeneration; CNV, choroidal neovascularization; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Akhtar-Schäfer I *et al. EMBO Mol Med* 2018; 10 (10): e8259; 2. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954;
3. Tarallo V *et al. Int J Mol Sci* 2020; 21 (2): 410; 4. Crespo-Garcia S *et al. Invest Ophthalmol Vis Sci* 2017; 58 (12): 4997–5006.

The role of VEGFR1 in retinal diseases: DR and DME

- Diabetes can affect vascular, neuronal, glial, and immune cells[1]
  - Levels of PlGF are elevated in patients with DME and proliferative DR[2]
  - Levels of PlGF and VEGF-A increase with levels of ischemia; mean concentrations increase from the diabetic state, to proliferative DR, and to neovascular glaucoma[3]
- In a pericyte-deficient retina, VEGFR1 facilitates motility of mononuclear phagocytes, which overexpress both VEGF-A and PlGF[4]

PlGF overexpression[5]	Absence of PlGF[5]
Microaneurysms and vascular sprouts Glial cell activation and proliferation	Prevention of retinal cell death, capillary degeneration, pericyte loss, and BRB breakdown

- Differences in efficacy and durability of anti-VEGF therapies in DME[6] may be a result of differences in relative VEGF-A potency or binding affinity between these agents, or may reflect specificity for VEGF-A only versus blockade of VEGFR1 via inhibition of VEGF-A, PlGF, and VEGF-B[7]

BRB, blood–retina barrier; DME, diabetic macular edema; DR, diabetic retinopathy; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Duh EJ *et al. JCI Insight* 2017; 2 (14): e93751; 2. Ando R *et al. Acta Ophthalmol* 2014; 92 (3): e245–246; 3. Kovacs K *et al. Invest Ophthalmol Vis Sci* 2015; 56 (11): 6523–6530; 4. Ogura S *et al. JCI Insight* 2017; 2 (3): e90905; 5. Kowalczuk L *et al. PLoS One* 2011; 6 (3): e17462; 6. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 7. Papadopoulos N *et al. Angiogenesis* 2012; 15 (2): 171–185.

The role of VEGFR1 in retinal diseases: RVO

- BRVO and CRVO can lead to retinal ischemia,[1] cause inflammation and associated vascular remodeling, and result in macular edema[2,3]
- In patients with CRVO or BRVO with macular edema, levels of soluble VEGFR1 were positively correlated with PlGF levels and inflammatory factors, which may implicate the VEGFR1-mediated activation of microglia and macrophages[2,3]
- Anti-VEGF therapies effectively improve VA and macular edema in patients with RVO and have shown good efficacy regardless of whether they target VEGF-A only or both VEGF-A and PlGF[1]
  - The impacts on inflammatory markers between therapies are similar[1]
- However, a study in patients with RVO demonstrated the need for less frequent treatment[4] when using anti-VEGF agents that target multiple ligands[5]
  - Similarly, patients with DME with worse VA at baseline experienced greater gains in VA when treated with anti-VEGF agents targeting multiple ligands[6,7]

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DME, diabetic macular edema; PlGF, placental growth factor; RVO, retinal vein occlusion; VA, visual acuity; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Noma H *et al. Invest Ophthalmol Vis Sci* 2014; 55 (6): 3878–3885; 3. Noma H *et al. Invest Ophthalmol Vis Sci* 2015; 56 (2): 1122–1128; 4. Hykin P *et al. JAMA Ophthalmol* 2019; 137 (11): 1256–1264; 5. Scott IU *et al. JAMA* 2017; 317 (20): 2072–2087; 6. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203; 7. Wells JA *et al. Ophthalmology* 2016; 123 (6): 1351–1359.

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Implications for treatment

Further considerations

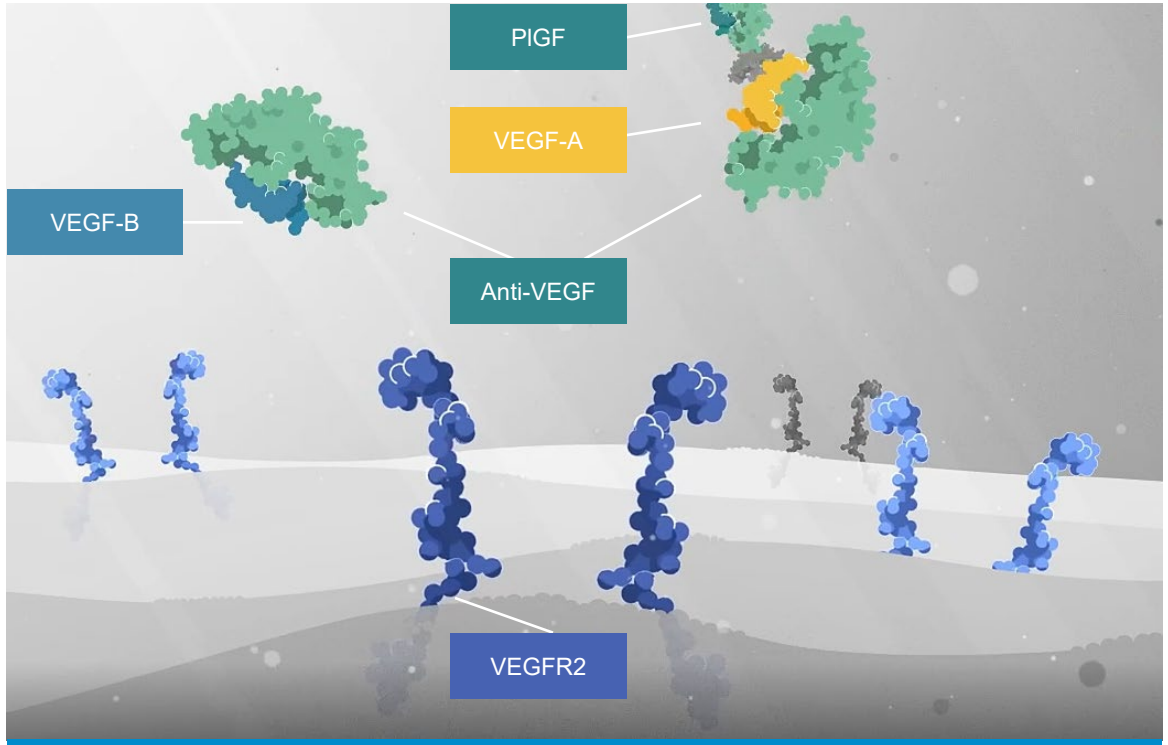
- Evidence is growing of the contributions of VEGF-A, VEGF-B, and PlGF through VEGFR1 to disease mechanisms, including the interplay between microinflammation and angiogenesis
- Although the functional roles of the VEGFR1 ligands in retinal pathologies are unclear, both PlGF and VEGF contribute to pathologic processes in retinal disease[1-3]
- The importance of VEGFR1 and its ligands has been examined in preclinical and clinical studies:
  - Anti-VEGFR1 antibodies more effectively prevent BRB breakdown than those specific to VEGFR2[4]
  - In patients with RVO, levels of ligands and inflammatory cytokines are correlated with aqueous levels of soluble VEGFR1 but not soluble VEGFR2[5]
- It is important to study the full range of relevant molecular interactions between VEGF-A, VEGF-B, and PlGF to elucidate the complex role of VEGFR1 pathways in the context of retinal disease

BRB, blood–retina barrier; PlGF, placental growth factor; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Crespo-Garcia S *et al. Invest Ophthalmol Vis Sci* 2017; 58 (12): 4997–5006; 3. Papadopoulos N *et al. Angiogenesis* 2012; 15 (2): 171–185; 4. Huang H *et al. PLoS One* 2011; 6 (6): e21411; 5. Noma H *et al. Invest Ophthalmol Vis Sci* 2015; 56 (2): 1122–1128.

Implications for treatment

- Anti-VEGF treatments have shown differences in efficacy and durability in retinal disease studies,[1-3] potentially due to differences in binding affinities for VEGFR1 ligands
- Therapeutic interventions targeting a single ligand may not be as effective as those targeting all VEGFR1 ligands[2,3]
  - It is as though we have closed the door to the storm but left the window open. It would be preferable for an effective treatment to close the window as well by binding to all VEGF ligands, thus halting the disease process
- Further research into processes underlying the pathology of retinal diseases may offer insight into the mechanistic basis behind variations in the efficacy of different VEGF inhibitors



It is preferable for an effective treatment to bind all VEGFR ligands[1-3]

PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Uemura A *et al. Prog Retin Eye Res* 2021; 84: 100954; 2. Crespo-Garcia S *et al. Invest Ophthalmol Vis Sci* 2017; 58 (12): 4997–5006; 3. Papadopoulos N *et al. Angiogenesis* 2012; 15 (2): 171–185.

More resources

The literature summary “VEGFR1 Signaling in Retinal Angiogenesis and Microinflammation” can be downloaded from: https://www.visionacademy.org

The video “VEGFR1 Signaling in Retinal Angiogenesis and Microinflammation” can be viewed here: https://vimeo.com/805902307

VEGFR, vascular endothelial growth factor receptor.