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REFERENCES

- 1 Baseler HA, Brewer AA, Sharpe LT, *et al.* Reorganization of human cortical maps caused by inherited photoreceptor abnormalities. *Nat Neurosci* 2002;**5**:364–70.
- 2 Sadato N, Pascual-Leone A, Grafman J, *et al.* Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* 1996;**380**:479–80.
- 3 Hoffmann MB, Seufert P, Schmidtborn LC. Perceptual relevance of abnormal visual field representations—static visual field perimetry in human albinism. *Br J Ophthalmol* 2007;**91**:509–13.
- 4 Käsammann-Kellner B, Ruprecht KW. Albinismus: Klassifikation und klinisches Spektrum. *Z Prakt Augenheilk* 1999;**20**:189–203.
- 5 Apkarian P, Reits D, Spekreijse H, *et al.* A decisive electrophysiological test for human albinism. *Electroencephalogr Clin Neurophysiol* 1983;**55**:513–31.
- 6 Hoffmann MB, Lorenz B, Morland AB, *et al.* Misrouting of the optic nerves in albinism: estimation of the extent with visual evoked potentials. *Invest Ophthalmol Vis Sci* 2005;**46**:3892–8.
- 7 Guillery RW, Hickey TL, Kaas JH, *et al.* Abnormal central visual pathways in the brain of an albino green monkey (*Cercopithecus aethiops*). *J Comp Neurol* 1984;**226**:165–83.
- 8 Hubel DH, Wiesel TN. Aberrant visual projection in the Siamese cat. *J Physiol (Lond)* 1971;**218**:33–62.
- 9 Huang K, Guillery RW. A demonstration of two distinct geniculocortical projection patterns in albino ferrets. *Brain Res* 1985;**352**:213–20.
- 10 Elekessy EI, Campion JE, Henry GH. Differences between the visual field of Siamese and common rats. *Vis Res* 1973;**13**:2533–43.
- 11 Garipis N, Hoffmann K-P. Visual field defect in albino ferrets (*Mustela putorius furo*). *Vis Res* 2003;**43**:793–800.
- 12 Hoffmann MB, Tolhurst DJ, Moore AT, *et al.* Organization of the visual cortex in human albinism. *J Neurosci* 2003;**23**:8921–30.
- 13 Schmitz B, Käsammann-Kellner B, Schäfer T, *et al.* Monocular visual activation patterns in albinism as revealed by functional magnetic resonance imaging. *Hum Brain Mapp* 2004;**23**:40–52.
- 14 Abadi RV, Pascal E. Incremental light detection thresholds across the central visual field of human albinos. *Invest Ophthalmol Vis Sci* 1993;**34**:1683–90.
- 15 St John R, Timney B. Sensitivity deficits consistent with aberrant crossed visual pathways in human albinos. *Invest Ophthalmol Vis Sci* 1981;**21**:873–7.

EDITORIAL

Eyes wide s-flt: clearly, avascular fidelity is a vascular endothelial growth factor family affair

Royce Mohan

Soluble vascular endothelial growth factor receptor-1 (s-flt) may be critical for a variety of human corneal angiogenic conditions

Every year, numerous patients successfully receive corneal transplants because this tissue is both immunologically privileged and it has a remarkable resilience to injury induced neovascularisation.¹ The biological explanation of this gift to man and woman in their quest for sustaining life-long vision, enabling corneal transplantation and the more recent corrective vision surgery a reality, has thus far remained an enigma. Notwithstanding, the search for molecules that allow the cornea to preserve its avascular status has rifled through a long list of known antiangiogenic agents, but the testing of experimental mouse models of their deficiencies have all come up without suitable answers.² This negated explanation for a single gene product being responsible for corneal avascularity spawned the next logical idea that biological redundancies in antiangiogenesis could explain the mystical properties of the cornea. Now, contrary to this belief, Ambati *et al.*, looking at eyes from a wide range of mammalian species, have concluded in a recent report that such a formidable antiangiogenic role is, after all, a vascular endothelial growth factor (VEGF) family affair; the bastion of cornea avascularity is soluble VEGF receptor-1 (s-flt).³ In this issue (*see page*

505), Ambati *et al.* provide important proof as to why it is this molecule that needs to be considered critical for a variety of human corneal angiogenic conditions.⁴

The VEGF family, comprised of VEGF-A, -B, -C, -D and placental growth factor, exhibit specific and varied levels of affinity for their receptors, VEGFR1, VEGFR2 and VEGFR3.⁵ Clearly, the requirement for VEGF is so critical to mammalian development that even loss of a single allele of its gene results in embryonic fatality.⁶ Therefore, it is ironic that the principal angiogenic stimulator VEGF-A is present in the avascular cornea. It is this conundrum that set Ambati *et al.* to suggest that not only humans, but other mammals that depend on visual acuity for survival may have adapted mechanisms to counteract VEGF-A in the cornea. Those honed in the yin and yang of the angiogenic balance hypothesis proposed by Judah Folkman⁷ will find vindication that these investigators discovered Nature's choice to select s-flt as the VEGF-A trap in the cornea, no doubt the antagonistic receptor with the highest binding affinity for VEGF-A. Indeed, the K_d for ligand binding of VEGF-A for VEGFR1 is approximately 2–10 pM, which is an order of

magnitude higher than that for VEGFR2.^{8,9} s-FLT is formed by alternative splicing of the pre-RNA and its expression serves as a natural dominant-negative inhibitor of VEGF action because this spliced variant lacks the vital transmembrane and kinase domain found in membrane bound VEGFR1 (mbFlt-1)¹⁰; embraced in this molecular coitus with s-Flt, VEGF-A is thus retained inactive.³

This rationale sounds good for the uninjured cornea where tissue homeostasis levels of VEGF-A are counterbalanced by s-Flt. But what happens when mutations in genes unrelated to vascular development severely compromise corneal epithelial barrier or structural functions causing chronic inflammation to ensue and leading to corneal angiogenesis? To gain support for their hypothesis that it is diminished s-flt levels that make VEGF-A become bioavailable, Ambati *et al.* assessed vascularised corneas of humans suffering from aniridia, a congenital disease caused by mutations in the gene encoding a master eye transcription factor pax-6.^{11,12} Patients with aniridia suffer from multiple eye problems because PAX-6 regulates developmentally controlled pathways that contribute to eye morphogenesis.¹³ This disease is manifested by the smaller size of the globe or “small eye” with differing levels of penetrance of the disorder, most often being characterised by a rudimentary iris. Interestingly, this disease is also naturally found in many other species that present with similar pathogenic anomalies as the human counterpart,¹² with the *Sey* mouse being a popular rodent model that has been relatively well characterised.¹⁴ Thus, when a collection of human aniridia corneas were investigated it was found that s-flt levels were dramatically lowered compared with those from normal human corneas, suggesting that vascularisation of human aniridia may also be regulated by this molecule.

Could these findings have broader impact on other clinical manifestations

that are known to elicit neovascularisation? When these investigators looked at samples from a series of patients having alkali burn injuries or those afflicted by interstitial keratitis, this theme of an sflt regulated corneal avascular ambit was reinforced. Indeed, sflt levels are found decreased in corneas that become vascularised because of chemical injury, while on the contrary, sflt levels are shown to be returned to normal in spontaneous resolution of childhood keratitis. These findings suggest modalities to restore sflt levels in the cornea to combat the potent angiogenic actions of endogenous VEGF-A,¹⁵ and that produced also by recruited inflammatory cells could serve many clinical applications in antiangiogenesis.

The meeting place for over three decades for testing hypotheses on the roles and efficacies of quite a diversity of angiogenesis modulators has sought the innate vascular resistance of the cornea,^{16,17} all the while unknowing of the mechanisms of how this tissue serves in this dutiful role. Now that the mask has been lifted on this mystery of *Fidelio*,¹⁸ we hope that the lesson learned about corneal avascular fidelity will shape treatments to prevent blindness

from corneal angiogenesis, and in seeking this ultimate clinical goal let us not forget to return this investment to our brethren who donate their eyes for research.

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REFERENCES

- 1 Dana MR, Streilein JW. Loss and restoration of immune privilege in eyes with corneal neovascularization *Invest Ophthalmol Vis Sci* 1996;**37**:2485–94.
- 2 Chang JH, Gabison EE, Kato T, et al. Corneal neovascularization *Curr Opin Ophthalmol* 2001;**12**:242–9.
- 3 Ambati BK, Nozaki M, Singh N, et al. Corneal avascularity is due to soluble VEGF receptor-1 *Nature* 2006;**443**:993–97.
- 4 Ambati BK, Patterson E, Jani P, et al. Soluble vascular endothelial growth factor receptor-1 contributes to the corneal anti-angiogenic barrier. *Br J Ophthalmol* 2007;**91**:505–8.
- 5 Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors *Nat Med* 2003;**9**:669–76.
- 6 Ferrara N, Carver-Moore K, Chen H, et al. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene *Nature* 1996;**380**:439–42.
- 7 Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease *Nat Med* 1995;**1**:27–31.
- 8 de Vries C, Escobedo JA, Ueno H, et al. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor *Science* 1992;**255**:989–91.
- 9 Sawano A, Takahashi T, Yamaguchi S, et al. Flt-1 but not KDR/Flk-1 tyrosine kinase is a receptor for placenta growth factor, which is related to vascular endothelial growth factor *Cell Growth Differ* 1996;**7**:213–21.
- 10 Tischer E, Mitchell R, Hartman T, et al. The human gene for vascular endothelial growth factor, Multiple protein forms are encoded through alternative exon splicing. *J Biol Chem* 1991;**266**:11947–54.
- 11 Jordan T, Hanson I, Zaletayev D, et al. The human PAX6 gene is mutated in two patients with aniridia *Nat Genet* 1992;**1**:328–32.
- 12 Glaser T, Walton DS, Maas RL. Genomic structure, evolutionary conservation and aniridia mutations in the human PAX6 gene *Nat Genet* 1992;**2**:232–9.
- 13 Matsuo T. The genes involved in the morphogenesis of the eye *Jpn J Ophthalmol* 1993;**37**:215–51.
- 14 Hill RE, Favor J, Hogan BL, et al. Mouse small eye results from mutations in a paired-like homeobox-containing gene *Nature* 1991;**354**:522–5.
- 15 Kendall RL, Thomas KA. Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor *Proc Natl Acad Sci U S A* 1993;**90**:10705–9.
- 16 Gimbrone MA Jr, Cotran RS, Leapman SB, et al. Tumor growth and neovascularization: an experimental model using the rabbit cornea *J Natl Cancer Inst* 1974;**52**:413–27.
- 17 Muthukkaruppan VR, Kubai L, Auerbach R. Tumor-induced neovascularization in the mouse eye *J Natl Cancer Inst* 1982;**69**:699–708.
- 18 Kubrick S, Raphael F, Schnitzler A. *Eyes Wide Shut*, Warner Books, New York, New York, USA, 1999.