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Editorial

A role for hepatocyte growth factor in diabetic retinopathy?

Since Michaelson's original hypothesis in 1948[1] that a diffusible biochemical agent was involved in diabetic retinopathy an extensive list of potential angiogenic factors has been generated.[2] Of these, insulin-like growth factor, transforming growth factor β, fibroblast growth factor, members of the interleukin family, and vascular endothelial growth factor (VEGF) are prominent in the neovascularisation associated with proliferative diabetic retinopathy (PDR). The most extensively studied of these is VEGF, which increases vascular permeability and is a potent stimulator of angiogenesis.[3 4] The ability to inhibit VEGF action both in vitro and in vivo by applying blocking antibodies, antisense oligonucleotides, or soluble receptor has heralded modulation of VEGF as the way forward in treating PDR. However, there is considerable evidence that VEGF levels are low or even absent in some patients with active PDR and that VEGF alone is insufficient to promote PDR in animal models.[5 6] Tolentino and colleagues demonstrated that repeated intravitreal injections of VEGF, while being sufficient to promote the hallmarks of non-proliferative diabetic retinopathy, were insufficient to generate preretinal neovascularisation in the monkey.[6] We have proposed that although VEGF promotes the early stage of diabetic retinopathy, other factors may be necessary to promulgate and perpetuate the oxygenated neovascular membranes typical of PDR. One such candidate is placenta growth factor, which has been shown to be present only in the proliferative stage of diabetic retinopathy,[7] while a more recent contender is hepatocyte growth factor (HGF)[8] (and paper by Shinoda *et al*, p 834).

HGF is a mesenchyme derived pleiotropic growth factor that is a member of the scatter factor family.[9–11] It is secreted as a single chain, biologically inactive, glycoprotein precursor which is converted into its active form by proteolytic digestion. Mature HGF is a heterodimer consisting of an α chain (62 kDa) and a β chain (32–34 kDa) attached by a disulphide bond.[9] The α chain contains a heparin binding domain and sulphated polysaccharides such as heparin and heparan sulphate can enhance the potency of HGF.[12] HGF exerts its biological effects through the c-met proto-oncogene (p190MET) product, a transmembrane heterodimeric tyrosine kinase receptor.[13] In addition to promoting cell growth and offering protection against apoptosis, HGF regulates cell dissociation, migration into extracellular matrices, and branching morphogenesis. While this factor plays an important role in development and tissue homeostasis there is considerable evidence that it may also be an important regulator of angiogenesis.[14 15] Firstly, the mitogenic action of HGF on human endothelial cells is the most potent among growth factors, including VEGF. Secondly, HGF acts directly on vascular endothelial cells, which possess the c-met receptor, to promote stimulation of cell migration, proliferation, protease production, tissue invasion, and organisation into capillary-like tubes, all essential facets of angiogenesis. Thirdly, the angiogenic activity of HGF can be blocked by specific neutralising antibodies.

Katsura and colleagues recently reported elevated HGF levels in vitreous samples of patients with active PDR compared with patients without retinopathy.[8] Support for this observation is provided by Shinoda *et al* in this issue of *BJO* (p 834) who report that aqueous HGF levels increase with progression of diabetic retinopathy, being greatest overall in patients with active PDR. The authors failed to demonstrate a correlation between aqueous HGF levels and either (a) serum levels of HGF which remained constant irrespective of the stage of diabetic retinopathy, or (b) aqueous levels of VEGF which, while showing an increase with severity of diabetic retinopathy, did not necessarily increase in parallel with HGF in the same patient sample. The failure to show a correlation between serum HGF and the stage of retinopathy is compelling evidence that the HGF identified in the aqueous is derived from intraocular cells. This is consistent with previous studies which demonstrate that HGF is produced by corneal cells and the retinal pigment epithelium, and that these cells express the c-met receptor.[16 17]

The observation that there was no correlation between aqueous VEGF and HGF levels suggests that the two growth factors operate independently of one another. To what extent HGF is under the control of other intraocular factors has yet to be determined, although there is evidence that fibroblast growth factor works in an additive fashion with HGF but not VEGF when stimulating endothelial cell function.[18]

An interesting observation from this and other studies is that there is tremendous interindividual variation in growth factor levels between patients with active PDR; some show near normal levels while others are excessively high. Is this evidence that the initiation and progression of

PDR can occur through a variety of growth factors but with the same pathological appearance? If this is the case then the concept of treating PDR by targeting a specific growth factor may only be effective in a subset of patients. Further papers such as that by Shinoda and colleagues are needed to confirm this issue.

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