Selective placental growth factor (PlGF) inhibition: a novel pharmacological approach in diabetic retinopathy

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Background: Diabetic Retinopathy (DR) is one of the most common complications of diabetes and the main cause of vision impairment in the working-age population. Current treatments of DR include intraocular injection of anti-VEGF or steroids despite safety concerns. The aim of the present study was to explore the role of placental growth factor (PlGF) as new pharmacological target in DR.

Methods: Primary human retinal endothelial cells (HREC; Innoprot) were used in this study. We assessed TNF- α , VEGF and ERK in HREC exposed (48 h) with high glucose (40 mM) with or without anti-PlGF antibody treatment at different concentrations (from 1 to 50 μ g/ml) by ELISA and Western blot. The effects of anti-PlGF antibody treatment were compared with aflibercept, a VEGF-trap, in order to discriminate the contribution of PlGF inhibition. The viability of HREC was determined using a colorimetric MTT assay. Cellular damage was also assessed by LDH release into the medium.

Results: Anti-PlGF protects HREC against the damage elicited by high glucose. High glucose significantly ($p<0.01$) increased the levels of activated/phosphorylated ERK, while anti-PlGF treatment significantly ($p<0.01$) counteracted ERK phosphorylation, induced by high glucose, in a concentration-dependent manner. HREC exposed to high glucose increased the TNF- α (40 pg/ml) and the VEGF (80 pg/ml) levels that were significantly ($p<0.01$) attenuated, in a concentration-dependent manner, by anti-PlGF treatment. No significant effects were observed with aflibercept treatment, except for VEGF levels.

Conclusions: In conclusion, our data indicate that selective inhibition of PlGF protects HREC against high glucose-induced damage through the inhibition of ERK pathway. Moreover the expression of cytokines such as TNF- α and VEGF were also decreased by anti-PlGF treatment. Such a mechanism, partially distinct from VEGF blockade, if occurring *in vivo* may contribute to the potential therapeutic effect of anti-PlGF antibody in diabetic retinopathy.