Factor XII contributes to VEGF-induced retinal edema and neuroretinal responses in mice

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Diabetic Macular Edema (DME)

- DME is a leading cause of vision loss in working aged adults in developed countries
- Anti-VEGF therapies provide incomplete or minimal improvements in visual acuity in ~40% of patients
- Preclinical studies have implicated Plasma Kallikrein as a mediator of both VEGF-dependent and -independent DME

Clinical Data

• Plasma kallikrein (PKal) is increased in vitreous of patients with DME compared to subjects with macular hole (MH)\(^1\).

• A Phase 2 randomized, sham-controlled, double-blind study assessed the efficacy, safety, and tolerability of monthly intravitreal KVD001 (3 or 6 µg) in 129 subjects with ongoing vision loss despite prior anti-VEGF treatment (NCT03466099)
  — Though this study did not meet the primary endpoint (change from baseline in BCVA letter count), it identified trends for improvement in visual acuity
  • At week 16, there was a significant decrease in the proportion of study eyes with any BCVA loss from baseline for KVD001 6 µg (p=0.0421)
  • In subjects with less severe vision loss (BCVA >55 letters), gains in letter score at week 16 favored KVD001 treatment compared to sham (p=0.0561)

Factor XII (FXII)

• FXIIa is the primary activator of the kallikrein-kinin system
• Both Plasma kallikrein and FXIIa inhibition reduce attacks in hereditary angioedema\textsuperscript{1,2}

\textsuperscript{1}Banerji et al JAMA 2018, \textsuperscript{2}Craig et al Lancet 2023
Factor XII is increased in human DME vitreous

Plasma Kallikrein (PKal) and Factor XII are increased in DME compared with macular hole (MH) vitreous

FXII protein levels correlate with kallikrein activity in DME vitreous


Purpose

To investigate the effects of FXII on retinal edema and neuro-retinal responses in mice.
**Effect of intravitreal FXIIa on retinal thickening**

**Method**
- Bioptogen Envisu SD-OCT
- C57bL6 mice
- 1uL/eye
- Saline/FXIIa (50ng)

- Intravitreal FXIIa induced a 15% (24h) and 24% (48h) increase in retinal thickening compared with baseline.
FXII contributes to VEGF induced retinal thickening

FXIIa contributes to VEGF induced retinal thickening

• FXIIa induced thickening is reduced by 77% in plasma prekallikrein (Klkb1) KO mice compared with WT mice

• VEGF induced thickening is reduced by 53.1% in FXII KO mice and 41.6% in Klkb1 KO mice compared with WT controls
VEGF stimulates increased ERG amplitude in a time-dependent manner

Method

- SD rat
- VEGF 10ng/eye
- Corneal surface electrode
- Dark adapted overnight
- Maximal stimulation flash
  - 5 ms duration
- Powerlab 4S/Labchart 6

VEGF-induced ERG amplitude abnormality is reduced in both FXII and plasma kallikrein knockout mice

- FXII deficiency protects against VEGF-induced neuroretinal dysfunction
Effects of FXII deficiency on ERG responses in mice with 4 months of STZ-induced diabetes

- FXII deficiency protects against diabetes-induced neuro-retinal dysfunction
Potential role of the Kallikrein Kinin System in retinal edema and visual dysfunction

VEGF-independent disruption of BRB tight junctions

FXIIa

Kallikrein Kinin System

BRADYKININ

RETINAL EDEMA

SD-OCT

VISUAL DYSFUNCTION

ERG/Optokinetics
Conclusions

• Intravitreal FXIIa induced retinal thickening in WT mice and this effect is mediated through plasma kallikrein.
• Factor XII deficiency reduced VEGF stimulated retinal thickening.
• Factor XII and Plasma kallikrein deficiency are protective against VEGF-mediated and diabetes induced ERG abnormalities.
• FXIIa may provide a therapeutic target for retinal edema and visual dysfunction
Thank You