Differential molecular signature in cone vs periphery and its impact on customised crosslinking

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Patient tear analyses as well as epithelial gene expression profiling revealed a strong correlation of increased MMP9, reduced LOX (lysyl oxidase) and elevated inflammatory cytokines and inflammation related metabolic factors in keratoconic eyes.

**Observations in the clinic**

- **KC Grade I**
- **KC Grade II**
- **KC Grade III**
- **KC Grade IV**

The disease is characterized by the focal thinning and protrusion.- Localised
Research question?

To evaluate if the gene expression profile of corneal epithelium from the cone area in Keratoconus (KC) differs from the peripheral non-ectatic areas.

Gene expression in corneal epithelium

35 KC patients
9 control subjects

Is there a difference?
Materials & methods

Epithelium (4.5 mm diameter) over cone

The cone vs periphery distinction is based on keratometry and location of the cone based on elevation map. Using a 4.5 mm trephine centered on the cone, epithelium was scraped separately for cone and rest as periphery. In non-ectatic controls, the central 4.5 mm area was taken as cone.
• **LOX** ↓
• **TIMP-1** ↓

- Lysyl oxidase levels were significantly reduced in the cone of KC patients (p=0.002).
- TIMP1 showed a reducing trend that was not significant (p=.09)

• **Col I A1** ↓
• **Col IV A1** ↓

- Structure related genes COL1(p=0.01) and COL4(p=0.008) were also reduced significantly in KC patient cones.

• **MMP9** ↑
• **IL6** ↑
• **TNFa** ↑

- The cytokines IL6 and TNFα did show an increased trend.
- Matrix remodeler MMP9 showed an increasing trend at the cone
Elevated Expression of Matrix Metalloproteinase-9 and Inflammatory Cytokines in Keratoconus Patients Is Inhibited by Cyclosporine A

Attenuation of lysyl oxidase and collagen gene expression in keratoconus patient corneal epithelium corresponds to disease severity

Our current study

Bench
- IL2
- TIMP
- TNF-α

Clinic
- MMP9
- NF κB
- IL 6

Influx of Matrix degrading enzymes

Loss of tight junctions...
..further inflammation

Our translational hypothesis

Biomechanical weakening

Conus Inflam-axis

Breach in the Bowman’s membrane
Conclusion

• Ectasia in KC may be driven by local molecular factors at the cone that possibly spreads to other parts of cornea as disease progresses

Implications

• Localized treatment in the form of customized corneal collagen crosslinking with focal irradiation can be justified.
• Therapeutic drugs targeting matrix degrading enzymes for treating KC

References
