Fuchs Dystrophy: A New Paradigm in Diagnosis and Treatment

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Disclosure

Shire – Consultant

None of the above are relevant to this talk.
I have no proprietary interest in any devices, drugs, or techniques discussed.

Fuchs Dystrophy

- Genetics and Pathogenesis
  - Molecular genetics and pathogenesis
  - Diagnosis and prognosis
- Treatment
  - Surgical therapy: DMEK
  - Medical therapy targets
Fuchs Dystrophy

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Fuchs Dystrophy

- Leading cause of corneal visual loss
  - 30% of US corneal transplants (14,000/year)
  - Visual loss due to corneal edema and/or guttata

Fuchs Genetics

- Minor forms of Fuchs caused by mutations in
  - COL8A, ZEB1, SLC4A11

CTG Expansion Causes Fuchs

- Trinucleotide repeat (CTG) expansion in TCF4 (transcription factor 4) intron (Wieben, 2012)
  - 25-73% Fuchs
  - 0-5% controls
  - More repeats = more severe disease
    (Soliman, 2015)
Molecular Pathogenesis

- Transcription of CTG repeats creates poly(CUG) RNA
- Poly(CUG) RNA sequesters MBNL1, a RNA splicing factor (Du, 2015)
- Splicing errors cause dysregulated transcription and accumulate toxic RNA (Mootha, 2016)
- Non-ATG translation of expansion repeats has been shown to create toxic homopolymeric proteins (Zu, 2011)

Trinucleotide Repeat Diseases

- CAG
  - Huntington’s disease, spinocerebellar ataxia
- CTG
  - Myotonic dystrophy, Fuchs dystrophy
- Other
  - Fragile X syndrome, Friedreich ataxia
Polymerase Slippage – Hairpin Loop

Looped hairpin is stabilized by the G and C nucleotides in the repeat

CTGCTGCTG
GTCGTCGTC

Loop repair may excise (contract) or incorporate (expand) the repeat segment

Above 35 repeats, the TNR expansion segment tends to persist/elongate

Trinucleotide Repeat Diseases

Implications

• Molecular diagnostic testing for Fuchs could have clinical relevance
  – diagnosis
  – risk profile assessment
• Understanding of pathogenesis can yield potential therapeutic targets

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Endokeratoplasty is Treatment of Choice for Fuchs Dystrophy

- DSAEK – Descemet Stripping Automated Endothelial Keratoplasty
  - posterior stroma + endo (80-200 μ)
- DMEK – Descemet Membrane Endothelial Keratoplasty
  - DM + endo (20 μ)

Evolution of Keratoplasty?

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US Data. EBAA 2015 Annual Statistical Report
Clinical Outcomes

- 94% of patients achieve 20/40 or better BSCVA by 3 months
  - 63-80% 20/25
  - 26-44% 20/20
- Compare 12% 20/20 for ultrathin DSAEK
- Fewer higher-order aberrations

**DMEK vs DSAEK**

• Speed of visual recovery
  
  ✓ DMEK
  26%-44% 20/20 at 3 mo
  
  UT-DSAEK
  12% 20/20 at 3 mo

  

• Endothelial cell density
  
  ✓ DMEK
  (16% loss at 6 mo.)
  
  UT-DSAEK
  (36% loss at 6 mo., p < 0.05)

  

• Primary Graft Failure
  
  ✓ DMEK
  (1.4%)
  
  UT-DSAEK
  (3.9%)

  
  Ciriović A. Cornea 2015;34:11-17.

• Rejection: 2-year rates
  
  ✓ DMEK
  (1%)
  
  UT-DSAEK
  (3.3%)

  
**DMEK vs DSAEK**

- **Rejection: 2 year rates**
  - ✓ DMEK
    - (1%)
  - UT-DSAEK
    - (3.3%)
  - *vs: conventional DSAEK (7-12%)*


- **Patient satisfaction**
  - ✓✓✓✓ DMEK
  - UT-DSAEK

  [Hwang/UCSF]

- **Patient satisfaction**
  - In two DMEK vs. DSAEK contralateral studies
  - Satisfaction score: DMEK > DSAEK (Goldich)
  - 9/10 prefer DMEK (Maier)

  Maier AK. Eye 2014 Nov 21 epub ahead of print]
Advantages

UT-DSAEK
- Donor preparation
- Graft deployment
- Rebubble rate
- Learning curve

DMEK
- Speed of visual recovery
- Endothelial cell loss
- Primary graft failure
- Allograft rejection rate
- Patient satisfaction

My EK Algorithm

- **DMEK ideal for**
  - Fuchs dystrophy or mod. corneal edema
  - Uncomplicated anatomy
  - Visual potential of 20/20
  - Preop vision 20/60 or better

My EK Algorithm

- **Ultrathin DSAEK ideal for**
  - Severe corneal edema
  - Tubes, iris defects, absent post. capsule
  - Status post vitrectomy
  - Visual potential of 20/25 or worse
  - Preop vision 20/70 - CF

My EK Algorithm

- **Reserve PK for**
  - Concurrent stromal scarring
  - Need for combined vitreoretinal surgery
  - Flat or absent anterior chamber requiring open sky reconstruction
  - Inability to comply with postop positioning
  - Visual potential of 20/200 or worse
  - Preop vision HM - LP
**Medical Therapy for Fuchs?**

- Understanding of molecular pathogenesis yields a variety of potential therapeutic targets to slow / halt progression
- Promotion of wound healing/repair is another potential treatment avenue
- Rho kinase has been shown to promote corneal endothelial wound repair

**Rho-Kinase Inhibitors in Fuchs**

Koizumi N. Cornea 2013;32:1167-70

Koizumi N. Cornea 2013;32:1167-70
Conclusions

- The CTG repeat expansion mutation in TCF4 is the major cause of Fuchs
- DMEK is an attractive option for surgical treatment of Fuchs
- Improved understanding of pathogenesis is leading to exploration of medical therapy for Fuchs dystrophy

Questions?

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