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Fuchs Endothelial Corneal Dystrophy:

A Neurodegenerative Disorder?

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First described more than a century ago, Fuchs endothelial corneal dystrophy (FECD) is a common disease characterized by progressive loss of endothelial cells, thickening of the Descemet membrane, and deposition of extracellular matrix in the form of guttae. Advanced cases result in corneal edema and vision loss occurring in patients aged 60 years or older.¹

Genetic studies have identified associated genes and chromosomal loci, while proteomic and genomic studies are elucidating molecular pathogenesis. These recent findings suggest a new context in which FECD may be considered—as a neurodegenerative disorder. In this Viewpoint, we explore parallels between FECD and neurodegenerative diseases with better-understood pathogenic mechanisms such as Huntington disease, Fragile X syndrome, and Alzheimer disease. By comparing FECD with this group, we propose some mechanistic themes that may give insight into pathophysiology and possible nonsurgical treatments.

Neural Origins of the Corneal Endothelium

One basis for considering FECD as a neurodegenerative disorder derives from the similarities between the corneal endothelium and neural cells. Corneal endothelial cells are postmitotic, terminally differentiated, and like neurons, must remain functional for an individual's entire life. Moreover, corneal endothelium originates from neural crest cells that migrate over the corneal stroma during embryogenesis. Adult human corneal endothelium contains precursor cells that retain neuronal markers with the capability to produce neuronal and mesenchymal cell proteins.² Further studies on corneal endothelial precursor cells confirm that they have characteristics of multipotent neural crest-derived stem cells, and functional corneal endothelium can be induced from these cells.³ Given the neural characteristics of the corneal endothelium, embryological origins in the neural crest, and

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expression of neuronal markers, it is only a small stretch to consider FECD in light of neurodegenerative disorder paradigms.

FECD as a Trinucleotide Repeat Disorder

Expansions in unstable DNA repeats underlie more than 20 neuromuscular and neurodegenerative disorders. The pathogenic basis for these trinucleotide repeat disorders stems from unstable DNA sequences composed of repeats of 3 nucleotide base pairs that become mutated during DNA replication, resulting in an increased number of repeated sequences in subsequent generations. A recent study demonstrated that more than 50 repeats of the trinucleotide base pair sequence thymine-guanine-cytosine in the third intron of the transcription factor 4 (TCF4) gene were present in 79% of FECD patients and only 3% of normal control participants. With 95% of control participants in this study having 40 repeat lengths of less than 40, a repeat length of more than 50 is highly specific for FECD.⁴ As with other trinucleotide repeat disorders, the heritable transmission and high penetrance of FECD are well-established,¹ but anticipation, the phenomenon in which subsequent generations manifest at earlier ages in some trinucleotide repeat diseases, has not been recognized in FECD.

Disease-causing trinucleotide repeats have been found in both coding and noncoding regions of DNA. Expansions of trinucleotide repeats in coding sequences, such as the polyglutamine mutations in Huntington disease and some spinocerebellar ataxias, are thought to change native protein conformation, which triggers dysfunctional interactions with normal downstream proteins and leads to neuronal loss.⁵ Polyglutamine peptides are also known to form aggregates and intracellular inclusions that may contribute to neuronal toxicity.

It is more difficult to ascertain mechanisms by which trinucleotide repeats in noncoding DNA sequences cause disease. Some noncoding repeats decrease gene expression and cause loss of protein function, such as those responsible for Fragile X syndrome and Friedrich ataxia. In other noncoding repeat disorders, including Fragile X tremor ataxia syndrome and muscular dystrophy, a toxic RNA gain-of-function hypothesis is favored.⁵

Corneal endothelial abnormalities have been reported in trinucleotide repeat disorders such as dentatorubral and pallidoluysian atrophy⁶ and spinocerebellar ataxia type I.⁷ Although the molecular explanation for how *TCF4* intronic repeat expansions cause FECD remains unknown, the fact that almost all trinucleotide repeat disorders affect neural or neuromuscular tissue strengthens the assertion that insights into FECD can be gained by considering it in the context of neurodegenerative diseases.

Role of Oxidative and Endoplasmic Reticulum Stress in the Pathogenesis of Neurodegenerative Disorders and FECD

Other parallels that can be drawn between FECD and neurodegenerative disorders are the roles of oxidative and endoplasmic reticulum stress, which have been implicated as contributors to neuronal apoptosis in Alzheimer, Parkinson, and Huntington diseases.^{8,9} More recently, an oxidant-antioxidant imbalance was detected in FECD endothelium,¹⁰ and

markers of endoplasmic reticulum stress were up-regulated in corneas of patients with FECD, suggesting that activation of unfolded protein response leads to endothelial cell apoptosis.¹¹ Endoplasmic reticulum stress has been shown to induce reactive oxygen species in neurodegenerative diseases associated with protein aggregates (eg, Alzheimer and Parkinson),¹² and a similar process could be occurring in FECD.

Future Directions

To clarify the parallels between FECD and neurodegenerative diseases, a few key questions must be answered. First, how does expansion of the *TCF4* trinucleotide repeat cause the FECD pheno-type? *TCF4* encodes a class I basic helix-loop-helix transcription factor and is ubiquitously expressed, particularly in the developing corneal endothelium and central nervous system.¹³ Insights may be gained from the pathogenic mechanisms of other noncoding trinucleotide repeat diseases. Null mutations or deletion of the *TCF4* gene cause Pitt-Hopkins syndrome, characterized by intellectual disability, developmental delay, breathing problems, epilepsy, and distinctive facies. Since these are absent in patients with FECD and patients with Pitt-Hopkins are not reported to have corneal endothelial dystrophies, it is unlikely that functional loss is the mechanism. Alternatively, an RNA-mediated hypothesis seems more likely. It is possible that the repeat expansion alters transcription start or expression levels of specific *TCF4* isoforms, or gain-of-function RNA aggregation and toxicity may be the basis for endothelial cell death.⁴ The precise role of *TCF4* in FECD should be explored further by characterizing the pathway from RNA transcription of the trinucleotide repeat expansion to protein translation and trafficking to any activation of oxidative or endoplasmic reticulum stress responses.

In addition to the molecular mechanism of FECD pathogenesis by trinucleotide repeat expansion, another major question arises as to potential modifying genes or proteins that interact with *TCF4*. Wieben et al⁴ described 2 control participants (3%) who had long trinucleotide repeat lengths but were unaffected, which may be due to reduced penetrance or delayed disease onset under the influence of modifying genes. Conversely, not all patients with FECD have a long trinucleotide repeat expansion (only 79% sensitivity in the study by Wieben et al⁴), further emphasizing the importance of other genes in the primary causation of FECD.

For clinicians and patients alike, understanding the molecular basis of this disease should bring benefits by providing insights into the development of new targeted therapeutics. Since nonsurgical FECD treatments currently do not exist, an additional benefit of associating FECD with neurodegenerative diseases may be the consideration of new compounds for drug discovery. Approved treatment options for neurodegenerative disorders are not highly effective in general, but recent strategies have focused on generating inhibitors to endoplasmic reticulum and oxidative stress, which play a role in neuronal apoptosis.

Additionally, a new study¹⁴ has shown a beneficial effect of lithium treatment in a mouse model of FECD. Lithium has long been used as a treatment for neuropsychiatric disorders, but this study revealed that lithium treatment induced autophagy, a cellular mechanism that

enhances cell survival in response to endoplasmic reticulum and oxidative stress, in the corneal endothelium. Given the similarities we have proposed between neurodegenerative diseases and FECD, it seems reasonable to suggest that successful treatment approaches that reduce oxidative and endoplasmic reticulum stress in the former may also warrant investigation in the latter.

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