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Review

The pathophysiology of Fuchs' endothelial dystrophy – A review of molecular and cellular insights

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ABSTRACT

Fuchs' endothelial corneal dystrophy (FECD) is the most common corneal endothelial dystrophy and commonly results in loss of vision. This review highlights the advances in our understanding of the pathophysiology of FECD through in vivo confocal microscopy (IVCM) and *in vitro* studies. All layers of the cornea may be affected by FECD, either primarily or secondary to corneal oedema. The primary changes include reduction of endothelial cell density and changes to endothelial morphology. Thickening of Descemet's membrane occurs, with addition of collagenous layers and formation of guttae. Changes secondary to corneal oedema include formation of epithelial bullae and sub-epithelial fibroblast and collagen infiltration, reduction of sub-basal corneal nerve density, and reduced anterior keratocyte density and fibroblastic transformation of stressed keratocytes in the stroma. Many of the microstructural changes occurring in FECD may be observed with IVCM, and these observations correlate well with histological studies. IVCM studies of early and mid-stage FECD are likely to provide further insight into the sequence of pathological processes that occur in this disease.

1. Introduction

Fuchs' endothelial corneal dystrophy (FECD) is the most common endothelial dystrophy. The Reykjavik Eye Study revealed a 9.2% prevalence in residents over 55 years old in Reykjavik, Iceland (Zoega et al., 2006); a study found a prevalence of 6.7% in an over-50 year old Chinese Singaporean population and 3.7% in an over-50 year old Japanese population (Kitagawa et al., 2002). It typically presents in the sixth decade but early onset cases have also been reported (Borboli and Colby, 2002). FECD demonstrates a female preponderance with a 3.5:1 bias in patients that underwent penetrating keratoplasty for FECD at Duke University Eye Centre, USA (Afshari et al., 2006). Prevalences of 11% females vs 7% males in Icelanders, 8.5% vs 4.4% in Chinese Singaporeans, and 5.5% vs 1.5% in Japanese were also found (Kitagawa et al., 2002; Zoega et al., 2006). An association with hypermetropia is common (Pitts and Jay, 1990).

Four clinical stages of the disease have been described (Adamis et al., 1993): In stage 1, endothelial excrescences called guttae (Fig. 1) are present in the central cornea, but vision is not affected. In stage 2, corneal endothelial cells become thinner, enlarged and reduced in number, along with confluence of guttae extending towards the peripheral cornea; mild corneal stromal oedema and painless reduction in vision is observed. In stage 3, the severity of corneal stromal oedema increases and is associated with epithelial and sub-epithelial bullae, and painful loss of vision. In stage 4, severe oedema is associated with opacification and vascularisation of the cornea, but the pain subsides (Elhalis et al., 2010).

Although still an enigmatic disease, our knowledge of FECD has expanded greatly in recent years due to a combination of clinical and laboratory studies. This review highlights the advances in our understanding of the pathophysiology of FECD through in vivo confocal microscopy (IVCM) and *in vitro* studies.

2. Genetic basis

To date, mutations in several genes have been shown to be linked to the disease. Most cases are sporadic and in familial cases autosomal dominant inheritance has been recognised (Cross et al., 1971; Krachmer et al., 1978). Two autosomal dominant mutations (L450W (Gottsch et al., 2005) and Q455K (Biswas et al., 2001)) in COL8A2, the gene encoding the α2 chain of type VIII collagen, have been reported in early onset FECD. Type VIII collagen is an important part of Descemet's Membrane (DM) secreted by the endothelium (Shuttleworth, 1997). Homozygous knock-in mouse models

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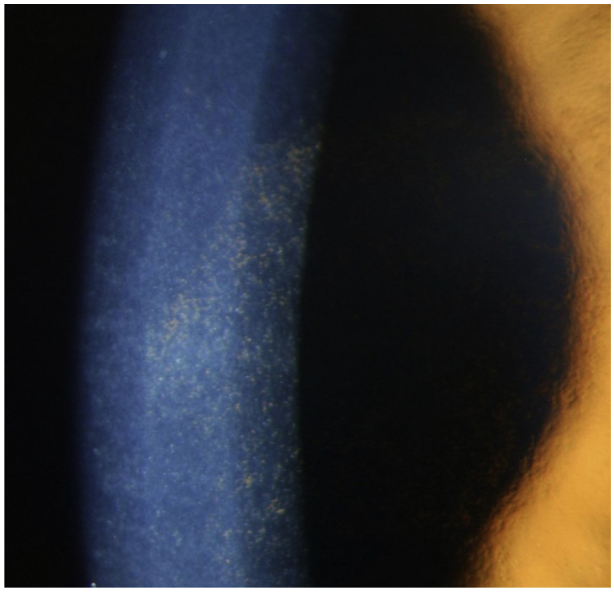

Fig. 1. Slit-lamp photograph of the cornea in FECD showing a "beaten metal" endothelial appearance associated with pigment and guttae (DV Patel, unpublished).

containing one of the two mutations demonstrate early onset FECD pathology (Jun et al., 2012; Meng et al., 2013); currently these are the only mouse models that display consistent FECD pathology. On the other hand, mice deficient in α1 and α2 subunits of collagen VIII exhibit reduced endothelial numbers with polymegathism and polymorphism, corneal opacification, and a thin DM despite absence of guttae, therefore the effects of collagen VIII deficiency are not the same as that caused by COL8A2 mutations (Hopfer et al., 2005). Loss of function missense mutations in TCF8, a gene encoding the ZEB1 protein, are sufficient to cause late onset FECD (Riazuddin et al., 2010b). Although the exact role of TCF8 is unclear, other TCF8 mutations that cause posterior polymorphous corneal dystrophy lead to over expression of COL4A3, suggesting the involvement of this collagen subunit in FECD pathology caused by TCF8 (Krafchak et al., 2005). Single nucleotide polymorphisms of the TCF4 gene, encoding the E2-2 protein, are thought to result in decreased expression of the protein (Baratz et al., 2010). E2-2 is a transcription factor known to up-regulate TCF8 (Sobrado et al., 2009), suggesting that both TCF4 and TCF8 are involved in the same pathway in FECD development.

A group of mutations in SLC4A11, encoding a sodium-borate co-transporter NaBC1, were also identified (Riazuddin et al., 2010a; Soumittra et al., 2014; Vithana et al., 2008). This transporter is located in the basolateral membrane of endothelial cells and was shown to facilitate transmembrane water movement (Vilas et al., 2013); FECD SLC4A11 mutations expressed in cells show intracellular retention of the protein (Vilas et al., 2012). SLC4A11 double knock-out mice did not exhibit any abnormalities in the endothelium and DM (Lopez et al., 2009). Therefore, SLC4A11 mutations alter endothelial water pump function, but NaBC1 is not essential for endothelial and DM function. A missense mutation in LOXHD1, a gene encoding a protein found in the plasma membrane, leads to over-expression and aggregation of the protein in the endothelium and DM, which could cause cell toxicity and endothelial breakdown (Riazuddin et al., 2012). In summary, mutations in two transcription factors (TCF4/E2-2 and TCF8/ZEB-1), one collagen subunit (COL8A2), and two membrane proteins (LOXHD1 and SLC4A11/NaBC1) have been found in FECD. Except LOXHD1, these mutations appear to converge on the collagen secretion and water pump functions of corneal endothelium.

3. Corneal endothelium

The normal corneal endothelium is a single cell layer, approximately 1.5–2.5 μm thick. The cells are thickest at the site of the nucleus and have a thick anterior cell membrane and a smooth posterior surface, with desmosomes and tight junctions between each cell, forming a continuous layer facing the aqueous humour (Kayes and Holmberg, 1964). The endothelium maintains corneal clarity by controlling water content in the stroma; it acts as a barrier to fluid entry from aqueous humour into the cornea, and a pump to remove fluid from the cornea (Bourne, 2010). When imaged by IVCM, healthy corneal endothelial cells appear as a regular array of mainly hexagonal cells which exhibit bright cell bodies and dark cell borders (Fig 2a) (Patel and McGhee, 2007). In contrast, the endothelium in FECD may resemble the surface of a strawberry, consisting of hyporeflective round areas separated by hyper-reflective regions (Fig 2b,c).

FECD is characterised by reduced endothelial cell density with cellular pleomorphism (variation in cell shape) and polymegathism (variation in cell size) (Alomar et al., 2011; Bourne et al., 1982;

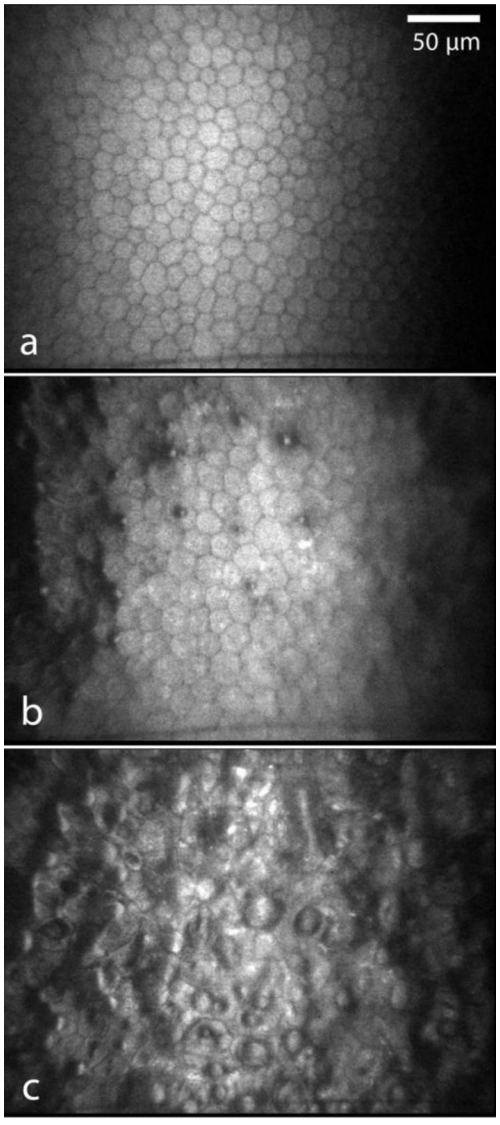

Fig. 2. Slit-scanning in vivo confocal microscopy images of (a) healthy corneal endothelium (b) mild FECD and (c) severe FECD (DV Patel, unpublished).