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Pathogenesis and treatments of *TGFBI* corneal dystrophies

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ABSTRACT

Transforming growth factor beta-induced (*TGFBI*) corneal dystrophies are a group of inherited progressive corneal diseases. Accumulation of transforming growth factor beta-induced protein (TGFBIp) is involved in the pathogenesis of *TGFBI* corneal dystrophies; however, the exact molecular mechanisms are not fully elucidated. In this review article, we summarize the current knowledge of *TGFBI* corneal dystrophies including clinical manifestations, epidemiology, most common and recently reported associated mutations for each disease, and treatment modalities. We review our current understanding of the molecular mechanisms of granular corneal dystrophy type 2 (GCD2) and studies of other *TGFBI* corneal dystrophies. In GCD2 corneal fibroblasts, alterations of morphological characteristics of corneal fibroblasts, increased susceptibility to intracellular oxidative stress, dysfunctional and fragmented mitochondria, defective autophagy, and alterations of cell cycle were observed. Other studies of mutated TGFBIp show changes in conformational structure, stability and proteolytic properties in lattice and granular corneal dystrophies. Future research should be directed toward elucidation of the biochemical mechanism of deposit formation, the relationship between the mutated TGFBIp and the other materials in the extracellular matrix, and the development of gene therapy and pharmaceutical agents.

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Abbreviations: ALKP, anterior lamellar keratoplasty; BAC, benzalkonium chloride; DALK, deep anterior lamellar keratoplasty; ECM, extracellular matrix; FAS1, fasciclin 1; FD-OCT, Fourier-domain optical coherence tomography; GCD1, granular corneal dystrophy type 1; GCD2, granular corneal dystrophy type 2; KE, keratoepithelin; LASEK, laser epithelial keratomileusis; LASIK, laser in situ keratomileusis; LCD, lattice corneal dystrophy; MMC, mitomycin C; mTOR, mammalian target of rapamycin; PKP, penetrating keratoplasty; PRK, photorefractive keratectomy; PTK, phototherapeutic keratectomy; RBCD, Reis-Bücklers corneal dystrophy; RGD, arginine–glycine–aspartate; RK, radial keratotomy; ROS, reactive oxygen species; TBCD, Thiel-Behnke corneal dystrophy; TGFBI, transforming growth factor beta-induced; TGFBIp, transforming growth factor beta-induced protein; UPS, ubiquitin/proteasome system; WT, wild-type.

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1. Introduction

1.1. What is TGFBIp and what is its function?

Transforming growth factor beta-induced gene (*TGFBI*; *BIGH3*; *βigh3*) encodes transforming growth factor beta-induced protein (TGFBIp), a 68-kDa extracellular matrix (ECM) protein composed of 683 amino acid residues. TGFBIp is also described as keratoepithelin (KE), BIGH3, βig-h3, or βigh3 depending on the major production site or the time of description. TGFBIp contains a secretory signal peptide sequence, a cysteine-rich EMI domain, four homologous fasciclin 1 (FAS1) domains which each contain 140 amino acid residues at the N-terminus, and an arginine-glycine-aspartate (RGD) motif which binds to integrin at the C-terminus. TGFBIp was first isolated from an adenocarcinoma cell line, where it was up-regulated after TGF-β treatment (Skonier et al., 1992). TGFBIp is known to exist ubiquitously in various organs including heart, liver, pancreas (Skonier et al., 1992), skin (Skonier et al., 1992), bone (Kitahama et al., 2000), tendon (Ferguson et al., 2003a, 2003b), endometrium (Carson et al., 2002), kidney (Lee et al., 2003) and blood plasma (Klintworth et al., 1998). The role of TGFBIp is not understood completely. TGFBIp is thought to play pivotal roles in physiologic and pathologic responses by mediating cell adhesion (Nam et al., 2005; Park et al., 2004, 2009; Skonier et al., 1992), migration (Nam et al., 2005; Park et al., 2004), proliferation and differentiation (Park et al., 2009). *In vitro*, TGFBIp is reported to mediate cell adhesion and/or spreading through integrins α1β1, α3β1, αvβ3, αvβ5, α6β4, and αmβ2 (Kim and Kim, 2008; Kim et al., 2002, 2003; Nam et al., 2006; Ohno et al., 1999; Park et al., 2004). TGFBIp is also associated with progression, dissemination, metastasis and suppression of malignant tumors (Fan et al., 2014; Massague, 2008; Nam et al., 2005). Recently, TGFBIp was reported to increase adhesion, migration and morphologic differentiation of human lymphatic endothelial cells so that inhibition of TGFBIp expression resulted in reduction of tumor lymphangiogenesis followed by reduction of metastasis of TGFBIp-producing tumors (Maeng et al., 2015a). TGFBIp is also known to increase the adhesion and migration of endothelial progenitor cells through integrins α4 and α5 (Maeng et al., 2015b). During development, TGFBIp has been detected in mouse corneal epithelium and stroma