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Review

Autophagy in granular corneal dystrophy type 2

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ABSTRACT

Autophagy is a lysosomal degradative process that is essential for cellular homeostasis and metabolic stress adaptation. Defective autophagy is involved in the pathogenesis of many diseases including granular corneal dystrophy type 2 (GCD2). GCD2 is an autosomal dominant disorder caused by substitution of histidine for arginine at codon 124 (R124H) in the transforming growth factor β-induced gene (*TGFBI*) on chromosome 5q31. Transforming growth factor β-induced protein (TGFBIp) is degraded by autophagy, but mutant-TGFBIp accumulates in autophagosomes and/or lysosomes, despite significant activation of basal autophagy, in GCD2 corneal fibroblasts. Furthermore, inhibition of autophagy induces cell death of GCD2 corneal fibroblasts through active caspase-3. As there is currently no pharmacological treatment for GCD2, development of novel therapies is required. A potential strategy for preventing cytoplasmic accumulation of mutant-TGFBIp in GCD2 corneal fibroblasts is to enhance mutant-TGFBIp degradation. This could be achieved by activation of the autophagic pathway. Here, we will consider the role and the potential therapeutic benefits of autophagy in GCD2, with focus on TGFBIp degradation, in light of the recently established role of autophagy in protein degradation.

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Abbreviations: GCD2, granular corneal dystrophy type 2; *TGFBI*, transforming growth factor β-induced gene; TGFBIp, transforming growth factor β-induced protein; ECM, extracellular matrix; ER, endoplasmic reticulum; UPS, ubiquitin-proteasome system; *ATG*, *AuTophaGy*; mTOR, mammalian target of rapamycin; GβL, G-protein β-subunit-like protein; SIN1, stress-activated protein kinase-interacting protein 1; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; ERK 1/2, extracellular signal-regulated kinase 1/2; IGF-1, insulin-like growth factor 1; PtdIns(4,5)P2, phosphatidylinositol 4,5-bisphosphate; PtdIns(3,4,5)P3, phosphatidylinositol 3,4,5-trisphosphate; 3-MA, 3-methylamphetamine; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; WT, wild-type; TGN, trans-Golgi network; EBSS, Earle's balanced salt solution; Atg7, autophagy-related 7; PARP1, poly (ADP-ribose) polymerase 1; TFEB, transcription factor EB.

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1. Introduction

Age-dependent progressive accumulation of transforming growth factor β-induced protein (TGFBIp) as hyaline and amyloid in the corneal epithelia and stroma, interfering with corneal transparency, is the hallmark of *TGFBI*-linked corneal dystrophies. Corneal fibroblasts, also known as keratocytes, have typical dendritic morphology and express keratan sulfate proteoglycans that are necessary for corneal structure and physiology, and particularly for the maintenance of corneal transparency (Cintron and Kublin, 1977; Cintron et al., 1973). Under pathological conditions, corneal transparency often cannot be maintained due to the degeneration of corneal fibroblasts (Jester et al., 1999; Qazi et al., 2010). Consistent with this, corneal fibroblasts from granular corneal dystrophy type 2 (GCD2) patients show degenerative features (Choi et al., 2012), including degenerated organelles such as mitochondria (Kim et al., 2011) and rough endoplasmic reticulum (ER) (Akhtar et al., 1999). Notably, TGFBIp is degraded by autophagy, and mutant TGFBIp extensively accumulates in autophagosomes and/or lysosomes, indicating defective autophagy may play a critical role in the pathogenesis of GCD2. In addition, inhibition of autophagy reduces the viability of GCD2 corneal fibroblasts through activation of caspase-3. In this review, we will cover the basics of the role of autophagy in the pathogenesis of GCD2. We will also discuss modulation of autophagy as a GCD2 therapeutic in light of the recently established role of autophagy in protein degradation.

2. *TGFBI*-linked corneal dystrophies

GCD2 is an autosomal dominant disorder caused by an arginine to histidine mutation (R124H) in *TGFBI*. Age-dependent progressive accumulation of hyaline and amyloid are hallmarks of GCD2, which is characterized by the production of TGFBIp deposits in the corneal epithelia and stroma, interfering with corneal transparency (Klintworth, 1999; Korvatska et al., 2000; Skonier et al., 1992). TGFBIp is an extracellular matrix (ECM) protein that is incorporated into deposits in the three major types of dominant corneal dystrophy caused by different mutations in *TGFBI*: the granular type (types 1 and 2), the lattice type (lattice corneal dystrophy types 1, 3, and 4), and the type with diffuse deposits in Bowman's layer (Reis Bücklers corneal dystrophies and Thiel–Behnke corneal dystrophy) (Klintworth, 1999). GCD2 has histological features of both granular and lattice corneal dystrophy (Kennedy et al., 1996). In GCD2, granular deposits are the earliest and most common manifestation (Ferry et al., 1997; Holland et al., 1992; Munier et al., 1997). On the other hand, lattice deposits are present in deeper stroma in some patients with granular lesions. So far, many cases of GCD2 have been reported worldwide (Akiya et al., 1999; Banning et al., 2006; Dighiero et al., 2000; El-Ashry et al., 2003; Konishi et al., 1997; Lee and Kim, 2003; Rosenwasser et al., 1993). The R124H mutation in *TGFBI* on chromosome 5 (5q31) in patients with GCD2 leads to abnormal deposits of TGFBIp, a major component of the corneal deposits in *TGFBI*-linked corneal dystrophies (Dunaief et al., 2001; Streeten et al., 1999). Among these dystrophies, GCD2 shows the highest prevalence (Kim et al., 2001; Mashima et al., 2000; Yamamoto et al., 2000; Yu et al., 2003). In Korea, GCD2 is estimated to have a prevalence of at least 11.5 affected persons per 10,000 individuals (Lee et al., 2010).

3. Autophagy in protein degradation systems

Cells have special surveillance systems to control the quality of cellular macromolecules and organelles. Despite this, several degenerative disorders are characterized by the accumulation of intracellular or extracellular protein aggregates, which eventually lead to cellular death.

3.1. Protein degradation systems in mammalian cells

Cellular homeostasis depends on the balance between the production and degradation of cellular macromolecules and organelles. There are two major degradation systems responsible for the removal of abnormal proteins from eukaryotic cells: the autophagy pathway and the ubiquitin-proteasome system (UPS) (Ciechanover, 2005). In addition to their importance in cellular homeostasis, these two systems play a vital role in cellular quality control by degrading misfolded or damaged proteins (Reggiori and Klionsky, 2002). There is growing evidence that accumulation of disease-related proteins is highly dependent on both autophagy (Levine and Kroemer, 2008) and the UPS (Maynard et al., 2009). The UPS degrades short-lived or soluble proteins that must be tagged by ubiquitin to be recognized by the proteasome (Ciechanover et al., 2000). The autophagy pathway degrades long-lived or aggregated proteins and cytoplasmic organelles (Mizushima et al., 2008). Recently, growing evidence has demonstrated the existence of cross-talk between the UPS and autophagy (Korolchuk et al., 2009; Lamark and Johansen, 2010). This cooperative process is outlined in Fig. 1.

Degradation of proteins by the UPS is a tightly regulated and highly specific process (Glickman and Ciechanover, 2002). Degradation of a target protein by the UPS involves two successive steps (Dantuma and Masucci, 2002; Reinstein and Ciechanover, 2006). The first step is the conjugation of several ubiquitin molecules to the target protein, a process that is catalyzed by ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and a substrate-specific ubiquitin-protein ligase (E3). The second step is the degradation of the tagged protein by the 26S proteasome complex. The 26S proteasome complex specifically recognizes ubiquitin-conjugated proteins and degrades them to small peptides (Fig. 1).

Autophagy is a conserved catabolic process that removes cellular macromolecules and damaged or excess organelles, to regulate their number and maintain quality control, through their encapsulation by a double-membrane structure known as the autophagosome (Mizushima, 2007; Yang and Klionsky, 2010). This process is outlined in Fig. 1. The discovery of ATG (AuTophaGy) genes has provided a key to the understanding of autophagy and its physiological or pathological functions (Klionsky et al., 2003). Autophagy mechanisms involve the sequestration of cytoplasmic components that are subsequently degraded by lysosomes. Autophagy is classified into 3 types: macroautophagy, chaperone-mediated autophagy, and microautophagy (Cuervo, 2004). Of these, macroautophagy (hereafter referred to as autophagy) is the most studied type of autophagy. A double-membrane-bound vesicle known as an autophagosome delivers bulky cytoplasmic materials and organelles to the lysosome by membrane fusion, before degradation of the contents by lysosomal enzymes (Mizushima, 2007) (Fig. 1). Autophagy can selectively degrade defective organelles, such as depolarized mitochondria, and aberrant protein aggregates. Therefore, autophagy is considered a major player in cellular quality control.

3.2. The regulation of autophagy

Autophagy is tightly regulated by several signaling pathways, the best characterized of which is the mammalian target of rapamycin (mTOR) pathway, a central regulator of autophagy (Nobukuni et al., 2005; Ravikumar et al., 2004). Autophagy is negatively regulated through the mTOR signaling pathway. mTOR

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