

# FBG1, A Novel Scavenger for A1AT-Z and other Misfolded Proteins Retained in Endoplasmic Reticulum?

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## Editorial

$\alpha$ 1-antitrypsin deficiency ( $\alpha$ 1-ATD) is a genetic disease which is featured with accumulation of  $\alpha$ 1-antitrypsin mutant Z proteins (A1AT-Z) in the Endoplasmic Reticulum (ER) of liver [1-4]. It is caused by a substitution of lysine for glutamate at residue 342 and occurs in 1 out 1800-2000 live births in the North America [1]. The mutant Z protein is prone to adopt polymerized conformation and aggregates in ER of hepatocytes (insoluble aggregates) rather than secreted appropriately into the serum and body fluids (soluble forms), leading to chronic liver damage, fibrosis and cirrhosis, and even Hepatocellular Carcinoma (HCC). Transplantation is the only curative therapy for the patients with severe liver disease. It has been reported that hepatocytes cope with the burden of accumulated intracellular protein by activating proteasomal degradation pathways (ERAD) and macroautophagy (called autophagy hereafter). As for degradation, autophagy is mainly responsible for disposal of the insoluble polymers and aggregates of A1AT-Z [5,6], while the proteasome is required for degrading soluble forms of A1AT-Z [7,8]. Therefore, research identifying strategies that reduces accumulation of  $\alpha$ 1-antitrypsin mutant Z proteins (ATZ) and/or promotes degradation of ATZ is of high priority and is greatly encouraged. Most evolving therapies will be aimed at removal of ATZ from hepatocytes.

Recently, John and colleagues reported a novel effector, F-box/G-domain protein 1 (FBG1), to promote degradation of A1AT-Z [9]. FBG1 is the substrate-binding component of a multisubunit SKP, Cullin, F-box (SCF) E3 ubiquitin protein ligase. The authors proposed that FBG1 facilitated the degradation of A1AT-Z through both the ubiquitin proteasome pathway and autophagy. Firstly, they started their work in an in vivo system with evidence that FBG1 was highly expressed in livers of wild-type mice and undetected in FBG1 knockout mouse, and proved that FBG1 could play a role in the degradation of misfolded A1AT. Then, they crossed the FBG1 knockout mice with A1AT-Z transgenic mice to evaluate whether SCF complex formation was required for FBG1-mediated degradation of A1AT-Z and the mechanisms through which degradation pathway FBG1 acted in clearing A1AT-Z. The data showed that FBG1 mediated degradation of A1AT-Z through the Ubiquitin-Proteasome Pathway (UPP) and the Autophagy-Lysosome System (ALS), indicating the critical role of FBG1 in clearance of A1AT-Z by re-ubiquitinating previously de-ubiquitinated A1AT-Z in the cytosol, and ameliorating liver disease associated with  $\alpha$ 1-ATD. These findings provide a novel insight that enhancing the ability of FBG1 to degrade A1AT-Z and other misfolded glycoproteins may have a positive impact on patients suffering from A1AT deficiency.

Interestingly, a research has shown that FBG1 can function through both the UPP and ALS to clear misfolded proteins in DYT1 dystonia [10], a dominantly inherited brain disorder featured with involuntary muscle twisting that leads to abnormal postures. DYT1 is caused by a GAG deletion in the gene TOR1A that encodes torsinA, an Endoplasmic Reticulum (ER) resident protein that belongs to the family of AAA+ATPases. The authors investigated the potential influence of the ubiquitin ligase component FBG1 on torsinA expression in cultured cells and on DYT1 phenotypes *in vivo*. They bred Tor1a+/ΔE mice with Fbg1+/- mice. According to Mendelian genetic, six genotypes were generated as expected. They focused on the Fbg1+/+ and Fbg1-/- mice as total loss of FBG1 and found that FBG1 bound torsinA (ΔE) and torsinA (wt) and influenced their steady-state levels through different mechanisms, indicating that FBG1 enhanced the degradation of torsinA through the UPP and autophagy.

The two studies have, at least, one thing in common: both A1AT-Z and torsinA are misfolded proteins that retained in cytosolic ER of cells instead of appropriately secreted into serum and body fluids. The similar conditions also have been observed in some neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis and Prion-related diseases that arise from ER lumen overload with misfolded proteins. The

questions raised here are whether targeting FBG1 will be helpful for improving the liver disease caused by alpha1-antitrypsin deficiency in humans and whether it will also be effective in ameliorating neurodegenerative conditions.

Accumulating evidence has shown that autophagy contributes to the disposal of mutant alpha1-antitrypsin and is strictly regulated by signaling pathway, such as mammalian Target of Rapamycin (mTOR), PI3K/Akt and AMP-dependent protein kinase (AMPK) [11]. Autophagy is initiated by coordination of two kinases, unc-51 like kinase 1 (ULK1) and vacuolar protein sorting-34 (VPS34). AMPK plays an important homeostatic role in the activation of ULK1 and mTORC1 and is modulated by the energy status in the cells. Therefore, additional investigation still needs to be performed to evaluate the role of FBG1 in the removal of misfolded proteins in  $\alpha$ 1-ATD and neurodegenerative conditions and whether cell signaling pathway is involved in this process.

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