

norUDCA, a Novel Therapeutic Approach to the Disposal of A1-antitrypsin Mutant Z Proteins

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Abstract

α 1-antitrypsin deficiency (AATD) is a well-known genetic disease. No effective medical therapy is currently available for the liver disease. 24-norursodeoxycholic acid (norUDCA) has shown potent anti-cholestatic, anti-inflammatory, and anti-fibrotic properties in experimental and human cholestatic liver diseases. In this minireview, we discuss the role of exogenous norUDCA in reducing accumulation of α 1-antitrypsin mutant Z proteins (AATZ) in the livers of PiZ mice and the *in vitro* model, HTOZ cells. In these model systems, norUDCA reduces AATZ accumulation and reduces the associated toxicity, but human trials will be needed to explore further use.

Keywords: NorUDCA, Autophagy, AATZ, AMPK

Mini Review

α 1-antitrypsin deficiency (AATD) is a well-known genetic disease which consists of three majors, but highly variable, clinical manifestations: emphysema (in adults), liver disease (in adults and children) and panniculitis (in adults) [1]. No effective medical therapy is currently available for the liver disease. norUDCA is a new therapeutic bile acid with a side chain-shortened C23 homologue of ursodeoxycholic acid (UDCA) and has shown potent anti-cholestatic, anti-inflammatory and anti-fibrotic properties in experimental and human cholestatic liver diseases [2,3]. In this mini review, we will discuss the role of exogenous bile acid 24-Norursodeoxycholic acid (norUDCA) in reducing accumulation of α 1-antitrypsin mutant Z proteins (AATZ) in the livers of PiZ mice, a well characterized model which recapitulates human AATD liver disease, and HTOZ cells, which are a useful system to the intracellular disease mechanisms [4,5].

AATD is characterized by AATZ accumulation in the endoplasmic reticulum (ER) of liver [6,7], which is caused by abnormal protein folding during biogenesis as a result of a

substitution of lysine for glutamate at residue 342. Individual homozygous for this Z mutation are found in 1 of 1,800-3,500 live births in North America and Europe [6]. The AATZ protein is prone to misfolding and polymerization during biogenesis and is retained in ER of liver cells (insoluble forms) instead of properly released into the serum and body fluids (soluble forms), resulting in chronic liver damage, such as inflammation, cell death, hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma [8]. Previous work showed that liver cells degrade the accumulated intracellular protein by promoting the role of endoplasmic reticulum-associated degradation pathways and autophagy. As for degradation, autophagy is mainly responsible for degrading the insoluble polymerized AATZ [9,10], while the proteasome is the primary mechanism for removing the soluble AATZ [11,12]. Therefore, research identifying strategies is highly encouraged to decrease AATZ accumulation and/or enhance AATZ degradation.

An increasing body of evidence has shown that autophagy contributes to reducing AATZ accumulation in hepatocytes [4,5,13,14]. Under ER stress, interaction between autophagy pathways and unfolded protein response pathways

contributes to restoring ER homeostasis [14,15]. Specific variants in autophagy genes could reduce the accumulation of α 1-antitrypsin variant Z in patient cells [16]. Autophagy enhancer drugs may act as a new therapeutic strategy to target cell biological mechanisms integral to the pathogenesis of liver disease due to ATD [11,14]. Further studies have proved that autophagy is strictly regulated by signaling pathways, such as mammalian target of rapamycin (mTOR), PI3K/Akt and AMP-dependent protein kinase (AMPK) [5,17]. Autophagy is initiated by coordination of two kinases, unc-51 like kinase 1 (ULK1) and vacuolar protein sorting-34. AMPK plays an important homeostatic role in the activation of ULK1 and mTORC1 and is modulated by the energy status in the cells [8].

Interestingly, our team found that norUDCA could act as a new therapeutic strategy to increase degradation of AATZ via activating autophagy *in vivo* [4] and *in vitro* [5]. We treated groups of PiZ transgenic mice, the best model of AAT liver injury, and wild-type mice with norUDCA or vehicle by oral administration and examined the effects on the liver [4]. Our data showed that mice treated with norUDCA displayed lowered liver cell death and apoptotic signaling. We also found that more than 70% reduction in hepatic mutant Z protein and 32% increase in hepatocellular autophagy were related to norUDCA. Our findings suggest that norUDCA treatment enhances autophagy, reduces A1AT protein aggregates, and lowers liver injury in a model of A1ATD [4]. To further elucidate the mechanism involved in the above process by which norUDCA modulates autophagy, we utilized HTOZ cells, modified from HeLa Tet-Off cells by transfection with the resulting pTRE1-ATZ plasmid and expressing mutant Z proteins [5]. We then examined the role of norUDCA in inducing autophagy, autophagy-mediated degradation of AATZ and the role of AMPK in norUDCA-induced autophagy. We found that NorUDCA promoted disposal of AATZ via autophagy-mediated degradation of AATZ in HTOZ cells. Activation of AMPK was required for norUDCA-induced autophagy and AATZ degradation. Moreover, mTOR/ULK1 was involved in norUDCA-induced AMPK activation and autophagy in HTOZ cells. Our results provide novel mechanistic insights into the therapeutic action of norUDCA in promoting the clearance of AATZ *in vitro* and suggest a novel therapeutic approach for the treatment of AATZ deficiency disease and its associated liver diseases.

Additionally, Kevin and colleagues reported a novel effector, F-box/G-domain protein 1 (FBG1), to promote degradation of AATZ [18]. The authors proved that FBG1 could play a role in the degradation of misfolded AATZ and provided a novel insight that enhancing the ability of FBG1 to degrade AATZ and other misfolded glycoproteins may have a positive impact on patients suffering from AAT deficiency.

There is, at least, one thing in common: both AATZ and torsinA are polymerized proteins accumulated in the ER of cells rather than appropriately secreted into serum and body fluids.

TorsinA is a causative protein in human neurologic disease [19]. There are also the similar conditions observed in some neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and Prion-related diseases that arise from ER lumen overload with misfolded proteins [19]. The questions raised here are whether NorUDCA will be effective in ameliorating neurodegenerative conditions and whether targeting FBG1 will also be helpful for improving the liver disease caused by AATD in humans.

A further question of dosage needs to be addressed as future human trials are planned. There are many examples of agents which induce autophagy in laboratory systems, but which require a ten-fold or greater mg/Kg dosage to have a similar effect on humans. The tolerability of many of the agents being tested at such high doses is doubtful. One possible advantage of norUDCA is the existing body of early human trials with reassuring safety signals, to date. The future of this therapeutic approach will require carefully constructed trials in humans. Patients with progressive AAT liver disease might be a reasonable population for initial studies.

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