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Wilson's disease: Prospective developments towards new therapies

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Abstract

Wilson's disease (WD) is an autosomal recessive

disorder of copper metabolism, caused by mutations in the *ATP7B* gene. A clear demand for novel WD treatment strategies has emerged. Although therapies using zinc salts and copper chelators can effectively cure WD, these drugs exhibit limitations in a substantial pool of WD patients who develop intolerance and/or severe side effects. Several lines of research have indicated intriguing potential for novel strategies and targets for development of new therapies. Here, we review these new approaches, which comprise correction of *ATP7B* mutants and discovery of new compounds that circumvent *ATP7B*-deficiency, as well as cell and gene therapies. We also discuss whether and when these new therapeutic strategies will be translated into clinical use, according to the key requirements for clinical trials that remain to be met. Finally, we discuss the hope for the current rapidly developing research on molecular mechanisms underlying WD pathogenesis and for the related potential therapeutic targets to provide a solid foundation for the next generation of WD therapies that may lead to an effective, tolerable and safe cure.

Key words: *ATP7B*; Stem cell-derived hepatocyte like cells; Methanobactin; Heat shock protein 70; p38; JNK; Correctors; Translational medicine; Precision medicine

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Core tip: Hepatocytes derived from human-induced pluripotent stem cells hold great promise for the drug discovery process, especially for Wilson's disease (WD). Therapeutic approaches offering correction of the *ATP7B* mutant function and/or less toxic suppression of copper accumulation are promising and could be available shortly. In particular, protein quality control components and their regulatory networks represent attractive new targets for WD-causing mutant correction. Cell and gene therapies, however, will require more studies before they can be considered for clinical trials. A key goal for WD advancement is international cooperation of specialized centers to overcome limited

availability of patients for study.

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INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder of copper (Cu) metabolism, caused by mutations in the *ATP7B* gene, which encodes Cu-translocating ATPase expressed primarily in the liver^[1]. *ATP7B* resides in the trans-Golgi membrane compartment and loads Cu onto newly synthesized apoceruloplasmin. In the case of Cu overload, *ATP7B* traffics to the canalicular membrane of hepatocytes and the associated cytoplasmic vesicular compartment, where it removes excess Cu through the bile. Therefore, all mutations that affect synthesis of *ATP7B*, its stability, correct localization in the trans-Golgi region and capacity of trafficking in the condition of intracellular Cu excess, determine toxic accumulation of Cu in hepatocytes, thereby leading to cell damage and subsequent release of Cu into the blood and ultimately affecting other organs^[2].

The main clinical presentations of WD are liver and neuropsychiatric diseases. Existing therapies comprise treatment with either zinc salts or Cu chelators. While these drugs allow for sufficient control of the symptoms, they do not cure the disease. Additionally, chelators induce multiple severe toxicities, requiring discontinuation in approximately 30% of patients; these include hypersensitivity reactions, significant bone marrow suppression, degenerative changes in skin, nephrotoxicity and autoimmune disease^[3]. Zinc therapy seems to fail in large cohorts of adult patients with liver disease when applied for very long periods, and its use in symptomatic Wilson's patients with liver disease remains controversial^[4,5]. Generally, the psychiatric symptoms of WD are poorly controlled by available drugs^[6]. Furthermore, an Italian study showed that, more than 36% of Italian pediatric WD patients responder to the available drugs, did not exhibit normalization of liver enzymes^[7]. Finally, among adults with WD there are substantial rates of non-adherence to medication regimens (30%-50%), corresponding to both a high index of patients who suffer liver failure and who develop potentially irreversible neurologic or psychiatric symptoms^[8].

Liver transplantation (LT) is a treatment option for the most severe (life-threatening) cases of WD. LT is a curative therapy, with biliary Cu excretion being restored, neurologic and psychiatric disease stabilizing or improving, and Kayser-Fleischer rings

disappearing over time^[9]. Unfortunately, LT does not represent a general therapeutic strategy, given the high rate of complications and the need for long-life immunosuppressive therapy^[9]. Thus, there remains a clear need for novel treatment strategies aimed at curing WD through correction of the cellular defect.

During the last few years, the perspective on alternative WD therapeutic strategies has been completely revolutionized, as summarized in this review. And, the field of WD translational research and clinical management is currently experiencing an unexpected burst that hopefully will lead to an expanded range of therapies available to patients.

DISEASE MODELING

The four animal models of WD - the Long-Evans Cinnamon (LEC) rat, the inbred mouse models (toxic milk, the Jackson Laboratory toxic milk) and the *Atp7B* knockout (*Atp7b*^{-/-}) mouse - lose *ATP7B* function and manifest liver disease due to Cu accumulation^[2]. Surprisingly, *Atp7b*^{-/-} mice does not exhibit susceptibility to neurological disease and LEC rats and toxic milk mouse develop only a mild neurologic involvement. Yet, no mice models carrying the most frequent missense mutations of *ATP7B* (H1069Q or R778L) are available. On the other hand, the metabolic pathways of rodents are frequently vastly different from those of man, and this is the pivotal reason that efforts persist to develop a platform of human cells.

Hepatocytes obtained *via* liver biopsy cannot be considered as a good model system for WD studies. Indeed, it is extremely difficult to keep human hepatocytes from biopsies in culture, as they do not proliferate and rapidly undergo apoptosis. In addition, these cells are generally already damaged at the moment of liver biopsy execution.

The recent development of stem cell-derived hepatocyte-like cells (HLCs) has circumvented this problem and opens new avenues for gene- and/or drug-based therapy to treat liver diseases. This new "*in vitro* model" better mimics patient cell biology. HLCs can be fairly easily derived from induced pluripotent stem cells (iPSCs) that are generated through the reprogramming of human fibroblasts^[10]. In this context, it would be particularly helpful to obtain HLCs from WD patients. Some steps have already been taken in this direction, with HLCs derived from patients with missense *ATP7B* mutation having been developed^[11].

iPSCs harbor the same unique characteristics of embryonic stem cells, *i.e.*, they can be indefinitely expanded *in vitro* and differentiated in all cells types derived from the three germ layers. Thus, iPSC technology features the potential benefits of embryonic stem cells while addressing their major ethical and scientific concerns: embryo destruction and immune-incompatibility. In this manner, human iPSCs represent an unlimited source of human hepatocytes for

translational research and hold great promise for drug screening and liver disease modeling in particular. In addition to their HLC differentiation capacity, iPSCs can differentiate into neurons, providing a serious advantage in studying whether and how certain *ATP7B* mutations contribute to neurologic dysfunction in WD patients.

CORRECTION OF DYSFUNCTIONAL *ATP7B*

Alternative therapeutic approaches offering correction of *ATP7B* mutant function and/or less toxic suppression of Cu import have been investigated in recent years. It is worth noting that most of the *ATP7B* mutations belong to the missense (58%) or small deletion/insertion (27%) categories, thereby resulting in aberrant protein products that frequently exhibit residual Cu-transporting activity but which undergo strong degradation due to misfolding and retention within the endoplasmic reticulum (ER)^[12]. This is the case for the most frequent *ATP7B* mutants, H1069Q (in 50%-60% of European and North American WD patients) and R778L (in 40% of East Asian patients). Thus, manipulating their translocation from the ER to ensure correct localization in the cell would be beneficial for a sizable portion of WD patients.

Correction strategy has been widely explored for the most frequent mutant in cystic fibrosis, the Δ F508 mutation of the cystic fibrosis transmembrane conductance regulator (CFTR)^[13]. Like the *ATP7B* mutant, Δ F508-CFTR exhibits residual ion-transporting activity but undergoes strong retention and degradation in the ER. Considering these similarities, several labs have tested the potential of Δ F508-CFTR correctors, such as curcumin and 4-phenylbutyrate, for *ATP7B* mutant rescue. Both correctors were demonstrated as capable of reducing degradation of *ATP7B* mutants expressed in HEK293 cells^[14]; however, curcumin failed to do so in HLCs expressing the R778L variant of *ATP7B*^[11]. It remains unclear to what extent these drugs rescue localization and function of *ATP7B* mutant^[14]. Curcumin has been reported to correct localization of *ATP7B*-R778L and to facilitate Cu efflux from patient-derived HLCs. However, in phase 1 clinical trials for CFTR correction, dietary curcumin was found to have very poor bioavailability and very low serum concentration^[15]. Thus, the efficacy of this corrector for WD treatment remains questionable.

In order to identify new drugs and targets for *ATP7B* mutant correction, it will be important to first identify the quality control mechanisms that drive ER retention and degradation of the mutants. A few proteins (*i.e.*, COMMD1, clusterin) and peptides (*i.e.*, alpha-crystallin B peptides) control *ATP7B* mutants retention in the ER and/or their degradation^[16,17]. However, these molecules do not belong to the "druggable" category and their potential for creation of drugs to cure WD remains

largely unknown.

On the other hand, a recent analysis of global gene expression in hepatic HepG2 cell lines expressing either wild type *ATP7B* or *ATP7B*-H1069Q mutant revealed that suppression of p38 and JNK reduces retention of H1069Q and a few other *ATP7B* mutants in the ER, inhibits their degradation, and facilitates Cu excretion from mutant-expressing cells^[18]. Therefore, p38 and JNK have become attractive targets for exploring approaches to mutant correction. Indeed, it has been recently reported^[19] that p38 and JNK control a cluster of ER quality control genes that promote *ATP7B*-H1069Q degradation. This cluster comprises a well-known chaperone, heat shock protein 70 (HSP70), whose silencing protects the *ATP7B* mutant from degradation and facilitates its export from the ER to the Golgi complex where *ATP7B* normally works.

The recognition of HSP70 and its upstream regulators p38 and JNK as attractive new targets for *ATP7B* mutant correction has also elucidated their potential for normalization of Cu homeostasis in WD. Considering the importance of these proteins for several critical processes of the normal physiologic state, such as protein quality control, stress response, signal transduction and apoptosis, safe (condition-specific) inhibitors of HSP70, p38 and JNK must be identified in the context of preexisting drug-approved libraries to avoid significant impact on overall cell/organism health. Nonetheless, these new modulators represent a great opportunity for repurposing safe drugs for WD treatment.

NEW COMPOUNDS WITH THERAPEUTIC POTENTIAL

The current pharmacological treatments have largely failed in rescue of Cu homeostasis in WD patients with acute liver failure, leaving LT as the only viable option for treatment. A recent study using the LEC rat model of WD offered an extra option for such patients called methanobactin (MB), a peptide produced by *Methylosinus trichosporium* with an extremely high affinity for Cu^[20]. Short-term MB treatment efficiently reversed acute liver damage due to Cu accumulation. This beneficial effect was associated with disposal of intracellular Cu, in particular from the mitochondria. Interestingly, the regular Cu chelators penicillamine and tetrathiomolybdate failed to clean toxic metal from the mitochondrial stores. As a consequence, MB treatment prevented hepatocyte death and the subsequent liver failure, elongating the life span of the LEC rat. Therefore this peptide seems to be a potential therapeutic agent for acute WD.

Findings from another recent study have suggested that liver X receptor (LXR)/retinoid X receptor agonist may be used to combat Cu toxicity in WD^[21]. This approach does not require Cu chelation. Careful investigation of the transcriptional and metabolic changes in

samples from WD patients and *Atp7b*^{-/-} mice revealed dysregulation of LXR as one of the key events in the pathogenesis of WD. Treatment with the LXR agonist T0901317 improved disease manifestations in the *Atp7b*^{-/-} mice despite substantial Cu overload. Moreover, liver fibrosis and inflammation significantly decreased in LXR agonist-treated animals, while lipid profiles normalized and liver function and histology improved. Thus, the potential of T0901317 for WD cure is likely to be further explored.

CELL THERAPY

Cell therapy, as well as gene therapy, targets the liver, which does not express functional *ATP7B* protein, aiming to restore hepatobiliary Cu excretion^[22]. Cell therapy in WD seems feasible because transplanted hepatocytes can integrate in liver parenchyma and restore deficient functions, including the transport of Cu into bile. Animal WD models, especially the LEC rat, has facilitated cell transplantation research in WD^[22]. It was through this animal model that it was found necessary to repopulate less than half of the liver with healthy hepatocytes in order to achieve sufficient Cu removal and therapeutic efficacy. However, in that study, not every animal subjected to cell therapy showed equivalent benefits^[22].

Extrahepatic cell therapy using engineering applications (*i.e.*, transplantation of liver tissue into small intestine or the abdominal cavity) is currently considered insufficient because Cu removal requires an intact bile excretion system. Thus, in the case of either cell or gene therapy in WD, liver is the first target considering the physiological restriction of *ATP7B* expression to hepatocytes as well as the availability of mechanisms to eliminate Cu from the body^[23]. Fortunately, transplantation studies using donor cells have confirmed the ability for biliary excretion, providing the first clue that biliary Cu transport is a feasible target for cell therapy in WD^[24].

IPSC-derived HLCs can repopulate the liver but they support only some hepatocyte functions, which are restricted to fetal-like stages^[10]. Therefore, transplanted cells can proliferate in the presence of native cells, having a low rate of proliferation. This happens when native liver cells have extensive DNA damage (as induced by toxins, ischemia and/or hepatectomy). Obviously these preconditioning regimens are undesirable in the setting of existing liver injury in WD. The ability of transplanted HLCs to express *ATP7B* was evaluated in liver of LEC mice, in which the transplanted cells did not increase in number over an observational period of several months^[25]. Therefore, liver repopulation over a very long period implies that therapeutic correction in WD will require significant time^[22].

GENE THERAPY

Gene therapy aims to correct the defect in native hepatocytes by providing healthy copies of *ATP7B* via introduction of a transgene by vectors capable of indefinitely integrating and/or persisting in cells. The proof-of-principle for gene therapy in WD came from adenoviral and lentiviral vector expression of *ATP7B* in the liver of rodent models, which achieved transient correction of Cu excretion and incorporation of Cu into ceruloplasmin^[26].

Recently, these initial observations were confirmed with an adeno-associated vector serotype 8 (AAV8) encoding the human *ATP7B* cDNA placed under control of the liver-specific α 1-antitrypsin promoter (AAV8-AAT-*ATP7B*). Expression of AAV8-AAT-*ATP7B* in *ATP7B*-deficient mice resulted in reductions of liver enzymes and recovery of physiological biliary Cu excretion^[27]. This study showed a solid background for future translational studies. AAV-mediated gene therapy should allow *ATP7B* to be permanently expressed in WD patient liver and, hence, would eliminate a need for lifelong intake of Cu-reducing drugs. On the other hand, such risks as immune response, tumor biogenesis and poor integration into damaged cells^[28] have to be weighted before AAV-mediated gene transfer therapy and will be a critical component of the repertoire of WD treatments. Furthermore, studies investigating the fate of genetically modified native cells within the liver in WD are still required^[22].

TRANSLATING NEW THERAPIES TO PATIENT BEDSIDE

To establish whether and when these new therapies will be appropriate for clinical trials, a number of key requirements must be met. First, the particular reference population must be identified for treatment. It is likely that potential candidates for this population will include asymptomatic or presymptomatic WD patients with an early disease, people with liver failure or severe neurologic deterioration who could benefit from rapid removal of Cu, and those with severe adverse reaction to preexisting therapy^[22]. Considering the potential latency of some treatments before they become effective and the severe risks linked to suspension of preexisting treatment in WD patients, it seems possible to consider the combination of existing drugs and new therapies to mobilize Cu for early clinical trials. Moreover, it will be important to define appropriate tests and effective endpoints that, in addition to clinical parameters, may be useful for demonstrating therapeutic efficacy, considering that drug monitoring necessitates use of noninvasive assays and biomarkers. In this context, the discovery of new biomarkers in WD will be of great significance to enable new effective treatment.

CONCLUSION

Emerging strategies for cure of WD foster new challenges that should be addressed by "precision" medicine, which takes in account the best available knowledge about disease mechanisms to establish approaches that yield an effective cure rate. Some compounds (tested in WD cell or animal models) seem to be close to translation into safe drugs and/or personalized treatments for WD patients. Advancing a WD cure will require an international cooperation to overcome the limited availability of affected patients who can be enrolled into clinical trials for development of new therapies. We hope that joint efforts between academia, industry, government and patient advocacy groups will allow for rapid progress and bring WD patient welfare to the forefront.

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