Ind J Clin Biochem (Oct-Dec 2019) 34(4):369–370
https://doi.org/10.1007/s12291-019-00855-8

EDITORIAL

New Horizons in Correction of Mutated ATP7B in Wilson Disease Using Pharmacological Agents: Precise Medicine

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Published online: 16 October 2019

Wilson disease is an autosomal recessive disorder of copper metabolism owing to mutations in the ATP7B which encodes a copper exporting P-type ATPase transporter [1]. Therefore mutation in ATP7B gene lead to accumulation of copper in those organs where there ATP7B gene expresses [2]. Patients may present with dominant hepatic abnormalities, neurological manifestations or a combination of both. Hepatic symptoms comprise liver cirrhosis, chronic liver inflammation and fulminant liver failure, whereas neurological manifestations include parkinsonian tremor disorders, seizures, personality change, depression and psychosis [3]. Worldwide frequency of Wilson disease is one in 30,000 individuals with a carrier frequency of 1/90 [4]. More recent data from population screening in the U.K using next generation sequencing revealed a considerable higher prevalence, perhaps as frequent as 1/7026 individuals [5].

The conventional therapy for WD includes copper chelating agents viz pencillamine, trientine and ammonium tetramolybdate and zinc therapy. Strikingly, approximately 30% patients have hypersensitive reactions to pencillamine viz. significant bone marrow suppression, degenerative changes in skin, nephrotoxicity, and autoimmune disease [6]. In view of these facts, there is a clear demand for novel treatment strategies in addition to conventional therapy. During, the last few years, alternative WD therapeutic strategies have been focused on the correction of underlying molecular and cellular defects due to specific mutations using pharmacological chaperon agents.

P- type ATPase which belongs to CPX-Type ATP7B is expressed in the trans Golgi network of cells in the liver and in basal ganglia of the brain, placenta, kidney, mammary tissues. Excessive copper concentrations result in delocalization of ATP7B to the plasma membrane [2, 3]. ATP7B contains the nucleotide binding domain (N) with Ser-Glu-His-Pro-Leu (SEHPL) motif, the phosphorylation domain (P) with the invariant aspartic acid in ASP-Lys-Thr-Gly (DKTG) motif and the actuator domain (N) with the Thr-Gly-Glu-Ala (TGEA) motif, which are all required for catalytic activity. The Cys-Pro-Cys (CPC) motif in the sixth transmembrane helix coordinates copper during export. The amino terminus contains six highly conserved metal binding domain (MBDs) containing Met-Xaa-Cys-Xaa-Xaa-Cys (MXCXXC) motifs. The catalytic activity of Cu-ATPase is mediated through coordinated action of the A-Domain and the ATP binding domain which consists of P-Domain, that includes the site of Catalytic phosphorylation and the signature motifs for the P-type ATPase [2].

Copper homeostasis is arbitrated by ATP7B which is dependent on both copper transport activity as well as localization to the correct intracellular compartment. The prominent role of ATP7B is to export excess copper out of the cell and into bile canaliculus for subsequent excretion from the body through the bile [6]. Other role of ATP7B is to deliver copper to apo-ceruloplasmin within the Golgi network. ATP7B is localized in the trans Golgi network of hepatocytes under low copper conditions whilst elevated level of intracellular copper, redistribute to cytoplasmic copper and then recycles back to the trans Golgi network when copper is removed [7]. These findings suggest that translocation of ATP7B from trans-Golgi network and subsequently localization to the plasma membrane is

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essential for copper efflux. The endoplasmic reticulum quality control system ascertains correct folding as prerequisite for coat protein complex II (COP II) dependent ER export. ER- associated degradation (ERAD) of mutants ATP binding cassette proteins led to several potentially lethal or deliberating human disease. The available evidence indicates misfolding and premature degradation caused by missense mutations as significant cause of membrane protein deficiencies due to aberrant folding and retro-translocation of proteins. The folding process may be considered a step wise process in which (sub) domain folding precedes correct positioning of domain or sub domains relative to each other for proper functioning.

Worldwide more than 800 mutations affecting the function of ATP7B have been reported in WD patients [8]. We have reported more than fifty mutation from Indian WD patients comprising a heterogeneous spectrum of mutation [9, 10]. Importantly, hitting towards the fact that no single treatment protocol can be generalized for treatment of WD patients. Indeed, pharmacological chaperons such as 4-PBA, cur-cumin, VX809 & VX770 have been successfully used in vitro to ameliorate protein folding in lysosomal disorders and functional recovery of the misfolded Cystic fibrosis trans-membrane conductance regulator (CFTR) protein involved in Cystic fibrosis [11, 12]. Henceforth, better understanding of underlying molecular and cellular defects of identified mutations is essential before to develop alternate therapy that may profoundly impacting the Course of disease in individuals with specific mutation class. Overall, 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 the patient.

Functional characterization of ATP7B mutations will provide immense insight into the pathophysiology of the disease. Precise understanding of ATP7B mutations is a prerequisite for rationale basis for mutation specific therapy (Personalized therapy). Mutational characterization will be helpful in diagnosis, and genetic counselling. Emerging strategies for cure of WD will promote new challenges that should be addressed by precision medicine which takes in account the best available knowledge about disease mechanism to establish approaches that yield an effective cure rate. The tested compounds in cell lines or animal models seem to be close to translation into the safe drugs and/or personalized treatments for WD treatments.

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