A Need to Understand Menkes Disease

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Mutations affecting ATP7A function leads to Menkes disease, an X-linked disorder combined with neurological and cardiovascular defects [1-3]. Affected male infants present hypotonia, seizures, and failure to thrive at six to eight weeks old, and usually die before the age of 3 years [4]. However, affected female infants appear healthy with normal development; affected female adults are asymptomatic except for subtle hair, skin abnormalities, and possible neurological sparing [5], and pass down the mutant gene to next generations. The prevalence rate of this disorder is approximately 1 in 100,000–250,000 births [2,6]. Many different forms of copper, such as copper-histidine and copper-acetate, have been used intravenously or subcutaneously [7], and accompanied by increase in serum copper levels. However, the benefits of these postnatal treatments on neurological and cardiovascular defects are limited [8]. Particularly, patients with gene deletions that disrupt the major translational reading frame are insensitive to early copper treatment [4]. Thus, there is an urgent need to understand this disease and to develop a better therapeutic regime. Here discussed two important challenges.

First, to understand the challenge to construct human ATP7A cDNA. Gene therapy, although facing many debates about its safety, should be an ultimate goal to heal this genetic disease. There are two basic steps for gene therapy: the first is to subclone the interest gene into a vector, and the second is to deliver the vector into human to compensate the defective gene function. So subcloning the human ATP7A cDNA is the first step towards a successful gene therapy. However, human ATP7A cDNA instability occurs in Escherichia coli vectors as first reported by Fontaine et al. [9]. For example, when the lab initially subcloned five sequential fragments of human ATP7A cDNA into pUC19, we found that approximately 1 kilo base pairs of a host Escherichia coli gene (mobile DNA) was inserted into the ATP7A cDNA when we integrated the five fragments together. The sequences of two mutant recombinants were deposited into GenBank (Accession No. GU255954 and GU300144). Our further study showed that it appears a special designed vector, Copycutter™ EP400™ (Epicerent, Madison, WI) can prevent this problem via dramatically reducing the plasmid copy number. However, additional studies are needed to verify this finding.

Recently, Donsante et al. convincingly reported the construction of a reduced-size human ATP7A cDNA in a viral vector and then delivering this vector into the brain lateral ventricle of a Menkes disease mouse model. This therapy results in accompanied by partial corrections of copper levels, a cuproenzyme activity, and pathology in brain when combined with copper treatment [10]. Thus, the strategy to develop a reduced-size human ATP7A cDNA holds another great promise for gene therapy. A future direction would be to understand the functional domains of ATP7A and to optimize the size of human ATP7A cDNA to reach the maximum of functional compensation.

Second, to further understand Menkes disease mice. Although human Menkes disease is rare, we fortunately have several Menkes disease mouse models. The murine ATP7A protein shows a high level of identity (89.9%) with the human ATP7A [11] based on sequence comparisons and structure predictions. To date, more than 30 mottled mice with mutations of ATP7A gene or a reduction in the ATP7A protein product have been identified to affect ATP7A function [12] with phenotypes ranging in severity from coat hypo-pigmentation to death in utero. Unfortunately, the molecular pathogenesis related to the disease models is poorly studied. In my view, this is largely due to our current system preferring the models like conditional knockout mice, which can study a specific protein function in a specific tissue, whereas the study using Menkes disease mice is easy to draw criticisms. For example, one common criticism is, this model is complicated by the dysfunction of multiplying systems, which makes the data interpretation very difficult. Although this criticism is reasonable from a pure scientific view, any finding from disease models has significant medical implications. Furthermore, based on the initial findings, additional interventional experiments such as pharmaceutical treatment can be designed to determine the contribution of each system. More important, the medical value of Menkes disease mice cannot be substituted by other models.

Overall, many basic researches are urgently needed to understand the pathogenesis of Menkes disease. This is an important mission for our scientific community.

References
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