Extended Abstract Journal of Clinical Medicine and Therapeutics 2020
Vol.5 No.2

Orphan Drugs 2020: Discovery of novel genes associated with mitochondrial diseases by NGS- Taosheng Huang- Cincinnati Children's Hospital Medical Center.

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Abstract:
Advances in next generation sequencing technology have resulted in a rapid increase in the molecular characterization of mitochondrial disease. Recent years, our laboratory has successfully used whole-exome sequencing to spot many novel disease causing genes related to mitochondrial disease. The mitochondrial asparaginyl-tRNAsynthetase (NARS2) mutations cause Leigh syndrome and nonsyndromic deafness (DFNB94). We found that some mutation can disrupt dimerization of NARS2 and reduce steady-state levels of mt-tRNAAsn without aminoacylation defects. The cells with NARS2 mutations also display impaired oxygen consumption rate and OXPHOS deficiency which will be rescued by overexpression of untamed type NARS2. Recently, we found that recessive SLC25A46 mutations cause nervus opticus atrophyand axonal peripheral neuropathy. Furthermore, we demonstrate the SLC25A46 role in mediating mitochondrial morphology in vivo and in vitro. In zebrafish, we found that loss-of-function affects the development and maintenance of neuronal processes and causes abnormal mitochondrial fusion morphology. Our result show many disease causing genes related to mitochondrial disease are yet to be identified and whole-exome sequencing is extremely cost-effective for this process. We also have some ways during which these challenges can overcome by manipulation in genetic strategies tailored specifically for mitochondrial diseases.

Remarkable strides have been made in the field of gene therapy in recent years, and there is a growing sense in the field that the power of gene therapy and gene editing techniques such as CRISPR will soon allow for the treatment of a broad range of genetic disorders. Indeed, regulatory approval has recently been granted to gene replacement therapies for several disorders, including Leber congenital amaurosis type 2 (LCA2),1 spinal muscular atrophy type 1 (SMA1),2 and β-thalassemia.3 The latter result has the potential to be particularly impactful, as β-thalassemia is one of the most common inherited blood disorders in the world, affecting approximately 1 in 100,000 people globally. It is clear that gene replacement therapy is coming into its own, and for those interested in brushing up on the subject, the recent review by High and Roncarolo5 is an excellent starting point for a brief, but thorough, overview of the current state of the field.

Despite this remarkable progress, gene therapy for inherited mitochondrial disorders may present a unique and fascinating set of challenges that are not fully appreciated by those less acquainted with mitochondrial biology. Mitochondria are, of course, integral to the functioning of the cell, producing the bulk of the energy (in the form of ATP) needed by the cell through the process of oxidative phosphorylation (OXPHOS). The consequences of mutations in the mitochondrial genome (mtDNA) and mitochondria-related nuclear genes are often severe, and the prognosis of such a patient is usually quite poor. Thus, the value in being able to correct such genetic defects in patients is readily apparent. Gene therapy and CRISPR gene editing provide a great deal of promise in the field of medical genetics, but have certain limitations in the treatment of mitochondrial diseases that must be addressed if they are to be employed successfully in this context. In the present review, we hope to address this issue by discussing ongoing clinical trials in the use of gene therapy and gene editing technologies to treat genetic diseases, with a particular focus on specific challenges in the use of such approaches for treating mitochondrial diseases.

Significance:
Recent successes in the field of gene therapy are truly encouraging and are likely only a glimpse of the progress to come in the near future. It is our belief that these cutting-edge genetic techniques can also significantly improve the lives of many of the patients and families who currently suffer under the burden of mitochondrial disease. However, caution must be taken to properly account for the unique qualities of the mitochondrial organelle in order to fully realize the potential of this technology in the treatment of mitochondrial disorders. For example, the current literature clearly demonstrates that mtDNA editing via protein-only nucleases such as TALENs or ZFNs is a much more effective approach than CRISPR/Cas9-based editing, and that the former approach must be prioritized for any near-term clinical trials. Furthermore, the delivery approach must take into account the relevant properties of each mitochondrial protein in question, in particular their localization within the mitochondrial organelle and how they will be properly targeted to that location without overwhelming the mitochondrial import machinery. The preliminary successes enjoyed by the recently published clinical trials suggest that these challenges, while significant, are far from insurmountable.

This work is partly presented at Annual Congress on Rare Diseases & Orphan Drugs on October 26-27, 2016 at Chicago, USA