

Pompe disease: further challenges to pursue

Doença de Pompe: novos desafios a serem conquistados

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Recent biotechnological advance with production of human recombinant enzyme was a breakthrough which has allowed the introduction of enzymatic replacement therapy (ERT) for monogenic deficiencies. This new therapeutic modality was also applied to Pompe disease or glycogen storage disease type II (GSDII; OMIM # 232300), an autosomal recessive disorder caused by acid maltase or acid α -glucosidase deficiency (GAA, OMIM # 606800). Indeed, ERT has been shown to reduce glycogen levels, improve morphology, and restore muscle function and strength.

Recent publications indicate that early diagnosis and initiation of treatment of infants have led to better clinical outcomes^{1,2}. However, the response to therapy has shown to be variable in Pompe disease³⁻⁵. Diversity in muscle fiber composition and damage, as reported by Werneck et al. in this present issue⁶, or also difficulties in delivery of therapeutic agent might be factors underlying these discrepancies. In fact, recent report has described selective and negative response of type II (fast-twitch) muscle fibers, associated to late start of treatment, resulting in poorer efficacy of enzyme therapy⁷. Furthermore, autophagic vacuole accumulation has been observed as limited to type II fibers in knockout mice^{8,9}, and also in single dissected type II muscle fibers in late-onset Pompe patients¹⁰. On the other hand, if the glycogen accumulation occurs in the intramuscular vessel on myoepithelial cell, blood flow impairment might be expected¹¹, and an additional hazard would jeopardize the response to the ERT. The irreversibility of muscle structural damage and skeletal muscle resistance to ERT remain as problems not yet solved. Persistent attempts have been made to the development of biomarkers for disease progression/severity and response to therapy. Genotype-phenotype correlation has been one of the adopted strategy to this end. Reuser's group has built up the Pompe Disease Mutation Database enumerating all GAA variations and describing their effect to facilitate diagnosis and counseling for patients and families with Pompe disease^{12,13}. This database available at <http://www.pompecenter.nl> provides a continuously enlarging list of 372 sequence variants in the GAA gene (MIM#606800; RefSeq NT_024871.11; NM_000152.3; NP000143.2). Among them, 248 were pathogenic, 2 were presumably pathogenic while the effect of 46 other variants were marked as unknown¹⁴.

In the most recent 2012 publication from this same group, 60 novel GAA sequence variants, and the effect of 33 missense mutations and one in frame deletion were reported¹⁵. In spite of this, cumulative data genotype/phenotype correlations through mutation analysis have been largely unsuccessful at identifying factors that can predict outcome. On the other hand, the GAA deficiency in Pompe disease leads to a series of transcriptional responses which, in combination with other genetic and environmental factors, contribute to the process and the clinical spectrum of the disease. In order to identify transcriptional differences that may contribute to the disease phenotype, the muscle gene expression profile of Pompe patients was examined through oligonucleotide microarray methodology. Many transcription markers of immature or regenerating muscle were found in infantile-onset Pompe patients, and also genes exhibiting correlation between expression at baseline and response to therapy¹⁶. These findings give a foundation for biological discovery and biomarker development to improve the treatment of Pompe disease. In parallel to these efforts to find biomarkers to monitor disease progression, and better understand the pathogenesis of Pompe disease, additional investments have been made to develop new generation of therapeutics. Tagged recombinant enzyme to facilitate its capture by muscle fiber, small molecules, and strategies to reduce the substrate are promising approaches to further improve the outcome of Pompe patients.

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