Autophagy and the Pathophysiology of Pompe Disease

Pompe disease is an inherited, autosomal-recessive deficiency of acid alpha-glucosidase (GAA), a lysosomal enzyme required for the breakdown of glycogen [1]. The prevailing pathology is a generalized build-up of glycogen within lysosomes leading to profound skeletal and cardiac myopathy with the severity of symptoms being directly correlated with residual GAA activity [1]. In the most severe form of the disease, having no detectable level of GAA, symptoms become apparent within the first months of life and include loss of muscle tone, failure to thrive, respiratory distress and hypertrophic cardiomyopathy [2]. Without pharmacological intervention, death often occurs before the age of 1 year [1]. While the enzymatic deficiency present in Pompe disease has been known for decades [3], the molecular mechanisms resulting in the extensive muscle damage observed in patients have remained elusive. Originally it was thought that the damage resulted from the rupture of glycogen-laden lysosomes and subsequent exposure of myofibers to lysosomal contents [4]. More recently, however, this mechanism has evolved to include a primary dysfunction of autophagy. Indeed, autophagy is induced in GAA knock-out mice, with autophagic build-up readily apparent in both type I (slow) and II (fast) skeletal muscle fibers [5]. Interestingly, type II (fast) muscle fibers also demonstrate an inability to effectively form autolysosomes [5]. The lack of functional autophagy leads to both physical impairment of muscle contraction (from the large amounts of vacuolar deposition) and an increase in the pool of potentially toxic material, such as ubiquinated proteins [5]. Therefore, the emerging picture of skeletal muscle damage in Pompe disease is autophagy induction with concurrent ineffective autophagy in type II muscle fibers [5].

References


