Autophagy – a fundamental cellular mechanism on the verge of clinical translation

Autophagy is a fundamental cellular degradative pathway conserved throughout evolution with important roles in the removal of defective proteins and organelles, defence against infections and adaptation to changing metabolic demands [1,2]. Autophagy involves a highly complex machinery and several tightly regulated steps, evolving from the initial phagophore to the formation of autophagosomes, whose fusion with lysosomes results in the final structure of degradation, the autolysosome. Although three major forms are distinguished depending on the specific type of cargo delivery to the lysosome – microautophagy, chaperone-mediated autophagy and macroautophagy – the latter is the most relevant and usually used synonymously with the term autophagy.

Based on the observation of intralysosomal digestion of mitochondria and other intracellular structures in rat hepatocytes, the term ‘autophagy’ (from the Greek auto phagein or ‘self-eating’) was first introduced in 1967 by the Belgian biochemist Christian de Duve [3], subsequently awarded the Nobel Prize for his discovery of peroxisomes and lysosomes. While initially attracting the attention mainly of cell biologists, the recent recognition as a fundamental mechanism implicated in a wide range of human disorders has made autophagy a potentially attractive therapeutic target, resulting in an explosion of autophagy-related research over the last decade (Figure 1).

The recent discovery of recessive mutations in the key autophagy regulator EPG5 as the cause of Vici syndrome [OMIM 242840] [4], a severe human multisystem disorder characterized by callosal agenesis, cataracts, sensorineural deafness, a skeletal and cardiac myopathy, combined immunodeficiency, hypopigmentation and variable thyroid, pulmonary, and hepatic and renal involvement, has emphasized that intact autophagy is a prerequisite for the normal formation and functioning of virtually every organ system. In addition to its roles in cancer biology, the immune system, and heart and lung disease [2], autophagy has now been linked to a wide range of neuromuscular, neurodevelopmental and neurodegenerative disorders, probably reflecting that baseline autophagy is already enhanced under physiological conditions in muscle and neurons and that these tissues are therefore particularly susceptible to primary autophagy defects. Both the ubiquitin-proteasome system and the autophagy-lysosome pathway contribute to loss of muscle mass in muscle atrophy [5]. In skeletal muscle, autophagosomes and autolysosomes are inconspicuous under physiological conditions; however, in the autophagic vacuolar myopathies (AVMs), the main neuromuscular manifestation of primary autophagy defects, they accumulate and become the most recognizable histopathological abnormality [6]. The AVMs include Danon disease [OMIM 300257] due to autosomal-recessive mutations in LAMP2 encoding a lysosome-associated membrane protein involved in autophagosome-lysosome fusion, and X-linked myopathy with excessive autophagy (MEAX) [OMIM 310440] due to X-linked recessive mutations in VMA21, encoding a protein regulating acidification of autolysosomal content.

Acid maltase deficiency (Pompe disease, or glycogen storage disease II, GSD II [OMIM 232300]) is due to recessive mutations in GAA, encoding the acid α-glucosidase enzyme with a crucial role in lysosomal glycogen degra-
dation. There is a wide clinical spectrum correlated to residual enzyme activity, ranging from a severe infantile form with profound cardiorespiratory involvement to more mildly affected late-onset cases. Enzyme replacement therapy (ERT) with recombinant α-glucosidase (rGAA) has shown some benefit in the severe infantile form but is not curative and associated with a more variable response in late-onset cases. The marked variability in individual responses to ERT is currently not fully understood but is likely to involve variable intracellular cell trafficking disturbances in Pompe disease patients, hampering effective delivery and processing of the rGAA precursor protein to variable degrees. Although usually classified with the glycogen storage disorders (GSDs), Pompe disease shares many features with the primary AVMs and is considered with these conditions by some authors [6]. Indeed, autophagic failure correlating with disease severity and extent of histopathological abnormalities has been identified as an important mechanism in humans and mouse models of Pompe disease [7].

In the present issue of *Neuropathology and Applied Neurobiology*, Nascimbeni and colleagues report that impaired ‘autophagy affects α-glucosidase processing and ERT efficacy in late-onset glycogen storage disease type II’. More specifically, they describe that the ability to process α-glucosidase (i) correlates conversely with the degree of autophagy failure in muscle fibres from GSD II patients, (ii) worsens over time as autophagic abnormalities progress but (iii) may be preserved if ERT is instituted before the latter abnormalities have become established [8]. This work confirms earlier observations in animal models, indicating a correlation between autophagosome accumulation and inefficiency of ERT treatment.

Although based on only a small number of samples and in need of confirmation in larger series, the study by Nascimbeni and colleagues suggests promising lines of enquiry concerning not only Pompe disease but also other conditions where defective autophagy has been implicated: First, the intricate link between autophagy and ERT efficiency suggests an important mechanism that may also be relevant for the treatment of other conditions where the genetic defect affects not only a very specific enzymatic function but fundamental aspects of intracellular trafficking, including autophagy. In such conditions, autophagy modifiers may be beneficial for optimizing the intracellular environment in order for ERT to realize its full therapeutic potential. Clinically applicable autophagy modifiers are still few [2,9]; further research will be required to elucidate currently unresolved aspects of the highly complex autophagy machinery, in order to develop pharmacological compounds capable of targeting this fundamental cellular mechanism in a more precise and safe manner. Second, in addition to Pompe disease and the AVMs, defective autophagy has now been implicated in a wide range of other neuromuscular disorders [10], including COL6-related myopathies and the centronuclear myopathies [11]. Moreover, an associated vacuolar myopathy is a consistent feature of primary autophagy-related multisystem disorders such as EPG5-related Vici syndrome [4], suggesting an intriguing continuum between conditions intricately linked through different defects concerning the same pathway. These observations indicate that insights into mechanisms and modification of autophagy derived from any of these conditions may be potentially transferable to a much wider range of neuromuscular, neurodevelopmental and neurodegenerative disorders due to defective autophagy.

Almost 50 years after its original description by de Duve and colleagues, autophagy as a fundamental cellular mechanism is finally beginning to complete its long journey from bench to bedside.

H. Jungbluth*†‡
*Department of Paediatric Neurology, Evelina’s Children Hospital, Guy’s & St. Thomas’ Hospital NHS Foundation Trust, †Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, and ‡Department of Basic and Clinical Neuroscience Division, IoPPN, King’s College, London, UK

References
6 Malicdan MC, Nishino I. Autophagy in lysosomal myopathies. *Brain Pathol* 2012; **22**: 82–8
8 Nascimbeni AC, Fanin M, Tasca E, Angelini C, Sandri M. Impaired autophagy affects acid α-glucosidase processing and enzyme replacement therapy efficacy in late-onset glycogen storage disease type II. *Neuropathology and Applied Neurobiology* 2015; **41**: 672–675
11 Jungbluth H, Gautel M. Pathogenic mechanisms in centronuclear myopathies. *Front Aging Neurosci* 2014; **6**: 339