Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 275–311

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Innovative Treatments for Lysosomal Diseases

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Keywords:
lysosome
organelle
protein targeting
sphingolipids
inhibitors of biosynthesis
substrate reduction
chaperone
therapeutic
innovation
gene transfer

Striking therapeutic advances for lysosomal diseases have harnessed the biology of this organelle and illustrate its central rôle in the dynamic economy of the cell. Further Innovation will require improved protein-targetting or realization of therapeutic gene- and cell transfer stratagems. Rescuing function before irreversible injury, mandates a deep knowledge of clinical behaviour as well as molecular pathology – and frequently requires an understanding of neuropathology.

Whether addressing primary causes, or rebalancing the effects of disordered cell function, true therapeutic innovation depends on continuing scientific exploration of the lysosome. Genuine partnerships between biotech and the patients affected by this extraordinary family of disorders continue to drive productive pharmaceutical discovery.

The lysosome as a gateway to treatment

The lysosome and assembly of its components during organelle biogenesis have, from the time of its discovery by Christian de Duve, incited interest for intervention. With the recognition of inborn errors of lysosomal function as single-gene defects causing multisystem diseases [1], the appetite for therapeutic exploration has burgeoned. Painstaking research to determine the nature of the substrates, which contribute to the phenotype of intracellular storage was simply a first step in understanding lysosomal disorders caused by deficiency of acid hydrolases; this classical approach provided critical insight into the central role of the organelle in macromolecular recycling for the economy of the cell.

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http://dx.doi.org/10.1016/j.beem.2015.01.001
1521-690X/

Subsequent molecular characterization of the genetic basis and protein defect(s) implicated in each disease revealed fundamental precepts and possibilities for definitive treatment – namely, replacing the primarily deficient factor required for normal lysosomal function. While much remains to be learnt about molecular pathogenesis of the individual conditions – many of which exhibit features of inflammation and other, compensatory, tissue reactions that await exploration – approaches based on complementing the function of proteins which are defective are fundamental to future therapeutic development.

De Duve shared the Nobel Prize for Physiology or Medicine in 1974 with Albert Claude and George Palade – an event which heralded Cell Biology as a radically new and interdisciplinary science [2]. With his colleagues, de Duve rapidly promoted the concept of a dynamic and interactive entity defined by a distinct acidic microenvironment within the living cell [3]. This functional definition immediately suggested that the lysosome was part of an interlinked membrane system in contact with the plasma membrane and its invaginations at the cell surface – thus participating in the processes of fluid-phase endocytosis, pinocytosis and receptor-mediated uptake, as well as autophagy. De Duve quickly realised that the lysosomal compartment would be continually exposed to the external environment and thus provide a direct access route for potential therapies [4].

Lysosomal diseases

Henri-Gery Hers, a former colleague of de Duve, pursued research into glycogen storage diseases – thereby encountering Pompe disease, in which all the known enzymes of glycogen breakdown and synthesis functioned normally. In a brilliant series of investigations, Hers ultimately identified the deficient enzyme which proved to be an acid α-glucosidase (maltase); and thus a lysosomal enzyme previously unconnected to glycogen metabolism. Other colleagues, notably François Van Hoof, joined to define the concept of inborn lysosomal diseases [1]; and thus numerous disorders representing defects in the recycling of cellular macromolecules were classified as 'lysosomal storage diseases'. More than 70 heritable diseases of lysosomes and lysosome-related organelles are now recognized – each best considered as a unique pathological domain [5,6]. Given the potential for access of proteins to the lysosomal compartment, and numerous enzyme defects responsible for lysosomal diseases, de Duve realised that by a succession of chance events: "thus was elucidated, with important consequences for diagnosis, prevention and therapy, a vast chapter of pathology that had remained totally mysterious …" [7].

Specific complementation of deficient lysosomal function

The dominant principle of functional complementation utilizing specialised pathways for protein delivery to the organelle, owes its origin to the discovery of the lysosome, and especially its dynamic rôle in cellular recycling. This led to an early prediction that, beyond its critical role in autophagy and renewal, a substantial network of membranes and compartments could be accessed by molecules presented at the cell surface [4].

De Duve had no concept of the mechanistic link of lysosomal protein targeting in biogenesis of the organelle – but remarkable experiments carried out by Elizabeth Neufeld and colleagues at the National Institutes of Health provided direct experimental support for this supposition [8]. Studies of fibroblasts cultured from genetically distinct forms of the human mucopolysaccharidoses ultimately led to an understanding of how nascent lysosomal enzymes were trafficked to the lysosome. With this came the realization that restoring function by enzymatic complementation of lysosomal defects might indeed be clinically tractable [8].

The complementing factors proved to be high molecular weight forms of the soluble lysosomal hydrolases deficient in each genetically distinct disorder; these glycoproteins are decorated by the critical mannose 6-phosphate moiety – and recognition signal which serves as a ligand for cell-surface receptors that mediate uptake and sorting to the lysosomal compartment after endocytosis. Contemporaneous studies of I-cell disease provided reciprocal information: in this disease, genetic defects in the formation of the recognition signal, leading to multiple deficiencies of acid hydrolases in the lysosome but elevated activities in plasma and other extracellular fluids [9,10]. These studies also