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From bedside to cell biology: A century of history on lysosomal dysfunction

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ABSTRACT

Lysosomal storage disorders (LSDs) are a group of rare genetic diseases, generally caused by a deficiency of specific lysosomal enzymes, which results in abnormal accumulation of undegraded substrates. The first clinical reports describing what were later shown to be LSDs were published more than a hundred years ago. In general, the history and pathophysiology of LSDs has impacted on our current knowledge of lysosomal biology.
Classically, depending on the nature of the substrates, LSDs can be divided into different subgroups. The mucopolysaccharidoses (MPSs) are those caused by impaired degradation of glycosaminoglycans (GAGs). Amongst LSDs, the MPSs are a major group of pathologies with crucial historical relevance, since their study has revealed important biological pathways and highlighted interconnecting pathological cascades which are still being unveiled nowadays. Here we review the major historical discoveries in the field of LSDs and their impact on basic cellular knowledge and practical applications. Attention will be focused on the MPSs, with occasional references to other LSDs. We will show as studies on the metabolic basis of this group of diseases have increased our knowledge of the complex degradative pathways associated with the lysosome and established the basis to the development of specific therapeutic approaches aiming at correcting or, at least ameliorating their associated phenotypes.

1. Introduction

The first clinical reports describing what were later shown to be Lysosomal Storage Disorders (LSDs) were published around a hundred years ago (Tay, 1881; Gaucher, 1882; Fabry, 1898; Niemann, 1914; Hunter, 1917). The lysosome itself, however, was only discovered five decades later, by Christian de Duve. The designation 'lysosome' is derived from the Greek words 'lysis' (destruction) and 'soma' (body), and was chosen to reflect its role as the major intracellular site for enzymatic degradation of macromolecules (de Duve et al., 1955). Another ten years were needed for the concept of LSD to be first proposed by H.G. Hers, who suggested that Pompe disease, a glycogen storage disorder, was due to deficiency of a lysosomal enzyme (acid maltase deficiency; Hers, 1963). Soon after the idea of enzymatic deficiency was established, several metabolic disorders that had been previously described by clinicians were catalogued as LSDs, and classified according to the storage material accumulated intralysosomally. Thus, disorders in which glycosaminoglycan (GAG, also called mucopolysaccharides) accumulation prevailed were classified as mucopolysaccharidoses; those dominated by lipid storage were called lipidoses; the ones in which the accumulation of sphingolipids prevailed were sphingolipidoses; those mostly characterized by the storage of oligosaccharides were oligosaccharidoses (Schultz et al., 2011).

By the same time, the concept of 'cross correction', first formulated by de Duve in 1964, was demonstrated by Elizabeth Neufeld and her group, who discovered that co-cultured fibroblasts derived from two patients with different lysosomal storage disorders mutually corrected each other, established the basis of 'enzyme replacement therapy' (ERT) (Barton et al., 1990; Brady, 2006). Then, all efforts turned to developing effective ERT for LSDs, starting with Gaucher disease (GD), the most common of these pathologies. Several teams centered efforts in purifying β-glucocerebrosidase (GCase) to supply GD patients with the enzyme in which they were deficient, in order to evaluate whether clinical advantage came from that therapeutic approach. Because of its high hydrophobicity, and of the lack of experience in its handling, it was extremely hard to get useful quantities of the requisite enzyme. Eventually, a small amount of sufficiently purified GCase was obtained and administered to two GD patients (Brady et al., 1974) leading to a reduction of GCase in the liver of both patients, together with a striking

Abbreviations: AD, Alzheimer's disease; ARSG, arylsulfatase G; AV, autophagic vacuole; CNS, central nervous system; CMA, chaperone-mediated autophagy; CS, chondroitin sulfate; DS, dermatan sulfate; EE, early endosome; ER, endoplasmic reticulum; ERT, enzyme replacement therapy; GD, Gaucher disease; GAGs, glycosaminoglycans; HS, heparan sulfate; KS, keratan sulfate; LE, late endosome; LSDs, lysosomal storage disorders; MPRs, mannose 6-phosphate receptors; MPSs, mucopolysaccharidoses; RE, recycling endosome; TGN, *trans*-Golgi network; UPS, ubiquitin–proteasome system; GCase, β-glucocerebrosidase.

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reduction in the quantity of GCase associated with circulating erythrocytes in the recipients. Nevertheless, a long way had to be walked before consistent clinical benefit of ERT was demonstrated in a cohort of patients with GD (Barton et al., 1991) and an even longest period was needed for the first therapies of such kind to reach the market and become commercially available.

Here we review the major historical discoveries in the field of LSDs and their impact on basic cellular knowledge and practical applications (Fig. 1). Attention will be focused on the MPSs, with occasional references to other LSDs. We will show as studies on the metabolic basis of this group of diseases have increased our knowledge of the complex degradative pathways associated with the lysosome and established the basis to the development of specific therapeutic approaches aiming at correcting or, at least ameliorating their associated phenotypes.

2. Early clinical descriptions: the Hurler and Hunter syndromes

To find, in the literature, the first medical report of a MPS, we have to go back in time until 1917. In that year, Charles Hunter provided the scientific community with a detailed description and radiological imaging of two brothers, aged 10 and 8 years, with multiple skeletal and somatic abnormalities, who were proposed to suffer from an endocrine disturbance. The two children were full-term and were normally delivered. Both were breast-fed and no digestive disturbances were observed in infancy; both were walking at the age of 17 months. The elder began to talk when aged around 1 year and had normal intelligence. The younger brother, however, was somewhat late in learning to talk and was making slow progresses at school by the time the original paper was published. Apart from throat trouble, both children were reported to have been healthy in every way. Both were operated on for tonsils and adenoids; both had hearing deficiencies. The brothers were described as "undersized" having "extremely large" heads, "curiously shaped, with very marked bulging of the squamous portion of the temporal bone and of the frontal bones; the hair of the head rather thin and very harsh (…)." Other features included "saddle nose, with large thick nostrils; (…) very large tongue; very short neck, with slight enlargement of right lobe of thyroid (…); knees (…) slightly flexed; [thick] knees and ankles (…) [and] hands [which could] not be clenched". Also common to both children's clinical course was the fact that their condition progressively deteriorated over time (Hunter, 1917). These early observations were later confirmed by the discovery of other patients harboring similar physical deformities, and the typical features of the severe form of this syndrome were established: coarse facial features, short stature, skeletal deformities, joint stiffness and mental retardation. A milder form of the same disorder was also recognized, with preservation of intelligence and survival into late adult life. Even though still presenting with an obvious somatic involvement, similar to the one observed in severely affected Hunter patients, this subtype of the disease presents later in life and with a much slower progression (Neufeld and Muenzer, 2001).

Two years later, in 1919, Pfaunder reported two cases to the Medical Society in Munich that were described in detail by his assistant Hurler, who at once suspected to be in the presence of another new syndrome. The patients displayed the following combination of congenital abnormalities: "clouding of the corneae, (…) oxycephaly, disproportionate dwarfism strongly resembling that of hypothyroidism and associated with some of the usual signs of that condition, [such as] saddle nose, mental defect, dry skin, inguinal and umbilical hernia, crura valga, pedes valgi". In addition, the patients presented "a contraction of the fingers, limitation of movement in other joints (shoulders, elbows,

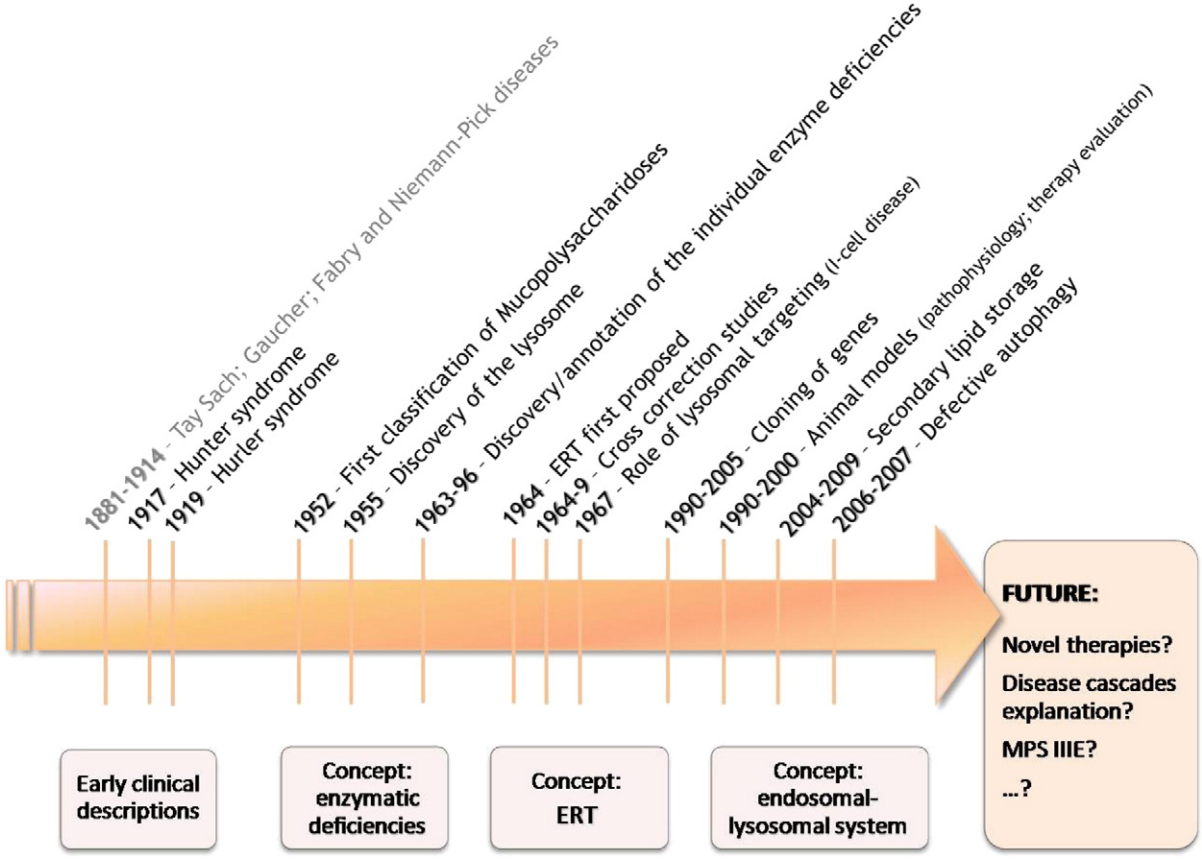

Fig. 1. Timeline for discoveries on lysosomal storage diseases and their impact on cell biology. Overview of the major discoveries concerning MPSs in particular, highlighting their impact on the establishment of some of the most important concepts on the LSD field: i) enzymatic deficiencies as the basis of disease; ii) enzyme replacement as a possible therapeutic approach and iii) the lysosome as central coordinator of a remarkably dynamic system, the *endosomal–lysosomal system*.