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Review

Overview of immune abnormalities in lysosomal storage disorders

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ABSTRACT

The critical relevance of the lysosomal compartment for normal cellular function can be proved by numbering the clinical phenotypes that arise in lysosomal storage disorders (LSDs), a group of around 70 different monogenic autosomal or X-linked syndromes, caused by specific lysosomal enzyme deficiencies: all LSDs are characterized by progressive accumulation of heterogeneous biologic materials in the lysosomes of various parts of the body such as viscera, skeleton, skin, heart, and central nervous system. At least a fraction of LSDs has been associated with mixed abnormalities involving the immune system, while some patients with LSDs may result more prone to autoimmune phenomena. A large production of proinflammatory cytokines has been observed in Gaucher and Fabry diseases, and wide different autoantibody production has been also reported in both. Many immune-mediated reactions are crucial to the pathogenesis of different inflammatory signs in mucopolysaccharidoses, and subverted heparan sulphate catabolism might dysregulate cellular homeostasis in the brain of these patients. Furthermore, an inappropriate activation of microglia is implicated in the neurodegenerative foci of Niemann-Pick disease, in which abnormal signalling pathways are activated by impaired sphingolipid metabolism. In addition, not the simple impaired catabolism of gangliosides *per se*, but also the production of antiganglioside autoantibodies contributes to the neurological disease of gangliosidoses. Even if the exact relationship between the modification of lysosomal activities and modulation of the immune system remains obscure, there is emerging evidence of different impaired immunity responses in a variety of LSDs: in this review we investigate and summarize the immune abnormalities and/or clinical data about immune system irregularities which have been described in a subset of LSDs.

1. Introduction: the lysosomal storage disorders

Lysosomal storage disorders (LSDs) are a group of rare genetic syndromes resulting from abnormal build-up of undegraded materials which accumulate in the lysosomes of different cells of the human body, as a result of total or partial functional loss of specific lysosomal enzymes or co-factors implicated in the degradation of those materials [1]: more specifically the upstream precursors accumulate, and LSD clinical presentation reflects the amount of residual enzymatic activity, ranging from infantile (little or no enzymatic function) to adolescent and adult disease (moderate or mild residual enzymatic function). In the mid 1950s, the biochemist Christian de Duve identified and characterized the “lysosome” as a subcellular organelle responsible for digestion and recycling of different macromolecules, using cell fractionation techniques and biochemical analyses [2]: this was the scientific breakthrough that would lead to understand the physiological basis of LSDs. Pompe disease (or glycogen storage disease type 2, OMIM 232300) has been the first disease to be identified as an LSD in 1963, caused by the inherited deficiency of acid maltase (α-glucosidase), necessary to break down glycogen and convert it into glucose [3]. All LSDs may be fatal, and many display profound neurological impairment or multi-organ dysfunction that begin in childhood. Each disease belonging to the group of LSDs encompasses several types that are named for the specific macromolecule that accumulates in each case, and the resulting disorders include Gaucher disease, Fabry disease, mucopolysaccharidoses, Niemann-Pick disease, and gangliosidoses, which are the syndromes analyzed in this review for their potential heterogeneous abnormalities in the immune system. With the exception of the X-linked recessive Fabry disease (and also mucopolysaccharidosis type II), LSDs share a common autosomal recessive inheritance pattern, and have an estimated overall incidence of 1 in 7.500–8.000 live births [4].

In all human cells the lysosome works as a highly complex regulatory and recycling district, and its discovery inaugurated a new era in cellular physiology, which was naturally followed by the

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identification of approximately 70 distinct LSDs, that collectively account for 14% of all inherited metabolic diseases, resulting from mutations in specific genes encoding for lysosomal hydrolases [5]. Lysosomes receive their substrates through various pathways, including endocytosis, phagocytosis, or autophagy, and substrates are degraded *via* a finely orchestrated network of membrane bound lysosomal proteins, soluble lysosomal hydrolases, lysosomal related organelles, and other cellular constituents [6]. As a consequence, the absence or reduction of a specific lysosomal enzyme leads to abnormal and progressive accumulation of non-metabolized substrates, which drives a constellation of signs and symptoms with wide range of severity, following the specific deficient enzymatic activity. Moreover, as a secondary effect of lysosomal dysfunction, inflammation and disrupted autophagy have been frequently reported in most LSDs [7]. Effects of lysosomal enzymatic deficiencies are dependent on the processes affected and type of accumulated macromolecules, but in most LSDs it is not the storage itself, which is necessarily the cause of disease manifestations, but also the secondary effects of lysosomal dysfunction to generate the overall phenotype, including disrupted cellular homeostasis, multi-site inflammation and autophagy. This may explain why many types of LSDs have very similar clinical features despite the accumulating macromolecule being different.

Historically, the structure and content of storage material was used for the diagnosis of a specific LSD and to number LSDs into subclasses. For many lysosomal hydrolases, microscopic evaluation of biopsied tissues and biochemical evaluation of urine provided evidence of accumulated cellular substrates and clues to identify the underlying enzymatic defect [8]. Evidence-based management of LSDs is nowadays limited by the lack of standardized and reliable biomarkers. A multitude of studies by Elizabeth Neufeld led to the discovery of a logical basis of enzyme replacement therapy for LSDs (the first drugs for clinical use date back to the period 1991–1995), though existing enzyme therapies had proven incomplete, non-uniform, and ineffective on many aspects critical to the whole amelioration of a LSD [9].

The occurrence of immune abnormalities has been examined in a fragmentary fashion for patients with LSDs: herein we have considered all papers accessible *via* PubMed, edited in English, matching the words “lysosomal disorder”, or the name of each specific disease, with “immune”, “autoimmune”, “autoantibodies”, and “autoinflammatory”. We have considered also case reports and studies related to the pathological mechanisms underlying the development of autoantibodies and/or overt autoimmune phenomena in patients with LSDs. Final goal of this manuscript was to find out interconnections between LSDs and immune abnormalities, providing a brief digest of some original contributions in the field until 2017 in pursuit of a better understanding of immune system involvement in these rare disorders.

2. An evolving pathophysiology among autoimmune, autoinflammatory and autophagy responses

The molecular clarification of LSDs has provided a better understanding of their pathogenesis and treatment opportunities, but also shown that many inflammatory manifestations might derive by autoimmunity and also self-produced inflammation. The connection between LSDs and autoimmune processes is not clear, though we know that autoimmune diseases encompass a wide spectrum of clinical signs as a reflection of their complex pathophysiology starting in the loss of self-tolerance and involving monocytes, macrophages, dendritic cells, and neutrophils as first-line immune effectors located in the interface between innate and adaptive immunity [10]. In particular, studying macrophages derived from patients with Gaucher disease has shown an increased secretion of proinflammatory interleukin-1β following activation of the inflammasome, a multiprotein complex that activates caspase-1 and releases bioactive interleukin-1, as a result of impaired autophagy [11]. Dysregulation of inflammasome is the common basis of a family of monogenic autoinflammatory disorders [12], characterized by seemingly unprovoked systemic inflammation in the absence of autoantibodies or autoreactive T lymphocytes, though it has been involved in the pathogenesis of different multifactorial polygenic diseases with an autoinflammatory component and even in different autoimmune diseases [13]. After the discovery of familial Mediterranean fever gene in 1997 and tumor necrosis factor receptor-associated periodic syndrome gene in 1999, we have witnessed an extraordinary revolution in the understanding of autoinflammatory disorders, with identification of multiple genes and new clinical entities, all characterized by subverted mechanisms of inflammation [14]. A number of mutations affecting the proteins of the inflammasome complex or proteins that regulate inflammasome function have been described, including hereditary recurrent fevers, pyogenic disorders, bone autoinflammatory diseases, immune-mediated granulomatous diseases, complement disorders, hemophagocytic and vasculitic syndromes [15]. A new classification of all human immunological diseases has been drafted, showing a spectrum from monogenic autoinflammatory disorders at one end and classical autoimmune disorders at the other, underscoring the existence of an immunological *continuum* between autoinflammation and autoimmunity [16]: indeed, a successful adaptive response requires also innate immunity, and – although the adaptive and innate responses would appear to be at opposite ends of the spectrum – they are integrally interconnected. The contribution of deregulated inflammasomes to the field of autoimmune disorders, such as rheumatoid arthritis and Sjögren syndrome, has also been corroborated by the clinical efficacy of interleukin-1 blockade in these conditions [17,18].

In particular, lysosome-based signalling and lysosome degradation are subject to complex regulations in order to match the evolving needs of a cell: alterations in these activities might lead to activation of autophagy, cause dysfunction of other intracellular structures such as mitochondria, and become crucial to the pathophysiology of immune-mediated manifestations through the expression of chemokines, costimulatory or protolerogenic factors in patients with LSDs. Moreover, the cellular turnover of proteins and organelles requires a strict cooperation between the autophagic and the lysosomal degradation pathways, and an important step in this process is the fusion of the autophagosome with lysosomes: the deficiency of specific lysosomal enzymes impairs the autophagosome-lysosome fusion and leads to the accumulation of undegraded macromolecules, such as complex lipids, mucopolysaccharides or other biologic substates [19]. Recently, for instance, the role of sphingolipids has been implicated in different cellular events, including cell survival, growth, senescence and apoptosis, but also in inflammation and neovascularization [20]. Nevertheless, the information available on the exact role of complex lipid metabolites or other macromolecules and their signalling in the pathophysiology of LSDs is very limited. Our challenge in this review has been to dissect the mixed irregularities of the immune system observed in these diseases in order to better understand their complex clinical sceneries or define potential new targets for treatment.

3. The proinflammatory scenery of Gaucher disease

Gaucher disease is the most prevalent LSD and is caused by two disease-causing alleles in the *GBA1* gene, leading to decreased activity of the lysosomal enzyme β-glucocerebrosidase, which leads to the accumulation of its substrate, glucosylceramide, in macrophages [21]. The consequence of this deficiency is attributed to the accumulation of glucosylceramides in the monocyte/macrophage lineage, inducing their transformation into Gaucher cells, enlarged cells with eccentric nuclei and cytoplasm with heterogeneous “crumpled tissue paper” appearance, related to the aggregates of undegraded glucosylceramide. The phenotype is variable and three clinical forms have been identified: Gaucher disease type 1 (OMIM 230800), the non-neuronopathic form of the disease, which affects the majority of patients, is characterized by pancytopenia, hepatosplenomegaly, and skeletal complications related