FEBS Letters 587 (2013) 1258–1267

journal homepage: www.FEBSLetters.org

Review

Extracellular matrix components: An intricate network of possible biomarkers for lysosomal storage disorders?

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ARTICLE INFO

Article history:
Received 28 December 2012
Revised 18 February 2013
Accepted 19 February 2013
Available online 26 February 2013

Edied by Wilhelm Just

Keywords:
Mucopolysaccharidoses
Lysosomal storage disorders
Biomarker
Extracellular matrix molecule

ABSTRACT

Biomarkers are extremely important in the case of multisystemic diseases, such as lysosomal storage disorders (LSDs), which are often difficult to assess in clinical practice. Several studies demonstrated significant alterations in the expression of extracellular matrix (ECM) components in LSD patients, raising important questions in relation to their possible involvement in disease pathogenesis and providing evidence for their possible utility as disease biomarkers. This article provides an overview of the possible pathogenic correlations between LSDs and ECM. Data regarding the expression of these molecules are discussed. Finally, the possible implication of ECM components as therapeutic targets in this group of diseases along with the impact of the differential expression of these components in current LSD treatment will be critically addressed.

1. Introduction

The lysosome represents an important organelle involved in multiple cell processes, usually through dynamic interactions with other cellular compartments. Thus, it is not surprising that deficiencies of specific proteins which are integral to lysosomal function give birth to a broad spectrum of almost 70 genetically distinct metabolic conditions, known as Lysosomal Storage Disorders (LSDs) [View metadata, citation and similar papers at core.ac.uk
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[2] and may present with a wide range of clinical manifestations and a variable degree of involvement regarding different organs and systems.

The multisystemic nature of LSDs, as well as the irreversibility of many features which characterize them, often render the assessment of patients with the use of common clinical, radiological and laboratory tests, difficult in practice. Thus – and in accordance with numerous other pathologic conditions – there is great ongoing effort for the discovery of specific chemical analytes, also known as biomarkers (BMs), indicative of a particular biological process. The advent of enzyme replacement therapy (ERT) for Gaucher disease, which gave rise to the current revolution in the search of novel treatment modalities, in combination with the great potential in diagnosis unraveled by the application of new molecular techniques, highlighted even more the need for efficacious BMs. The are expected to play a significant role in orphan drug development [3].

In the case of LSDs 3 categories of BMs are currently distinguished [3,4]. The first category includes molecules that accumulate directly as a result of the genetic defect, which leads to the enzymatic deficiency. The second category comprises molecules whose expression is modified in affected tissues as a result of the primary pathological storage. A third category of less specific markers includes proteins generally released in the circulation due to the lysosomal dysfunction, which could potentially be more representative of total body burden rather than reflect a particular organ or system involvement [5]. All these molecules should have certain specific characteristics in order to ensure that their application is safe and reliable for the assessment of patients in the clinical setting [4]. Some of the features of an ideal BM include the simple and rapid assessment in easily accessible tissues and body fluids, the ideal reflection of total body burden of the disease, the narrow

Abbreviations: LSDs, lysosomal storage disorders; BMs, biomarkers; ERT, enzyme replacement therapy; ECM, extracellular matrix; MPS, mucopolysaccharidoses; PGs, proteoglycans; HA, hyaluronic acid; GAGs, glycosaminoglycans; RHAMM, receptor for HA mediated motility; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; CNS, central nervous system; LINCL, late-infantile neuronal ceroid lipofuscinoses

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0014-5793
http://dx.doi.org/10.1016/j.febslet.2013.02.035

range in the variation of the BM concentration or activity in the general population and the absence of overlap between the quantity of the analyte in naive patients and healthy subjects [4]. Apart from the identification and common employment of plasma chitotriosidase as a first screen in Gaucher disease [6], there are currently very few BMs in LSDs, of which even fewer are engaged in clinical use [7–16].

The extracellular matrix (ECM) represents an intricate network of macromolecules whose components represent research targets concerning BM discovery in numerous pathologic conditions. Extensive research over the last 30 years has led to a great appreciation of the widespread functional importance and dynamic roles of the ECM in diverse cellular processes. Following a brief summary about the various components of the ECM and their functions, this article provides an overview of the possible pathogenic correlations between LSDs and ECM. Data regarding the expression of these molecules, in both animal models and human subjects, in mucopolysaccharidoses (MPS) and other LSDs will be discussed. Along with the possible implication of these molecules as therapeutic targets in various LSDs, existing literature, regarding the impact of the differential expression of the ECM components in current treatment applied in this group of diseases, will be also critically addressed.

2. The ECM: molecules & functions

The ECM represents an interconnected meshwork of macromolecules, a physical scaffold for cell and tissue organization, as well as a microenvironment providing contextual information that influences processes of any cell type [17]. Through its function, it regulates growth factors, chemokine and cytokine availability, contributes to tissue homeostasis maintenance and influences cell proliferation, differentiation, motility and survival [18–22]. The ECM is composed of several distinct families of molecules, presenting dynamic interactions with each other and with diverse types of cells. As it has been widely acknowledged, alterations of its composition trigger the manifestation of numerous pathologic conditions [17,23,24]. Components of the ECM include diverse fibrous elements, different classes of proteoglycans (PGs), hyaluronic acid (HA) and finally a great number of proteolytic enzymes which are responsible for the dissolution of the ECM.

The fibrous elements of the ECM represent a vast portion of its macromolecules in most tissues and are divided in collagens and a diverse array of non-collageneous proteins. Collagens are distinguished in 28 different types among which type I, III, IV, and VI are the most prominent [25]. Although they are often thought as inert structures that provide tensile strength, they have been found to hold both pro- and anti-inflammatory properties [26–28]. It was demonstrated that they regulate cell adhesion and chemotaxis, while they also promote direct tissue development [22]. Apart from collagens, numerous glycoproteins, like laminins, fibronectin, thrombospondins and tenascins, represent fibrous elements of the ECM, too [18,19]. They are known for their function as growth factor repositories and, hence, are implicated in cell adhesion and signaling, as well as ECM-cell interactions [18,19].

Glycosaminoglycans (GAGs) represent the most abundant polysaccharides of the ECM and, at the same time, the primary storage material in MPS. They are linear polymers consisting of repeating disaccharide units and, according to their biochemical structure, they are divided in HA, chondroitin sulfate, dermatan sulfate, keratan sulfate and finally heparin and heparan sulfate. With the exception of HA, all the other GAGs are covalently attached to protein structures in order to form PGs [29]. There are more than 30 different PG molecules which can be divided in several distinct families [19,29,30]. PGs are found predominantly in the ECM or associated with the cell surface of most eukaryotic cells where they bind to other matrix- and cell-associated components and are implicated in numerous cell processes. Cell proliferation, migration and adhesion, tissue morphogenesis and development, inflammatory response reaction, growth factor availability and water and calcium homeostasis are only some among the numerous pathways and cell functions where these molecules are involved [19,29–32].

HA is the only member of the GAG family found in the ECM without a protein core and is detected in tissues as high or low molecular mass macromolecule. It is synthesized by numerous cell types and is abundant in many tissues of the human body [33]. Thus, it is not surprising that the concentration of HA is altered in a plethora of pathologic conditions affecting diverse organs such as the brain, bones, liver, kidneys, heart and lungs [33]. Its metabolism is regulated by three hyaluronan synthase genes [34] and the various isoforms of degrading hyaluronidases [35]. In order to exert its functions, HA is recognized by cell surface receptors, notably CD44 and receptor for HA mediated motility (RHAMM) [36,37]. Interaction of this highly metabolically active molecule with its receptors has a triggering effect on several intracellular signaling pathways, which in turn regulate cell proliferation, migration and differentiation [37,38]. It is also known that HA acts as an immune regulator and activates a wide range of inflammatory cells [33,38].

The ECM represents a constantly changing environment with macromolecules whose expression is regulated driven by two opposing forces: synthesis and deposition on one hand, and proteolytic breakdown on the other. There are numerous families of proteolytic enzymes involved in the dissolution of the ECM [39,40]. Most prominent among them are matrix metalloproteinases (MMPs), a growing family of 24 zinc-dependent endopeptidases classified according to domain structure into collagenases, gelatinases, stromelysins, matrilysines, membrane-type and others [41]. They represent key enzymes involved in tissue remodeling [42] and have been implicated in diverse normal and pathological processes, usually related to inflammation and cell apoptosis [43–45]. All MMPs are secreted as inert zymogens and require a proteolytic cleavage of a propeptide in order to be activated, whereas their transcription, translation and pro-enzyme activity are regulated by a wide spectrum of molecules, such as growth factors, cytokines and tissue inhibitors of metalloproteinases (TIMPs) [46,47]. TIMPs represent a family of 4 distinct members that bind to MMPs in a 1:1 stoichiometric ratio in order to block MMP activity [46]. They have different affinity patterns with various MMPs and their expression is regulated by cytokines and growth factors [47]. During the last years they have been found to exert additional properties, being implicated not only in the blockage but also in the activation of MMPs [48].

3. Pathogenic correlations between LSDs & ECM molecules

Unraveling the affected cellular pathways that cause the manifestation of each LSD represents the first and probably the most important step for the discovery of specific disease BMs. Yet, this relationship is rather bidirectional: the study of molecules, which are differentially expressed in response to a metabolic defect, has been extremely fruitful in providing mechanistic insight into the molecular pathogenesis of this group of diseases. In addition, the finding that some chemical analytes, such as chitotriosidase, were found to be elevated in a number of LSDs, has enhanced the notion that although each disorder is best considered as a singularity, most LSDs share common aetiopathological mechanisms [6]. The initial hypothesis postulated that the primary enzyme deficiency is followed by the intralysosomal accumulation of a single major substrate normally degraded by that enzyme, causing lysosomal

Table 1
Summary of the main findings of various studies concerning the expression of ECM molecules in LSDs.

ECM molecule	Disease	Subject	Findings	Ref. no.
Fibrous elements	MPS IVA	Human	Increased collagen fibril diameter of articular cartilage	[92,93]
	MPS IVA	Human	Increased collagen type I expression	[93]
	MPS IVA	Human	Decreased collagen type II expression in chondrocytes	[94]
	MPS VI	Animal	Decreased collagen IIA1 and X in articular chondrocytes	[95]
	MPS I	Human	Increased fibril diameter of the cornea	[96–99]
	MPS IIIA, IIIB and VI	Human	Increased fibril diameter of the cornea	[96]
	MPS IVA	Human	Increased fibril diameter of the cornea	[100]
	MPS VII	Human	Decreased fibril diameter of the cornea	[76]
	MPS IIB	Human	Unaltered collagen expression in fibroblasts	[102]
	MPS IIIB	Human	Decreased fibronectin expression in fibroblasts and increased neural stem cells	[102]
	MPS IIB	Human	Decreased elastin expression in fibroblasts	[102]
	MPS I	Animal	Increased elastin fragmentation in ascending aorta	[103–104]
	MPS VII	Animal	Increased elastin fragmentation in aorta	[104]
	Fabry	Human	Increased collagen type IV and fibronectin expression in podocytes	[105]
	GM_1 Gangliosidosis	Animal	Decreased collagen type II expression in chondrocytes	[106]
	I-Cell	Human	Decreased collagen fibril diameter in chondrocytes	[107]
	Sialidosis	Animal	Increased collagen and a2-laminin expression in skeletal muscle	[89]
	Krabbe	Animal	Increased laminin and fibronectin production from activated scwann cells	[109]
	Aspartyglucosaminuria	Human	Abnormal variation in collagen fibril diameter and reduction in their production	[110]
	Aspartyglucosaminuria	Human	Decreased collagen type I and III expression in fibroblast cell cultures	[111]
	Aspartyglucosaminuria	Human	Variation in collagen fibril diameter in gingival tissue	[112]
	Chediak-Higashi	Animal	Decreased collagen production in the oral mucosa	[113]
	Pompe	Human	Increased collagen biosynthesis in the gingival tissue	[114]
Proteoglycans	Various MPS types	Human	No alteration in proteoglycan turnover in fibroblast cell cultures	[115]
	MPS IV	Human	Alteration in the arrangement and increased production of PGs in articular cartilage	[92–93]
	MPS IV	Human	Decreased aggrecan expression in articular cartilage	[93]
	MPS IV	Animal	Up-regulation in aggrecan expression in chondrocytes	[94]
	MPS IX	Animal	Decreased expression of proteoglycans in articular cartilage	[77]
	MPS IIIA and B	Animal	Increased glypican 1 and 5 expression in the medial entorhinal cortex	[116]
	MPS I	Human	Elongation of proteoglycan filaments with alterations in their architecture in the cornea	[97–98]
	MPS IVA	Human	Elongation of proteoglycan filaments with alterations in their architecture in the cornea	[100]
	MPS VII	Human	Elongation of proteoglycan filaments with alterations in their architecture in the cornea	[76]
	MPS VI	Human	Increased amounts of proteoglycans in the cornea	[117]
	MPS VII	Animal	Increased amounts of proteoglycans in the interphotoreceptor matrix	[118]
	Niemann-Pick C	Animal	Decreased heparan sulfate proteoglycan degradation in fibroblasts	[119]
	Neuronal lipofuscinoses	Human	Increased versican expression in fibroblasts	[120]
	Aspartyglucosaminuria	Human	Alteration in the epimerization of proteoglycans	[110]
	Aspartyglucosaminuria	Human	Decreased biglycan and increased decorin production	[111]
	Mucolipidosis	Human	Alteration in proteoglycan expression in cartilage	[107]
	I-Cell	Human	Alteration in proteoglycan expression in cartilage	[121]
	GM_1 gangliosidosis	Animal	Decreased proteoglycan expression in chondrocytes	[106]
Hyaluronic acid	MPS IX	Human	Increased concentration in serum hyaluronic acid	[122]
	MPS IX	Animal	No alteration in circulating levels of hyaluronic acid	[77]
	Unknown MPS type?	Animal	Increased circulating levels of hyaluronic acid	[124]
	MPS I	Human	Abnormal hyaluronic acid metabolism with increased synthesis in skin fibroblasts	[125]
	MPS IIIA	Human	Increased serum levels of hyaluronic acid with decreased hyaluronidase I activity	[126]
	MPS IV	Human	No alteration in hyaluronidase I enzyme activity	[126]
	MPS VI	Human	Increased hyaluronic acid concentration in dentigerous cysts	[127]
	MPS II	Human	Increased hyaluronic acid content in the adenoids	[128]
	Mucolipidosis	Human	Contradictory results in relation to the production of hyaluronic acid by fibroblasts	[129–130]
	I-Cell disease	Human	Increased circulating levels of hyaluronic acid	[126]
	GM_1 gangliosidosis	Human	No alteration in the enzyme activity of hyaluronic acid degrading enzymes	[126]
Matrix metalloproteinases	MPS I	Animal	Increased expression and enzyme activity of MMP-12 in aorta	[103–104]
	MPS VI and VII	Animal	Increased expression of MMP-1 and MMP-13 in synovial membranes	[131]
	MPS VI and VII	Animal	Increased expression and activity of MMP-2 and MMP-9 in synovial membranes	[132]
	MPS VII	Animal	Increased expression and enzyme activity of MMP-12 in aorta	[104]
	MPS VII	Animal	Increased expression of MMP-3 in growth plates	[133]
	MPS VII	Animal	Increased expression of MMP-2 and MMP-9 in cerebral tissues	[134]
	MPS VI	Human	Decreased expression of MMP-9 in white blood cells	[135]
	MPS IIIB	Human	Decreased expression of MMP-1 in human pluripotent stem cells	[102]
	MPS I, III and VI	Human	Altered expression and enzyme activity of MMP-2 and MMP-9 in serum	[136]
	Neuronal lipofuscinoses	Animal	Increased expression of MMP-2, MMP-3 and MMP-9 in cerebral tissues	[140]
	Niemann-Pick A and B	Animal	Increased expression of MMP-12 in the lungs	[10]
	Fabry disease	Human	Increased circulating levels of MMP-9	[141]
	Sialidosis	Animal	Increased expression and enzyme activity of MMP-2 and MMP-9 in muscles	[89]
	Chediak-Higashi	Animal	Increased enzyme activity of collagenases and gelatinases in the oral mucosa	[142]

enlargement, cell function abnormality, and eventually death. Today it is widely accepted that this pathogenic concept is relatively simplistic and rather misleading. Since lysosomes do not represent end-organelles but rather a component of a highly complex regulatory system [49], it is nowadays recognized that LSDs result from perturbation of various cellular mechanisms. For example a block in autophagy represents an almost universal aetiopathogenetic pathway affected in many LSDs [50–55]. Other cellular pathways affected in several disorders of this group include biochemical injury due to toxic metabolites, derangements in calcium/iron homeostasis, abnormalities in endoplasmic reticulum stress responses and immune-inflammatory processes [1,56]. Since abnormal autophagy, inflammation and apoptosis represent cellular processes dependent on lysosomal storage [57] and upon each other [58,59] the molecules involved in all these distinct pathways could potentially represent BMs for LSDs. Knowing that many of the ECM components play significant roles in the above mentioned cellular processes, a search for an LSD BM among this intricate network of macromolecules could be easily justified.

In addition, in the case of LSDs with neurological involvement, the setting in the discovery of analytes specifically related to central nervous system (CNS) is even more obscure. These disorders often require more imaginative approaches and represent an area of intense investigation in BM discovery, since there are very few available analytical tools which could potentially demonstrate CNS involvement [60–62]. The composition and spatial orientation of ECM varies significantly, both quantitatively and qualitatively, from organ to organ and is carefully regulated. Concerning the CNS, the extracellular space represents a developmentally decreasing compartment with a quite unique composition, mainly based on HA and PGs [63]. Through its functions, it regulates various aspects of pre- and postsynaptic differentiation, synaptic maturation and plasticity and neuronal development, migration and patterning [64–67]. It is nowadays acknowledged that there are major changes in the expression of numerous ECM molecules in a great number of diseases. The latter mainly affect the adult brain, such as Alzheimer disease, Parkinson's disease, and multiple sclerosis [68–72]. Nevertheless, the differential expression of ECM molecules in the young brain of LSD patients would not be of great surprise, based on the fact that the pathogenic models explaining the brain pathology in both neuro-LSDs and adult CNS diseases share common features [73], with neuro-degeneration and neuroinflammation representing the hallmark for both groups of diseases [74]. Thus, all the above mentioned molecules could potentially represent surrogate BMs demonstrating CNS involvement.

Although the main cell pathology in LSDs involves the intralysosomal accumulation of various molecules, it was recently demonstrated that substrate deposition is evident in the extralysosomal milieu and the ECM, as well. Increased levels of the specific substrate of each disorder have been found in the extralysosomal and/or ECM in several LSDs, such as in MPS IIIB [75], MPS VII [76], MPS IX [77], Fabry disease [78–80] and Pompe disease [81]. Partially degraded intracellular substrate breakdown fragments could potentially be trafficked into the extracellular space in every LSD, where they could bind to other ECM components and modify diverse signaling pathways, cell–matrix and cell–cell interactions [82–83]. In accordance with that, Moro et al. have recently demonstrated that the reduced iduronate sulfatase activity in a knockdown animal model of zebrafish results in serious abnormalities in early vertebrate development [83]. The authors hypothesized that the alterations found (which characterize human Hunter disease patients as well) are the result of the interaction between secreted PGs or the extracellular portion of membrane-associated PGs with diverse morphogens which finally affect transforming growth factor β signaling [83]. Similar findings have been reported in the case of Hurler syndrome: heparin and heparan sulfate can modulate the biological activity of bone morphogenetic protein-4, which is an extracellular signaling molecule [84]. In addition, it was recently shown that the formation of cardiac aneurysms in Hunter and Maroteaux-Lamy patients results from the extracellular accumulation of mucopolysaccharides, highlighting the significant role of GAGs and PGs in the maintenance of normal cardiac structure and function [85,86]. Finally, with the use of diffusion weighted magnetic resonance imaging, Moore et al. demonstrated that Fabry disease patients exhibit an elevated CNS average diffusion constant, which is consistent with increased ECM water, probably due to increased cerebral blood flow [87]. All the above data represent the sound proof that the ECM is actually affected in various LSDs and, thus, the expression of its molecules could be significantly altered.

Despite all the encouraging results from successful treatment in some LSDs, there is still poor understanding of the biological functions of lysosomal proteins. Recent studies have demonstrated that many of these enzymes have biological functions which are related to the ECM. Bhattacharyya et al., have recently found that the silencing of arylsulfatase B and galactose-6-sulfatase, the responsible enzymatic deficiencies in Maroteaux-Lamy and Morquio syndrome respectively, up-regulates the expression of decorin and syndecan-1 [88]. Subsequently, the authors hypothesized that these enzymes play an additional role in cellular metabolism of GAGs and PGs, beyond their known association with MPS. In addition, another research group recently demonstrated that neuraminidase 1, a lysosomal enzyme whose deficiency is the basis for sialidosis, is also related to the ECM [89]. This group has shown that neuraminidase 1 is capable of influencing the behavior of ECM molecules by altering the sialic acid content of various substrates, pointing a role of this enzyme in ECM remodeling. This finding provided direct evidence for the explanation of several systemic abnormalities that characterize this LSD, such as the neuromuscular symptoms of patients, which could potentially result from alterations in the ECM, causing muscle fiber degeneration [89]. In agreement with all previous data, two other lysosomal enzymes, β-glucuronidase and β-*N*-acetylglucosaminidase, were demonstrated to be involved in a new pathway of intermediary metabolism of HA [90], enhancing the notion that the biological functions of several lysosomal proteins are connected to the ECM. Finally, a recently published work provided direct evidence that lysosomal enzymes are not only related to the extracellular space, but can be themselves components of the ECM. Fujita et al. have demonstrated that arylsulfatase A, the enzyme whose deficiency leads to the manifestation of metachromatic leukodystrophy, is capable of stimulating adhesion of human microvascular endothelial cells in vitro, of affecting the architecture of the cytoskeleton and the distribution pattern of the cell adhesion-associated proteins and, finally, of modulating cytoskeletal rearrangement [91]. These functions of arylsulfatase A represent properties attributed to an ECM molecule.

All the above data represent direct evidence of the pathogenic correlations between LSDs and ECM molecules. An alteration in the expression of these components could therefore impact LSD pathogenesis and finally be reflected in body fluids as a potential BM.

4. Differential expression of ECM molecules in LSDs

Numerous components of the ECM have been studied in various tissues in both LSD animal models and human patients. Common characteristic of all this work is the altered expression of several studied molecules. The research has been relatively productive especially in the case of MPS where the primary storage material is actually a component of the ECM. This review will focus on data regarding the expression of four different groups of extracellular space molecules. Research findings concerning the expression of

fibrous elements, PGs, HA and MMPs in the case of MPS, as well as other LSDs, will be critically discussed. The results of the main findings of various studies concerning the expression of these groups of ECM components in LSDs are summarized in Table 1.

4.1. Fibrous elements expression in LSDs

The expression of fibrous elements of the ECM in MPS has been studied in a wide range of cells and tissues. Since MPS patients exhibit signs of bone and joint involvement it is not surprising that research has focused on the articular cartilage of such patients. This tissue was histologically and biologically characterized and alterations in collagen morphology, especially concerning the diameter of collagen fibrils, were identified. This diameter was demonstrated to be increased in MPS IVA [92,93]. More recent studies have shown that the expression of fibrous elements is altered at the mRNA level, as well. Concerning MPS IVA, collagen type I expression was found significantly increased, while a decrease was evident in type II collagen [93,94]. Regarding MPS VI, the expression of collagen IIA1 and X was lower in articular chondrocytes in relation to control healthy cells, but normalization was demonstrated following the administration of combination therapy with ERT and an anti-TNF-alpha drug [95]. All those differences in the expression of collagen fibrils have been hypothesized as the possible cause of osteoarthritis which occurs at an early age in some MPS patients [92]. Moreover, alterations in collagen fibril morphology have been reported in the cornea of patients with various types of MPS. The average fibril diameter was increased in MPS I [96–99], IIIA [96], IIIB [96], IV [100] and VI [96], whereas a decrease was demonstrated in MPS VII [76]. Numerous MPS patients exhibit ocular signs and, although the mechanism which leads to the dysregulation of the shape of collagen is unknown, it was hypothesized that corneal opacity found in several types of the disease is partly a consequence of the structural abnormalities in collagen morphology. Although the research concerning collageneous elements of the ECM revealed significant alterations in chondrocytes and corneal cells, the expression of various types of collagen seemed unaltered in MPS fibroblast cultures [101]. Finally, there are few research findings concerning the expression of non-collageneous fibrous elements, such as fibronectin [102], elastin [102–104] and tenascins [102]. Those studies have also pointed to diverse modifications of ECM components in MPS.

Various changes in both the expression and morphology of diverse fibrous elements of the ECM have been described in a variety of inherited LSDs. Those alterations are suggestively reflected in the clinical signs and symptoms of each disease. In accordance with that, a significant increase in the expression of collagen type IV and fibronectin, both at a protein and mRNA level, was recently identified in cultured human podocytes in Fabry disease, following the exposure to lysoGb3 [105]. Thus, the authors hypothesized that lysoGb3 promotes glomerular injury through the release of secondary mediators, such as ECM molecules, leading eventually to the nephropathy of the disease. Another illustrative example of the connection between fibrous elements' alterations and the symptomatology of a specific disease is that of GM_1 gangliosidosis. In an effort to create an in vitro model to study cartilage maturation in this group of patients, Aulthouse and Alroy have demonstrated a decrease in collagen type II expression in deficient canine chondrocytes, as opposed to normal cells [106]. This dysregulation in matrix production could represent a possible theory for the explanation of skeletal abnormalities, not only in GM_1 gangliosidosis but in other LSDs, as well, such as in I-cell disease where a decrease in collagen fibril diameter was noticed in cultured chondrocytes [107]. In addition, it was recently demonstrated that neuraminidase-1 deficient mice have an abnormal expansion in the epimysial and perimysial spaces of their skeletal muscles [89]. This expansion was attributed to an increased synthesis of ECM molecules, which was in accordance with the significantly up-regulated mRNA levels for various types of collagens and a2-laminin [89]. In agreement with the fact that the same mice exhibited an alteration in aorta and lung elastic fiber deposition [108], this impaired ECM assembly could potentially provide a pathogenic theory for the explanation of the multisystemic nature of sialidosis. Expansion of the ECM due to an up-regulation in the expression of its various fibrous elements was also demonstrated in Krabbe's disease [109]. Kagitani-Shimono et al., have shown that activated Schwann cells from an animal model of globoid cell leukodystrophy secrete large amounts of various ECM molecules including laminin and fibronectin [109]. Aspartylglucosaminuria represents another example of LSD with alterations in the expression of collagen. An abnormal variation in the diameter of collagen fibrils, in combination with a reduction in their synthesis, was pointed to be the cause of impaired mechanical properties of the skin which characterize this group of patients [110]. These experimental data were verified in fibroblast cell cultures (of two patients with aspartylglucosaminuria), which demonstrated a reduction at the mRNA levels of collagen type I and III [111]. Finally, taking into consideration that collagens represent molecules abundant in the oral mucosa, collageneous elements of the ECM were studied in several LSDs in this tissue as well. In aspartylglucosaminuria, a variation in the diameter of collagen was prominent in gingival tissue [112]. In addition, Beige mice, which represent the analog for human Chediak-Higashi disease, were demonstrated to have a reduction in collagen biosynthesis in oral mucosa [113]. Finally, an increase in immature collagen biosynthesis was found in the gingival tissue from a female patient with Pompe disease [114]. This finding may be indicative of disturbed collagen homeostasis, although it was not possible to make a pathogenic correlation in order to explain the gingival overgrowth of the patient.

4.2. PG expression in LSDs

Since all GAGs, with the exception of HA, are attached to protein cores to form PGs, it is easily understood why this family of ECM molecules has been studied in various MPS animal models, as well as human patients. A common finding of those studies is the alterations in PG arrangement, size and expression, which are universal in almost all types of the disease and in a wide range of cells and tissues; nevertheless, no alterations were found concerning PG turnover in fibroblast cell cultures [115]. In an effort to provide an explanatory theory regarding skeletal features of the disease, PG expression was studied in the articular cartilage in MPS types characterized by bone and joint involvement. In relation to MPS IV an alteration in the arrangement and increased amount of PGs were demonstrated [92,93], with a parallel decrease of aggrecan expression both at the protein and mRNA level [93]. In contrast to the previous study using human articular cartilage, experiments in animals have shown an up-regulation in aggrecan expression in MPS IV chondrocytes in comparison to unaffected cells [94]. Concerning MPS IX, where osteoarthritis represents a characteristic feature of the disease, a loss in PGs was demonstrated in an animal model with prominent signs of skeletal involvement since the age of 3 months [77]. Knowing that PGs are ECM molecules that play a significant role in the developing brain, Ohmi et al. studied the expression of glypicans in the medial entorhinal cortex of various types of MPS mice [116]. The authors found a significant increase in the expression of glypican 1 and 5 in MPS IIIA and IIIB mice, which are two disease types characterized by profound cognitive impairment. In addition, an extralysosomal accumulation of PGs was demonstrated, probably leading to the formation of amyloid-beta peptide and Ptau. The latter provides direct evidence for the

presence of similarities between the neuropathogenic mechanisms of MPS and Alzheimer's disease [116]. Finally, numerous studies concerning PG molecules have been conducted in order to explain corneal opacification which can result from abnormal GAG accumulation and dysregulation of the fibrillar order in this tissue. A significant elongation of PG filaments in addition to their various size changed their architecture and arrangement in MPS I [97,98], IVA [100] and VII [76], in relation to the findings of a normal cornea. Increased amounts of these molecules were also found in the cornea of a 16-year-old patient with MPS VI [117] and in the interphotoreceptor matrix of MPS VII affected animals [118].

PGs have been also studied in several other LSDs where the alteration in the expression of those molecules has been proposed to be implicated in the aetiopathogenesis of the disease. Such an example is the identified decrease in heparan sulfate PG degradation of Niemann-Pick type C fibroblasts [119]. This flaw in PG metabolism leads to the accumulation of an excess of reactive nitrogen species, providing direct evidence of possible pathogenic correlations with the neuro-degeneration characterizing the disease [119]. The late-infantile type of neuronal ceroid lipofuscinoses (LINCL) represents another illustrative example of how a difference in PG expression could potentially be involved in disease development and progression. Teixeira et al. have shown that LINCL fibroblasts exhibit a 48-fold increase in the expression of versican, which is a significant molecule in ECM of the brain [120]. This increased versican expression was hypothesized to be a potential disease causing mechanism, especially concerning the CNS involvement of the disorder, due to possible defects in cell to cell interactions and intracellular organization resulting from the specific PG differential expression. In aspartyglucosaminuria an alteration in the epimerization of PGs [110], in combination with a reduction in the synthesis of biglycan and an increase in the production of decorin, were identified [111]. This differential expression of PGs was hypothesized as the possible causative mechanism for the observed alterations in the skin collagen fiber expression and arrangement [110,111]. In the same disorder, a PG-rich ECM in gingival tissue of a patient was found [112]. Finally, concerning LSDs with prominent skeletal involvement, an alteration in PG expression was found in the cartilage of mucolipidosis and I-cell disease patients [107,121], while a reduction in PG expression was characteristic in chondrocytes obtained from a GM_1 gangliosidosis canine animal model [106].

All the above mentioned alterations in the expression of various PGs could be reflected in the concentration of their circulating levels in body fluids, such as blood and cerebrospinal fluid, and, thus, these ECM components could potentially represent potential BM in diverse LSDs.

4.3. HA expression in LSDs

Concerning HA, MPS are the kind of LSD where, this highly complex in function molecule, is mainly involved. The first relevant description concerned a 14-year-old female patient with a deficiency in one hyaluronan metabolizing enzyme [122]. This patient had a surprisingly mild phenotype with periarticular soft masses and short stature as the main clinical features of the disorder. Two disease causing mutations were identified in the gene which encodes hyaluronidase 1 [123]. The patient displayed a significant increase in HA serum concentration [122]. In addition, a mouse model of MPS IX was generated, where hyaluronidase 1 was completely deficient, as well [77]. In this animal model hyaluronidase 3 was up-regulated, while, as opposed to the human patient, no alteration in the circulating levels of HA was found. A few years ago, the generation of a viable mouse model with hyaluronidase 2 deficiency [124], raised suspicion about the possible existence of additional, not yet described, MPS types in humans, resulting from a deficiency in an enzyme involved in HA metabolism. This animal model was characterized by the presence of abnormal chondroskeletal features and was demonstrated to have a 10-fold increase in circulating HA levels. Abnormal hyaluronan metabolism was additionally found in cultured skin fibroblasts from a patient suffering from MPS I [125]. These experiments, conducted almost 40 years ago, led to the conclusion that Hurler-derived fibroblasts have an increased capacity of HA de novo production. Concerning the expression of HA in body fluids, apart from MPS IX, there is, to the best of our knowledge, only one study in a patient with Sanfilippo A syndrome [126]. This patient exhibited a 5-fold increase in serum HA providing evidence for a possible use of this macromolecule as a marker of bone involvement, while also a reduction in hyaluronidase 1 activity was noted. In the same study, MPS IV patients were characterized by normal hyaluronidase 1 enzyme activity. In relation to other body tissues, the identification of GAG content of multiple dentigerous cysts in one MPS VI patient revealed an increased amount of HA, which nevertheless was not associated with the disease, since hyaluronan represents the main GAG in this type of cysts in general [127]. Finally, an increase in hyaluronan content was found in the adenoids of an MPS II patient [128].

Concerning other LSDs, experiments in fibroblasts derived from patients with mucolipidosis have shown contradictory results. Bach et al., have demonstrated a 10-fold increase in the synthesis of HA [129], while no differences have been found in hyaluronan production by Goldin et al. [130]. This inconsistency in findings was probably the result of different experimental procedures, since in the first scientific group, GAGs were determined according to their migration using cellulose acetate electrophoresis [129], while the second employed high-performance liquid chromatography analysis for the direct quantification of GAGs [130]. In relation to the circulating levels of HA, there is only one study in a patient with I-Cell disease who exhibited a 4-fold increase in serum HA levels, but a normal hyaluronidase activity [126]. In the same study a patient with GM_1 gangliosidosis showed no alteration in the activity of HA degrading enzymes, as well.

Taking into consideration that high concentrations of HA have been demonstrated in a wide range of diseases involving organs affected in LSDs [33], the need for the study of circulating hyaluronan levels is imperative in this group of disorders, as well.

4.4. MMP expression in LSDs

Many members of the MMP family have been investigated in a wide range of tissues in animal models of various MPS types, such as in MPS I [103,104], VI [131,132] and VII [104,131–134]. A common characteristic of all these studies was the alteration in the expression of the studied proteolytic enzymes, concerning MMP-1 [131], MMP-3 [133], MMP-12 [103,104], MMP-13 [131], as well as the two members of the gelatinase family, MMP-2 and MMP-9 [132,134]. Taking into consideration that MMPs are secreted as proenzymes and require proteolytic activation in order to exert their functions, the study of their enzyme activity represents a promising research field, as well. In this respect, Simonaro et al., have shown a prominent increase in the enzyme activity of MMP-2 and MMP-9 in the MPS VI and MPS VII animal models [132]. Despite the above mentioned findings, there is still scarce data regarding the expression of MMPs in human patients with MPS. Recently, Di Natale et al., studied the expression of MMP-9 in a small cohort of MPS VI patients [135]. The authors have found a decrease in the expression of MMP-9 which, however, has not reached a statistically significant level. In addition, it was shown that the expression of MMP-1 is decreased in human pluripotent stem cells which were generated from skin fibroblasts of MPS IIIB children [102]. We have recently demonstrated that gelatinase

expression is altered in the serum of various types of MPS patients [136]. MMP-2 was significantly increased concerning both the enzyme activity and circulating levels, while a decrease in gelatinolytic activity and serum expression of MMP-9 was observed. Those differences were even more pronounced in MPS III patients. Given the fact that alterations in circulating levels of gelatinases have been demonstrated in Alzheimer's disease [137,138], in combination with the finding that an over production of these enzymes is coupled with an increased permeability of the blood–brain-barrier [139], those ECM molecules could possibly represent BMs demonstrating CNS involvement. In relation to treatment responsiveness, we have additionally demonstrated alterations in circulating levels and enzyme activity of gelatinases in an MPS VI patient under ERT, classifying these molecules as possible candidates for follow-up markers [136].

Several studies for other LSDs have described alterations in MMP expression. Among those studies, a research team has found a disruption in the blood–brain-barrier in neuronal ceroid lipofuscinosis mice, due to an MMP dependent degradation of tight-junction proteins [140]. This scientific work has raised important questions in regards to other diseases of the group, characterized by CNS involvement, since an up-regulation in MMP expression could be implicated in the brain pathology of other LSDs with neurological features, as well. Most importantly, dietary supplementation with an antioxidant/anti-inflammatory polyphenol resulted in a reduction in MMP expression and an increase in tight-junction proteins, providing for the first time evidence of a possibly effective therapy for the maintenance of blood–brain-barrier integrity [140]. Dhami et al., have demonstrated an almost 10-fold increase in the expression of MMP-12 in the lungs of an acid sphingomyelinase-deficient mouse model [10]. Pulmonary involvement is a significant manifestation in human patients with Niemann-Pick disease; thus, the up-regulation of a proteolytic enzyme could potentially represent a BM correlating to lung pathology. Shah et al. made the first significant attempt to identify a BM among the members of the MMP family in an easily accessible body fluid [141]. This research team hypothesized that an abnormal ECM turnover could potentially characterize Fabry disease patients and explain the cardiac manifestations of the disorder. They have found a statistically significant increase in MMP-9 circulating levels, which correlated with the endocardial fractional shortening observed in Fabry disease patients, providing evidence of a possible use of this molecule as a BM for cardiac involvement. Concerning the enzyme activity of MMPs, it was recently demonstrated that sialidosis' mice show an increase in their gelatinase activity [89]. This was not surprising, since this animal model was at the same time shown to present an excessive synthesis of ECM molecules, which represent the substrates of MMP-2 and MMP-9 [89]. Finally, collagenase and gelatinase activity were increased in the oral mucosa of an animal model of Chediak-Higashi disease, which provided an explanatory mechanism for the inflammatory periodontal features of the disorder [142].

5. Therapeutic implications of ECM molecules in LSDs

Taking into consideration that several ECM molecules are differentially expressed in various LSDs, an important question is raised: whether the alterations in the ECM could have an effect on current treatment modalities used in LSDs. An illustrative example concerning this matter is that of globoid cell leukodystrophy or Krabbe's disease. Patients suffering from this devastating disorder are characterized by peripheral neuropathy which is resistant to hematopoietic stem cell transplantation [143]. Kagitani-Shimono et al., have recently demonstrated that the generation of ECM in the endoneurial spaces in globoid cell leukodystrophy mice could be potentially the cause of persistent peripheral nerve system dysfunction even after bone marrow transplantation [109]. Since ERT represents the treatment modality drawing great attention and offering new potential in LSD management, another important question is raised at this point: do the ECM alterations interfere with the cellular delivery of recombinant therapeutic enzymes? This question represents a matter which needs further research.

Providing proof of the possible involvement of ECM components in the aetiopathogenesis of LSDs could orientate research towards the use of those molecules as pharmaceutical targets and may pave the way to more specific treatment modalities. It is already known that HA expression is correlated with various malignant tumors, whereas HA oligomers have been used therapeutically because of their ability to inhibit tumor growth [43]. Furthermore, MMPs represent significant drug targets and various synthetic MMP inhibitors have been used in numerous pathological conditions, such as cancer, as well as other brain, cardiovascular, respiratory and inflammatory diseases [144–147]. Since LSDs are diseases affecting multiple organs, the application of such therapeutic options could be beneficial for patients suffering from this group of disorders.

Finally, apart from the possible use of the above mentioned molecules as therapeutic regimens for LSDs, the use of ECM components could potentially lead to the development of novel treatment modalities. Sarrazin et al., have recently demonstrated that the conjugation of a specific activated ester of guanidinylated neomycin to two lysosomal enzymes enhanced the binding of these complexes to heparan sulfate PGs [148]. Deficient for the specific enzymes cells took up significant amounts of the conjugated forms, resulting in the normalization of substrate accumulation and providing evidence of an efficient alternative method for enzyme delivery.

6. Conclusions

LSDs represent devastating diseases affecting multiple tissues and organs. Recent findings regarding the extracellular accumulation of diverse substrates in various disorders of the group have directed research towards ECM molecules. Several studies demonstrated significant alterations in the expression of ECM components, raising important questions in relation to the possible involvement of this intricate network of macromolecules in disease pathogenesis and providing evidence for their possible use as disease BMs; yet, a sound proof of their true value is needed before they can be used in clinical decision making. It remains to be seen whether new BMs for LSDs will arise from the rational application of novel molecular techniques or the imaginative concepts of investigators. Most importantly, scientists must always keep in mind that body tissues are made up of both cells and surrounding ECM and that in complex diseases, such as LSDs, these components should ideally be studied simultaneously.

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