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Minireview

Pathogenesis and treatment of spine disease in the mucopolysaccharidoses

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ABSTRACT

The mucopolysaccharidoses (MPS) are a family of lysosomal storage disorders characterized by deficient activity of enzymes that degrade glycosaminoglycans (GAGs). Skeletal disease is common in MPS patients, with the severity varying both within and between subtypes. Within the spectrum of skeletal disease, spinal manifestations are particularly prevalent. Developmental and degenerative abnormalities affecting the substructures of the spine can result in compression of the spinal cord and associated neural elements. Resulting neurological complications, including pain and paralysis, significantly reduce patient quality of life and life expectancy. Systemic therapies for MPS, such as hematopoietic stem cell transplantation and enzyme replacement therapy, have shown limited efficacy for improving spinal manifestations in patients and animal models. Therefore, there is a pressing need for new therapeutic approaches that specifically target this debilitating aspect of the disease.

In this review, we examine how pathological abnormalities affecting the key substructures of the spine – the discs, vertebrae, odontoid process and dura – contribute to the progression of spinal deformity and symptomatic compression of neural elements. Specifically, we review current understanding of the underlying pathophysiology of spine disease in MPS, how the tissues of the spine respond to current clinical and experimental treatments, and discuss future strategies for improving the efficacy of these treatments.

Contents

1. Introduction

The mucopolysaccharidoses are a family of lysosomal storage disorders characterized by deficient activity of enzymes that degrade glycosaminoglycans (GAGs) [1]. In healthy individuals, GAGs are trafficked to the lysosomes where they are sequentially broken down into basic sugars by an array of hydrolytic enzymes. In individuals with MPS, decreased activity of one of these enzymes due to a mutation in the associated gene results in incomplete degradation of GAGs. GAGs then accumulate within cells and tissues leading to progressive cellular dysfunction. There are 11 distinct subtypes of MPS, each characterized by deficient activity of a specific lysosomal enzyme (Table 1) [1].

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Skeletal disease manifestations have been reported for all MPS subtypes except MPS IX, the most recently identified subtype for which only a handful cases have been described. The severity of skeletal disease varies considerably both between and within subtypes, and while the biological basis of this variation is not well understood, it is likely attributable to differences in both the type and quantity of the accumulating GAG fragments. The spectrum of severity within each subtype is likely attributable to variations in the exact mutation site amongst patients, which in turn results in enzyme activity ranging from a mild deficiency to complete absence. For example, amongst patients with MPS I, one of the more prevalent subtypes, in excess of 200 distinct mutations in the α-L-iduronidase (IDUA) gene have been identified [2], while amongst patients with MPS VII, one of the least prevalent subtypes, around 50 distinct mutations in the β-glucuronidase (GUSB) gene have been described [3].

Within the spectrum of skeletal disease, spinal manifestations in MPS patients are particularly prevalent. Developmental and degenerative abnormalities affecting the substructures of the spine, including the intervertebral discs, the vertebral bones, the odontoid process and the spinal dura can result in compression of the spinal cord and neural elements. Resulting neurological complications, including pain and paralysis, significantly reduce patient quality of life and may in severe cases directly impact on patient mortality. Systemic therapies that aim to correct the metabolic defect in MPS such as hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) have shown limited efficacy for improving spinal manifestations in patients. Therefore, there is a strong need for new therapeutic approaches that specifically target the debilitating spinal aspects of MPS.

While the mucopolysaccharidoses are foremost diseases of aberrant GAG accumulation, the precise mechanisms by which accumulating GAGs contribute to cellular dysfunction remain poorly understood. Glycosaminoglycans are unbranched polysaccharide chains, distinguished in composition by repeating disaccharide units and linkage types, and are almost always found covalently attached to core proteins to form proteoglycans [4]. Intracellular GAG accumulation, not just in lysosomes but secondarily in other organelles, likely contributes to dysfunction by increasing cell stress. Extracellular GAG accumulation may contribute to pathology through multiple pathways, from disrupting the distribution and availability of growth factors that regulate cell differentiation, to initiating an inflammatory cascade through activation of the innate immune system. Elucidating the molecular etiology of tissue specific, GAG-induced cellular dysfunction during skeletal patterning, growth, homeostasis and aging in MPS is a crucial prerequisite to the development of new and effective therapies.

Naturally-occurring animal models including cats, dogs, mice, rats and other species have been identified for all MPS subtypes except MPS IV, for which only knockout mouse models exist [5]. These animal models in many instances closely recapitulate the skeletal disease present in human MPS patients, and are invaluable platforms for studying disease pathogenesis and evaluating therapeutics.

In this review, we examine how developmental and degenerative changes affecting the key substructures of the spine – the intervertebral discs, vertebrae, odontoid process and spinal dura – contribute to the progression of spinal deformity and symptomatic compression of neural elements. Specifically, we review current understanding of the underlying pathophysiology of spine disease in MPS, how the tissues of the spine respond to current clinical and experimental treatments, and discuss strategies for improving the efficacy of these treatments in the future.

Table 1
Mucopolysaccharidosis subtypes. HS, DS, CS and KS are heparan, dermatan, chondroitin and keratan sulfates, respectively.

Subtype	Enzyme deficiency	Accumulating GAGs
MPS I Hurler, Scheie, Hurler/Scheie syndromes	α-L-iduronidase (IDUA)	HS and DS
MPS II Hunter syndrome	Iduronate sulfatase (IDS)	HS and DS
MPS III (A–D) Sanfilippo syndrome	A: Heparan *N*-sulfatase (SGSH) B: *N*-acetylglucosaminidase (NAGLU) C: heparan-α-glucosaminide *N*-acetyltransferase (HGSNAT) D: *N*-acetylglucosamine 6-sulfatase (GNS)	HS
MPS IV (A and B) Morquio syndrome	A: *N*-acetylgalactosamine 6-sulfatase (GALNS) B: β-galactosidase (GLB1)	A: CS and KS B: KS
MPS VI Marateaux-Lamy syndrome	*N*-acetylgalactosamine 4-sulfatase (ARSB)	DS
MPS VII Sly syndrome	β-glucuronidase (GUSB)	HS, DS and CS
MPS IX Natowicz syndrome	Hyaluronidase (HYAL1)	Hyaluronic acid

2. Pathophysiology of spine disease in MPS

2.1. Overview

The underlying causes of progressive deformity and spinal cord compression in MPS patients are multifactorial, and can be attributed to a combination of accelerated degeneration of the intervertebral discs, dysplasia of the vertebral bones, hypoplasia of the odontoid process and thickening of the spinal dura. While it is generally accepted that GAG accumulation contributes directly to these disease manifestations, the specific underlying molecular mechanisms linking GAG accumulation to spine disease pathophysiology across each of the MPS subtypes are not well understood. While all subtypes are characterized by a deficiency in the activity of a single enzyme in the GAG degradation pathway that results in aberrant accumulation of incompletely digested GAG fragments [1], there is a wide range of spinal disease severity and varying rates of disease progression between subtypes [6–8]. As GAGs perform crucial regulatory roles in many physiological processes including homeostasis, growth factor signaling, cell migration, differentiation, and cellular development [4], it is likely that disease pathophysiology is more complex than can be attributed to physical stress from lysosomal overload. Potential variables underlying the disparities of incidence and severity of disease include types, localization, size, sulfation levels, amount, and rate of accumulation of the incompletely digested polysaccharide chains that build up in each MPS subtype. As outlined (Table 1), each subtype has a specific deficiency in the GAG degradation pathway that results in aberrant accumulation of one or more incompletely degraded types of GAGs. Even between different subtypes for which the same types of GAGs accumulate, there are intrinsic differences in the structure of the accumulating fragments due to the fact that the different enzymes that are deficient affect disparate parts of the degradation pathway. For example, enzymes such as α-L-iduronidase (IDUA) and β-glucuronidase (GUSB), deficient in MPS I and VII respectively [9,10], hydrolyze bonds between saccharide rings, whereas enzymes such as iduronate sulfatase and heparan *N*-sulfatase, deficient in MPS II and IIIA respectively [11,12], remove specific sulfate groups from GAGs.

The types of GAG fragments that accumulate in the different MPS subtypes likely play a role in disease severity. For example, MPS III accumulates heparan sulfate (HS) and presents with mild skeletal disease [13], whereas MPS VII accumulates heparan (HS), dermatan (DS), and chondroitin sulfates (CS) and presents with severe skeletal disease [6,14,15]. MPS I and II both accumulate HS and DS and present with skeletal manifestations that are generally milder than MPS VII but more severe than MPS III [16,17]. MPS IV has two subtypes, IVA, which accumulates both keratan sulfate (KS) and CS, and IVB, which only accumulates KS [18,19], and MPS IVB patients tend to present with a milder skeletal phenotype than those with MPS IVA [20–22]. MPS VI patients accumulate DS [23], and spine disease manifestations are similar to