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Animal models for mucopolysaccharidosis disorders and their clinical relevance

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Abstract

Progress in understanding how a particular genotype produces the phenotype of an inborn error of metabolism, such as a mucopolysaccharidosis, in human patients has been facilitated by the study of animals with mutations in the orthologous genes. These are not just animal models, but true orthologues of the human genetic disease, with defects involving the same evolutionarily conserved genes and the same molecular, biochemical, and anatomic lesions as in human patients. These animals are often domestic species because of the individual medical attention paid to them, particularly dogs and cats. In addition, naturally occurring mouse models have also been found in breeding colonies. Within the last several decades, advances in molecular biology have allowed the production of knockout mouse models of human genetic disease, including the lysosomal storage diseases. The ability to use both inbred strains of a small, prolific species together with larger out-bred animals found because of their disease phenotype provides a powerful combination with which to investigate pathogenesis, develop approaches to therapy, and define biomarkers to evaluate therapeutic success. This has been true for the inborn errors of metabolism and, in particular, the mucopolysaccharidoses.

Conclusion—Animal models of human genetic disease continue to play an important role in understanding the molecular and physiological consequences of lysosomal storage diseases and to provide an opportunity to evaluate the efficacy and safety of therapeutic interventions.

Keywords

Animal models; Lysosomal storage diseases; Mucopolysaccharidosis

ANIMAL MODELS OF LYSOSOMAL STORAGE DISEASES (LSDs)

The genes involved in many genetic disorders have been isolated and pathogenic mechanisms understood in terms of the underlying molecular derangements. However, to fully understand and treat genetic diseases in human patients, the use of authentic animal models is required to perform studies that for ethical and practical reasons are not possible in human patients. The advent of large colonies of mice bred for research, together with a systematic approach to look for naturally occurring models of genetic disease, has led to the

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discovery of mouse models of human genetic diseases. Gene knockout technology has been a powerful approach that has contributed in a major way to the understanding of gene function in health and disease and can be used in cases in which the gene of interest has been cloned. The mouse and other small laboratory animals will continue to be a very valuable source of disease models and have the advantage of being available in well-characterized inbred strains, which can be bred easily to produce large numbers of affected as well as unaffected control animals with the same genetic background. For initial studies of pathogenesis and therapy, these naturally occurring LSDs and knockout mouse models have proven extremely valuable.

Clinical veterinary medicine provides a vast and sophisticated screening mechanism in which animal patients are examined individually and in detail by diagnostic methods approaching in accuracy and sensitivity those used in human patients. Furthermore, the naturally occurring genetic diseases in dogs and cats exist in various genetic isolates (breeds) maintained by members of the public. Once identified, these models of human genetic disease can be established in special research colonies that are frequently associated with veterinary schools. Dog and cat breeders have been eager to cooperate in these endeavours because the scientific knowledge gained aids in understanding and controlling animal diseases as well as contributing to human health (1). Also, because large animal models are discovered through their clinical phenotype, they are more suitable than some knockout or point mutation mouse models, which may have lesions that are lethal *in utero*, or may lack the full range of clinical disease, as has been the case in mice with Tay–Sachs disease, Fabry disease, cystinosis and Gaucher disease (2–6). In addition, for some knockout models, such as those for type 2 and type 3 Gaucher disease, animals die within a few days of birth, limiting their value for therapy research (6,7). Of course, not all genetic diseases have been found in large animals, and knockout mice have been essential to fill the gaps.

Perhaps due to the often progressive nature and striking clinical signs of LSDs, domesticated animals have been a rich source of models of these diseases (Fig. 1). Some of these were recognized in veterinary medicine prior to the time when LSDs were understood at the level of the specific enzymes involved. Because of the distinctive central and peripheral nervous system lesions, the first of these diseases to be described was globoid cell leukodystrophy in Cairn and West Highland white terriers in 1963 (8). Affected dogs of these two breeds are now known to have the same mutation in galactosylceramidase (9). The mutation apparently originated in the 19th century from a common ancestor of both breeds, which diverged around the beginning of the 20th century. The first LSD in animals that was identified by its deficient enzyme (β -galactosidase) was GM1 gangliosidosis in a Siamese cat in 1971 (10). Since then, naturally occurring LSDs have been recognized in cats, cattle, dogs, guinea pigs, goats, mice, pigs, rats, sheep, quail, emus and horses (11,12) (Table 1), as well as in flamingos (48). Breeding colonies of various species have been established and exist for a large number of LSDs (13,49). Larger species, such as the dog and cat, have the advantages of a heterogeneous genetic background more similar to humans, and a size and longevity more suitable for repeated sampling from an individual and assessment of the long-term consequences of therapy over many years. These advantages, along with the accumulated

background of physiological and clinical veterinary knowledge in these species, make these large animal models extremely useful.

While much progress has been made in defining the molecular basis of genetic diseases in man, there remain large gaps in our understanding of the complex chain of events between the underlying genetic defect and the phenotypic abnormalities at various levels – from cells, tissues and organs to the whole organism. For example, while we know the genes and many of the mutations underlying the mucopolysaccharidoses (MPSs), and the clinical and pathological features of the articular cartilage lesions have been described, the pathogenesis of how the substrate storage results in the cartilage lesions is just beginning to be understood from investigations in cats and rats with MPS (50,51). For many lethal or debilitating genetic disorders in man, there are still no satisfactory means of treatment. One of the most exciting prospects for the use of animals with orthologous genetic diseases lies in testing new approaches to therapy. The monogenic inborn errors of metabolism are particularly attractive targets for the development of therapies because they constitute a significant proportion of genetic diseases, and they are usually autosomal recessive disorders involving the deficiency of a single specific protein gene product.

CLINICAL RELEVANCE TO THERAPY

The animal models of MPS have significant clinical signs and lesions in the same organ systems as human patients, including the CNS, skeleton, eye, cardiovascular system and liver. Hence, the models offer the opportunity to test systemic therapy as well as approaches limited to a single organ system such as the CNS or synovial joints. What has become clear over the last several decades is that many of the LSDs are unique and one approach to therapy will not fit them all. This is true even in subclasses such as the MPSs. Thus, having animal models for each disease is important for evaluating therapy. Testing the efficacy and safety of a therapy in both a mouse and large animal model increases the confidence that such an approach will be helpful to human patients.

The basic approach for the treatment of most LSDs, including the MPSs, relies on the phenomenon of cross correction, which permits cells to take up exogenous normal enzyme and deliver it to the lysosome, usually by a mannose 6-phosphate receptor-mediated process (52,53). Fortunately, the amount of enzyme needed in the lysosome for phenotypic correction of an individual cell is only a small percentage of normal. In general, the most difficult target tissue is the CNS, for which systemic therapy is limited by the blood–brain barrier. The three approaches to providing normal enzyme to a patient's cells are enzyme replacement therapy (ERT), bone marrow transplantation and gene therapy.

ERT

The parenteral injection of purified recombinant enzyme (ERT) has been tested in various animal models including MPS VII mice (54–58), MPS I dogs (59) and cats (60), MPS VI cats (61–65) and MPS II mice (19). While ERT is currently the standard therapy for patients with non-neuronopathic Gaucher disease and was developed without an animal model, similar therapy has been tested in animal models and is approved or under evaluation for treatment of human patients with MPS I, MPS II and MPS VI. The major limitations of ERT

remain the inability of intravenously injected enzyme to reach the CNS (and synovial joints in some diseases), the cost, an immune response in some patients and the need for frequent, life-long injections. That said, for some MPS disorders the clinical benefits are well established (66–68).

Bone marrow transplantation (BMT)

Heterologous BMT as therapy for LSDs has been performed for decades in animal models and human patients (reviewed in Refs. 69–75). This approach provides both normal bone marrow and bone marrow-derived cells that are available to release enzyme continuously for uptake by other cells. In addition, monocyte-derived cells can cross the blood–brain barrier, become microglia and secrete enzyme that is available to neurons. BMT has been performed in animals including MPS VI cats (76–80), MPS VII mice (81–83), and MPS VII dogs (84) (Fig. 2). A combination of neonatal ERT followed by BMT at 5 weeks of age in MPS VII mice had long-term positive effects (57). In humans, the central limitations of BMT include the difficulty in finding a matched donor, the mortality and morbidity of the procedure, and the variable results achieved in the CNS in some diseases. When successful, BMT has improved the quality of life of patients.

Gene therapy

The basic premise in gene therapy for LSDs is to provide some autologous cells with the relevant normal cDNA to produce and secrete normal enzyme for uptake by abnormal cells. Thus, the phenomenon of cross correction in MPSs obviates the need to transfer the normal cDNA to all cells, as a small percentage of transduced cells can be therapeutic at the organ or whole animal level by secreting enough of the normal enzyme for mannose 6-phosphate receptor-mediated uptake by other deficient cells. Although simple in concept, and a number of human trials have been reported, the cure of inherited metabolic diseases in human patients by somatic cell gene therapy has been limited (85), and not without complications, including insertional mutagenesis (86). The major difficulties in the field at this point are obtaining adequate levels of gene product in the specific cell types in which they are needed (e.g. in the CNS), maintaining expression over long periods of time *in vivo*, and regulating the levels of gene expression. The necessary research requires animal models that are true orthologues of the human disease due to a defect in the homologous gene and that have the same molecular, pathological and clinical phenotype as the human disease. A series of *in vitro* and *in vivo* experiments have been performed to evaluate gene therapy in animal models of MPS. In spite of the rarity of MPS VII (< 1 in 250 000), the mouse and dog models of MPS VII have become a paradigm for LSDs in general because of the ability to detect the normal enzyme (β -glucuronidase, encoded by the gene *GUSB*) activity directly using a histochemical technique. Many gene transfer approaches have been used in the naturally occurring MPS VII mouse (49). Some of the most striking clinical results of gene therapy involving an MPS have been those seen in a series of neonatal gene transfer studies conducted using retroviral vectors in the canine model of MPS VII, with treated dogs now over 6 years of age (87–90). Even so, although a constant serum β -glucuronidase activity that is 50–60-fold greater than normal by 1 week of age in MPS VII dogs has been achieved, the dogs are not completely cured. Importantly, this finding has established limits to what systemic enzyme therapy can achieve in MPS VII. Other MPS disorders have also been used

in gene therapy experiments with varying degrees of clinical and pathological improvement (49).

Feline and canine models are also useful for addressing gene transfer in relatively long-lived species that are more similar in size to human infants, particularly to evaluate the effect of direct injection of vectors into a relatively large CNS. Additionally, viral vector tropism in the mouse may not be the same as in other model species or humans. For example, in normal cats, human *GUSB* has been used as a reporter gene, due to the fact that it can be distinguished from feline *GUSB* by its heat stability. Recombinant adeno-associated viral (AAV) vectors of serotypes 1, 2 and 5 were injected into six areas of the brain of 8-week-old cats (91). The brains were evaluated for gene expression using *in situ* hybridization and enzyme histochemistry 10 weeks after injection. The AAV2/2 vector transduced cells in the grey matter, while the AAV2/1 vector surpassed both the AAV2/2 vector in grey matter transduction and also transduced cells of the white matter. The AAV2/5 vector did not result in detectable transduction in the cat brain (91). This last finding was in contrast with what had been reported in the mouse brain when using AAV2/5 (92), although the murine study utilized the AAV2/5 inverted terminal repeat for expression, making direct comparisons difficult. Following this experiment, kittens with β -mannosidosis were treated by direct injection into the brain, producing widespread correction of storage with clinical improvement (93).

Substrate reduction therapy (SRT)

Rather than treat LSDs by providing normal enzyme, an alternate approach involves limiting the amount of substrate that requires degradation. This therapy, SRT (94–97), uses pharmacological agents that are inhibitors of the enzymes responsible for the production of substrates. The aim of SRT is to limit the accumulation of substrate to a point that can be accommodated by any residual enzyme activity. Hence, SRT therapy would either require some residual enzyme activity be present or could be used as an adjunct to other therapies.

CONCLUSION

Finding spontaneous mouse models, as well as producing knockout mice with a disruption of the gene of interest, provides the ability to evaluate the effects of disease and therapy on a relatively large number of animals with a uniform genetic background. Domestic animals with spontaneous genetic disease can be of great importance in understanding pathogenesis and in the development of therapy. Veterinary medicine provides an increasingly high degree of medical scrutiny of animals, particularly the dog and cat, and new orthologues of human genetic diseases are being recognized with increasing frequency. These models provide an opportunity to monitor therapeutic efficacy and the possible development of untoward side effects in out-bred, long-lived animals that can be monitored as individuals using the same methods that are applicable to human patients. The ideal is to have a mouse, dog or cat model, together with an authentic primate model. Currently, this exists only for globoid cell leukodystrophy (Krabbe disease) with the twitcher mouse (98), the dog (9) and the rhesus monkey (99) which are all spontaneous models of the human disease.

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Figure 1.

Three cats with mucopolysaccharidosis (MPS) showing the typical features of this class of disease including small ears, wide-spaced eyes, thick eyelid margins, tear staining due to occluded naso-lacrimal ducts, flattened face with protuberant tongue and corneal clouding. (A) MPS I (β -L-iduronidase deficiency). (B) MPS VI (4-sulphatase deficiency). (C) MPS VII (β -glucuronidase deficiency).

Figure 2.

Two dogs with MPS VII. The dog standing on the left was treated with heterologous bone marrow transplant at 6 weeks of age and was able to stand and walk for 6 years. The dog on the right is typical of those with the disease and was unable to stand by 6 months of age. Similar results were obtained treating affected dogs at 3 days of age with intravenous gene therapy with a retroviral vector containing the human α 1-antitrypsin promoter, canine β -glucuronidase cDNA and woodchuck hepatitis post-transcriptional regulatory element.

Table 1

Animal models of mucopolysaccharidoses (MPSs)

Disease	Deficient enzyme	Species and selected references
MPS I	α -L-Iduronidase	Domestic cat [†] (14,15) Plott hound dog [†] (16) Rotweiler dog (unpublished) Boston terrier dog (unpublished) Knockout mouse (17)
MPS II	Iduronate sulphatase	Labrador retriever dog (18) Knockout mouse (19)
MPS IIIA	Heparan <i>N</i> -sulphatase	Wirehaired dachshund dog [†] (20,21) Mouse [†] (22,23) Huntaway dog [†] (24,25)
MPS IIIB	α - <i>N</i> -Acetylglucosaminidase	Emu [†] (26) Schipperke dog [†] (27) Cattle (J.J. Hopwood, personal communication 2006) Knockout mouse (28)
MPS IIID	<i>N</i> -Acetylglucosamine 6-sulphatase	Nubian goat [†] (29,30)
MPS IV	<i>N</i> -Acetylgalactosamine 6-sulphate sulphatase	Knockout mouse (31)
MPS VI	<i>N</i> -Acetylglucosamine 4-sulphatase (arylsulphatase B)	Siamese cat [†] (32–34) Domestic short-haired cat (unpublished) Miniature Pinscher dog [†] (35,36) Welsh corgi dog (unpublished) Chesapeake Bay retriever dog (unpublished) Miniature Schnauzer dog [†] (37) Rat [†] (38–40) Knockout mouse (41)
MPS VII	β -Glucuronidase	German shepherd dog [†] (42,43) GUS mouse [†] (44,45) Cat [†] (46,47)

[†]The mutation is known. (Adapted from Ref. 13 with permission.)