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Review

Current strategies for the treatment of inborn errors of metabolism

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ABSTRACT

Inborn errors of metabolism (IEMs) are a large group of inherited disorders characterized by disruption of metabolic pathways due to deficient enzymes, cofactors, or transporters. The rapid advances in the understanding of the molecular pathophysiology of many IEMs, have led to significant progress in the development of many new treatments. The institution and continued expansion of newborn screening provide the opportunity for early treatment, leading to reduced morbidity and mortality. This review provides an overview of the diverse therapeutic approaches and recent advances in the treatment of IEMs that focus on the basic principles of reducing substrate accumulation, replacing or enhancing absent or reduced enzyme or cofactor, and supplementing product deficiency. In addition, the challenges and obstacles of current treatment modalities and future treatment perspectives are reviewed and discussed.

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1. Introduction

Inborn errors of metabolism (IEMs) are a large group of inherited disorders characterized by disruption of metabolic pathways due to defects in enzymes, cofactors, or transporters (Lanpher et al., 2006). The defect invariably leads to the toxic accumulation of substrate and a deficiency of product. From a logical, if not over-simplistic view, this imbalance of substrate and product is the principle pathophysiologic mechanism as well as the framework for rational treatment design.

This review will focus on several modalities that essentially seek to restore the imbalance between substrate and product. Fig. 1 represents the biochemical logic behind various treatment strategies and serves as a simple "bird's eye view" of the treatment rationale for IEMs. We will discuss three ways to reduce substrate and its alternative metabolite accumulation: 1) dietary restriction, the traditional approach; 2) substrate reduction therapy (SRT); 3) toxin removal. Often substrate reduction necessitates the supplementation of product for normal cellular function. Since the enzyme, cofactor or transporter is missing or reduced, attempts to restore these proteins or factors make good biochemical sense. Enzyme replacement therapy (ERT), cell/organ transplantation, cofactor supplementation and chaperone therapy have all been used to replace or enhance enzyme activity. Gene therapy, more of a cure rather than treatment, would provide an unlimited supply of the missing protein, and exciting advances in this area have been made after some initial disappointing clinical trials.

Each of these modalities is discussed with emphasis on the more "common" IEMs. This review is not meant to be exhaustive, but a comprehensive overview of the principles and practice of the treatment of IEMs. To facilitate understanding and give the reader a concise reference, Table 1 provides an excellent overview.

2. Dietary therapy

Dietary therapy is the mainstay of treatment for many IEMs, especially small molecule metabolic diseases, such as amino-acidopathies, organic acidurias and urea cycle disorders (UCDs), carbohydrate metabolism defects, such as galactosemia and hereditary fructose intolerance, and energy metabolism defects, such as glycogen storage diseases and fatty acids oxidation defects. The main approaches of dietary therapy in IEMs include restricting the offending substrates or metabolites and providing deficient products or alternative energy sources to bypass the defective pathway. The ultimate goal is to maintain normal growth and development.

Phenylketonuria (PKU) is the classic example. PKU is caused by

Abbreviations: BBB, blood-brain barrier; ERT, enzyme replacement therapy; IEMs, inborn errors of metabolism; LC-FAODs, long chain fatty acid oxidation disorders; LSD, lysosomal storage disease; LT, liver transplantation; PC, pharmacological chaperone; PKU, phenylketonuria; SRT, substrate reduction therapy; UCD, urea cycle disorder.

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phenylalanine hydroxylase (PAH) deficiency. PAH converts its substrate phenylalanine to its product tyrosine. The deficiency of PAH results in the buildup of phenylalanine to a neurotoxic level and a decreased tyrosine production, which makes it a conditional essential amino acid in patients with PKU. Traditional therapy for PKU involves dietary management with protein restriction. The goal is to limit the accumulation of toxic amounts of phenylalanine, an essential amino acid. Often a combination of natural protein and phenylalanine-free, tyrosine-rich formulas is needed to provide adequate amounts of tyrosine for growth and neurotransmitter synthesis with just enough phenylalanine for anabolism.

Although traditional dietary therapy remains successful in treating PKU and other many IEMs, major challenges still exist. Dietary compliance is a major problem for many reasons. Many formulas are not particularly palatable, and while unpalatability is often not so much an issue during the first year of life, during the toddler and school-age years, taste becomes an important determinant of compliance. Family demands and diet schedule also affect compliance (Boyer et al., 2015). Careful oversight by a metabolic dietitian is imperative to prevent potential associated nutritional deficiencies that can lead to suboptimal outcomes in cognitive function. On one hand, new tools have been developed to improve self-monitoring and adherence (Ho et al., 2016); on the other hand, newer dietary therapies targeted at disease-specific pathogenesis have been developed to improve outcomes in recent years.

2.1. Large neutral amino acids and glycomacropeptides for PKU

Two new strategies for the dietary treatment of PKU are now available: large neutral amino acids (LNAAs) and glycomacropeptides (GMPs). The use of LNAAs (usually is a mix of tyrosine, tryptophan, methionine, valine, isoleucine, leucine, histidine, and threonine) is based on competitive inhibition of intestinal and blood-brain barrier (BBB) amino acid transporter (Fig. 2). Phenylalanine and LNAAs are proposed to share the same transporter in the intestine and BBB (Pietz et al., 1999). The addition of LNAAs into the diet decreases the flux of phenylalanine into the bloodstream and brain; therefore, substrate accumulation is reduced and essential amino acids and neurotransmitter concentrations in the brain are increased (van Spronsen et al., 2010; Ho and Christodoulou, 2014). Since the long-term safety and efficacy of LNAA therapy are unknown, and routine monitoring of CSF (cerebrospinal fluid) amino acids is impractical, LNAA treatment is currently an alternative treatment for adult patients who are unable to achieve metabolic control with a traditional phenylalanine restricted diet or other adjunctive therapy. LNAAs are not recommended for young children or pregnant women (Rocha and Martel, 2009; Singh et al., 2016).

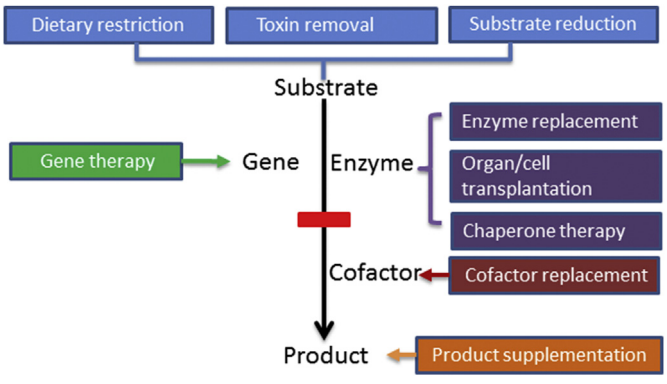

Fig. 1. Therapeutic approaches for inborn errors of metabolism (IEMs). The basic principle of IEMs is illustrated. A genetic defect in enzyme or cofactor production (red box is the metabolic block) leads to the toxic accumulation of a substrate, and a decrease in production of product. The rationale of treatment of IEMs is based on efforts to restore the normal substrate/product balance of a specific metabolic reaction. All the different strategies discussed in this review are depicted in boxes. Blue boxes are strategies that target substrate accumulation. Purple boxes are ways to restore or augment enzyme expression. The restoration of enzyme expression or a cofactor (an enzyme helper molecule), serves to facilitate the conversion of substrate to product. Gene therapy is a potentially curative method to restore enzyme production. For some IEMs, product supplementation is important.

GMPs are a naturally occurring phenylalanine-free protein source derived from whey. When isolated, GMP contains other proteins and thus includes small amounts of phenylalanine. Given the low-phenylalanine content of GMP, it is useful as an ingredient in the manufacture of low-phenylalanine foods for PKU patients. A small study of GMP use in patients with PKU identified no adverse events and demonstrated short-term efficacy in maintaining therapeutic serum phenylalanine levels compared to the use of traditional phenylalanine-free medical formulas (van Calcar et al., 2009). Further, long-term studies of the use of GMP in patients with PKU are necessary.

2.2. Low-lysine, high-arginine diet for glutaric aciduria type I

Glutaric aciduria type I (GA-I) is caused by a defect in the degradation pathway for lysine, tryptophan, and hydroxylysine. The mainstay of treatment is a low-lysine and low-tryptophan diet, carnitine supplementation to effect toxic glutaric acid removal, and the avoidance of a catabolic state by the provision IV glucose and lipids during intercurrent illnesses. The cationic amino acid transporter (CAT1, y^+ system) moves lysine and arginine across the BBB in the central nervous system (CNS) (O'Kane et al., 2006). Based on a competitive inhibition model as already noted for LNAAs for the treatment of PKU, it was hypothesized that a high-arginine diet would compete with lysine for uptake via CAT1 in the BBB, reducing lysine influx into the brain. Based on an early clinical study, the use of a standard, lysine-free, arginine-fortified formula in addition to natural protein restriction and carnitine was associated with a reduction of neurological risk of brain injury and better outcome than protein restriction and carnitine alone (Strauss et al., 2011). However, due to the insufficient evidence of neuroprotective effect of extra high-dose arginine supplementation in GA-1 patients (Kolker et al., 2012), the revised GA-I practice guideline does not recommend the use of extra high-dose oral arginine supplementation in addition to the standard lysine-free, tryptophan-reduced, arginine-containing formula in patients with GA-I (Boy et al., 2017).

2.3. Triple diet therapy for pyridoxine-dependent epilepsy

Based on the concept of competitive inhibition of cerebral amino acid flux, a triple diet therapy, including low-lysine, high-arginine and supplemental pyridoxine, has been used in the treatment of pyridoxine-dependent epilepsy (PDE). PDE is a primary seizure disorder caused by mutations in *ALDH7A1* gene resulting in deficiency of α-aminoadipic semialdehyde dehydrogenase in the catabolic pathway of lysine. PDE typically causes intractable epilepsy controlled by pharmacological doses of pyridoxine. Despite seizure control with pyridoxine, intellectual disability still occurs in some PDE patients, which is likely due to the accumulation in the brain of toxic intermediates in the lysine catabolic pathway. Several clinical studies reported that triple therapy in PDE patients decreased the accumulation of PDE biomarkers and reduced the cognitive impairment as well as improved the neurodevelopmental outcome (Coughlin et al., 2015; van Karnebeek and Jaggumantri, 2015; Yuzyuk et al., 2016; Al Teneiji et al., 2017). However, the observed benefits of triple therapy may

Table 1
Summary of diverse treatments of inborn errors of metabolism.

Treatment Strategy	Advantage	Disadvantage	Disease discussed
Dietary therapy	Directly restrict the offending substrate(s); Modify to supplement deficient product; Usually very effective; Disease specific newer medical foods available	Compliance (high demands); Unpalatability; Medical food unavailability; Insurance coverage; Require close monitoring for nutritional deficiencies	Aminoacidopathies (e.g., PKU[a]); Organic Acidemias (e.g., GA-I[a]); Carbohydrate diseases (GSDs[a], Galactosemia); LC-FAODs[a]
Toxin removal	Effective in both acute and chronic setting	Intravenous infusion (IV) required for acute intoxication; Expensive	UCDs[a]
Substrate reduction	Small molecule; Oral administration; Non-immunogenic; Usually cross BBB	Long-term consequences are unknown; Applicable to limited diseases	Tyrosinemia type1; Gaucher disease ; Niemann-Pick C
Enzyme therapy	ERT – direct delivery of deficient enzyme; New modality – enzyme substitution therapy for PKU	Weekly/biweekly IV infusion; Tremendous burden of time; Costly, $50,000–$200,000/year; Usually does not cross BBB; Immunogenic	Gaucher disease; Fabry disease; Pompe disease; Mucopolysaccharidosis type I, II, IV-A and VI; LALD[a]
Cell/organ transplantation	Permanent supply of deficient enzyme, occasional cure; Domino or carrier transplantation in certain condition is life-saving with donor shortage	Narrow treatment widow; Cannot restore irreversible damage; May not fully treat CNS disease; Surgical complications; Graft-versus-host disease; Immune suppression	MLD[a]; X-ALD[a]; Mucopolysaccharidoses; Krabbe disease; UCDs; MSUD[a]; MMA[a] and PA[a]
Chaperone therapy	Oral administration; Broad bioavailability; Crosses BBB; Non-immunogenic; Enhancement of endogenous enzyme activity; Acceptable safety profiles	Not all patients suitable depending on mutation	Fabry disease; Gaucher disease
Cofactor replacement	Enhancement of endogenous enzyme activity; Most oral administration	Some require intramuscular injection	PKU; Biotinidase deficiency; Cobalamin disorders
Product supplementation	Dietary supplement only	Compliance	PKU and UCDs; Biotindase deficiency
Gene therapy	A cure rather than treatment; Ideal personalized therapy	BBB represents a challenge; Immune response; Cellular toxicity; Potential oncogenesis; Technological limitations; Ethical issues	MLD; X-ALD; LI-CLN2

[a] PKU: phenylketonuria; GA-I: glutaric aciduria; GSDs: glycogen storage diseases; LC-FAODs: long chain fatty acid oxidation disorders; UCDs: urea cycle disorders; LALD: lysosomal acid lipase deficiency; MLD: metachromatic leukodystrophy; X-ALD: X-linked adrenal leukodystrophy; LI-CLN2: late infantile neuronal ceroid lipofuscinosis; MSUD: maple syrup urine disease; PA: propionic aciduria; MMA: methylmalonic aciduria.

be confounded by the earlier diagnosis in this cohort of patients. The long-term safety and effectiveness of this burdensome dietary therapy require further study.

2.4. Triheptanoin

Triheptanoin is a medium odd chain (C7) triglyceride. Fatty acid oxidation of triheptanoin removes two carbon units per cycle to C5 and then to C3 or propionyl-CoA. Subsequent carboxylation converts propionyl-CoA to succinyl-CoA, which can enter or refill (anaplerosis) the TCA cycle resulting in net glucose production. Long-chain fatty acid oxidation disorders (LC-FAODs) can lead to life-threatening energy deficiency during times of fasting and physiologic stress. Triheptanoin, given its anaplerotic potential, may be a novel energy source for the treatment of LC-FAODs. A study of 52 patients with LC-FAODs treated with triheptanoin and carnitine supplementation over 4 months to 7 years demonstrated a reduction of the average frequency of serious clinical complications and mortality compared to previous studies with conventional diet therapy (low-fat high-carbohydrate and/or rich medium chain triglyceride oil) (Roe and Brunengraber, 2015). Subsequently, one retrospective study from compassionate use of triheptanoin showed that it significantly decreased the frequency of hospitalization, hypoglycemia events and hospital stay in LC-FAODs (Vockley et al., 2015), and another study demonstrated improved cardiac ejection fraction (EF) in the management of acute cardiomyopathy associated with LC-FAODs (Vockley et al., 2016). Recently, a single-arm, open-label phase 2 study of triheptanoin use in severe LC-FAODs showed increased exercise endurance and tolerance. However, it is difficult to draw a definitive conclusion due to the clinical heterogeneity of LC-FAODs and the lack of a randomized control group in these studies. Importantly, triheptanoin has significant side effects. 62% patients had treatment-related adverse events, predominantly mild-to-moderate gastrointestinal distress (55%). Tolerance of triheptanoin increased by a gradual dose reduction (Vockley et al., 2017). Further studies are needed to investigate the clinical meaningful advantages of triheptanoin compared to standard medium chain triglyceride oil treatment.

3. Toxic metabolites removal

Urea cycle disorders (UCDs) affect the cell's endogenous

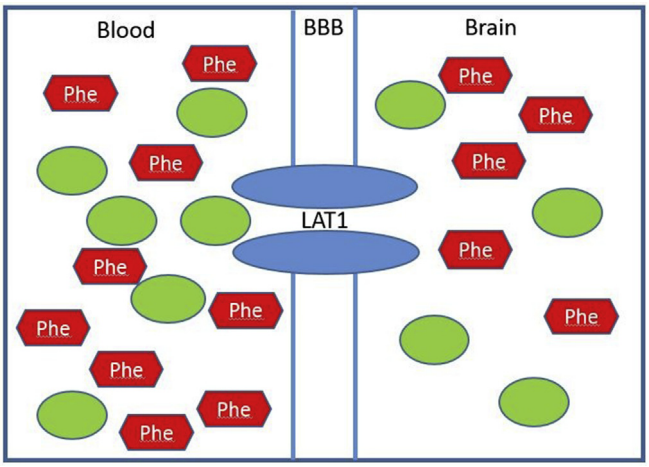

Fig. 2. Competitive inhibition effect of large neutral amino acids (LNAAs) on phenylalanine transport into the brain. LNAAs (green ovals) compete with phenylalanine (Phe) for the same large amino acid transporter (LAT1) to pass across blood brain barrier (BBB).

ammonia detoxification pathway that converts ammonia into urea. UCDs cause the accumulation of ammonia in the blood and brain of affected patients. Ammonia is neurotoxic. Hyperammonemia can lead to potentially life-threatening encephalopathy without appropriate and prompt treatment. Dietary restriction of protein intake (limiting the substrate, ammonia) is the cornerstone of long-term UCD management in conjunction with ammonia scavenging drugs. The major scavenging drugs during an acute hyperammonemic crises is intravenous ammonul, a mixture of sodium benzoate and sodium phenylacetate. Sodium benzoate complexes with glycine to form the non-reabsorbable hippurate. Sodium phenylacetate complexes with glutamine to form phenylacetylglutamine. Therefore, per equivalent of sodium benzoate and sodium phenylacetate, three equivalents of nitrogen can be eliminated. Oral sodium phenylbutyrate, which is metabolized to phenylacetate, has been the only ammonia-scavenging drug for the chronic management of UCDs for many years. Dosing, unpalatability, and gastrointestinal side effects make the use of this drug challenging for families, patients, and caregivers. A newer drug, glycerol phenylbutyrate (GPB), is a recent development for patients with UCDs (Matoori and Leroux, 2015).

3.1. Glycerol phenylbutyrate

GPB consists of three molecules of phenylbutyrate linked to a glycerol backbone. Pancreatic lipases hydrolyze GPB in the small intestine to release phenylbutyrate, and then to phenylacetate. Phenylacetate is released more slowly than sodium phenylbutyrate, resulting in more favorable pharmacokinetics and superior overnight ammonia control (McGuire et al., 2010). In addition, this preparation is sodium free, odorless, tasteless, available as an oral liquid, and consequently well tolerated by patients. In clinical trials, GPB provides effective ammonia control and improves executive functioning in adult and pediatric UCD patients (Lichter-Konecki et al., 2011; Diaz et al., 2013; Smith et al., 2013; Berry et al., 2014; Laemmle et al., 2017).

3.2. Carglumic acid

The first enzyme of the urea cycle, carbamoyl phosphate synthetase 1 (CPS-1) catalyzes the condensation of ammonia and bicarbonate to form carbamoyl phosphate. CPS-1 requires an activator, N-acetylglutamate, for normal enzymatic activity. N-acetylglutamate synthetase (NAGS) is responsible for N-acetylglutamate synthesis. Patients with defects in NAGS present with hyperammonemia due to inadequate N-acetylglutamate for optimal CPS-1 activity. Carglumic acid is not an ammonia-scavenging drug *per se*, but a synthetic analog of N-acetylglutamate that reactivates CPS-1, restoring normal urea cycle function (Daniotti et al., 2011; Haberle, 2011). Based on the model in Fig. 1, carglumic acid supplements the product of the defective NAGS reaction, to enhance CPS-1 activity. Given the rarity of NAGS deficiency, trials to determine the optimal dose for therapeutic efficacy remain difficult. Carglumic acid also seems to be effective for hyperammonemia due to NAGS inhibition caused by valproic acid and organic acidurias (Kasapkara et al., 2013; Valayannopoulos et al., 2016).

4. Substrate reduction therapy

Another therapeutic modality is substrate reduction therapy (SRT). The general principle of SRT is to use a small molecule drug to decrease biosynthesis of any toxic substrates that accumulate because of primary defects in substrate degradation. SRT, therefore, targets an enzymatic pathway upstream of the inborn error. The goal of SRT is to restore balance between production and degradation of specific substrates and offers an approach to treat certain IEM.

4.1. Nitisinone: 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC)

NTBC is an excellent example of a successful substrate reduction drug that has been in use for many years to treat hereditary tyrosinemia type 1 (HT1). HT1 is caused by the deficiency of fumarylacetoacetate hydrolase (FAH), the last step of tyrosine degradation. The substrate fumarylacetoacetate (FAA) accumulates and is converted to a toxic succinylacetone (SA) (Fig. 3). SA is a biomarker for toxicity in HT1 and plays important roles in the pathogenesis of HT1. NTBC blocks parahydroxyphenylpyruvic acid dioxygenase (*p*-HPPD), a precursor in the tyrosine degradation that results in decreased production of FAA and, consequently, its conversion to SA. NTBC decreases hepatocellular damage and malignant transformation, neurologic crises, and renal dysfunction (Lindstedt et al., 1992; Masurel-Paulet et al., 2008; Larochelle et al., 2012).

4.2. Miglustat and eliglustat

Despite the success of enzyme replacement therapy (ERT) in some lysosomal storage disease (LSDs, see below), compared to ERT, SRT has its advantages: 1) using a small molecule instead of protein-based drug (modified enzyme) in ERT avoids immune-mediated reactions; 2) oral administration is more convenient than ERT which requires several hours of intravenous administration at home or at an infusion center; 3) the ability to penetrate BBB may benefit the neurologic manifestations. Two SRT drugs, miglustat and eliglustat, have been approved by FDA for the treatment of Gaucher disease (GD).

GD is caused by a deficiency of the lysosomal enzyme glucocerebrosidase, leading to the accumulation of the substrate glucosylceramide. Both miglustat and eliglustat inhibit glucosylceramide synthase, an enzyme necessary for substrate glucosylceramide synthesis. Both drugs are orally administered. Eliglustat is more specific and more potent than miglustat. Clinical trials of eliglustat treatment in patients with GD demonstrated statistically significant effects in hematological, visceral, and skeletal endpoints (Lukina et

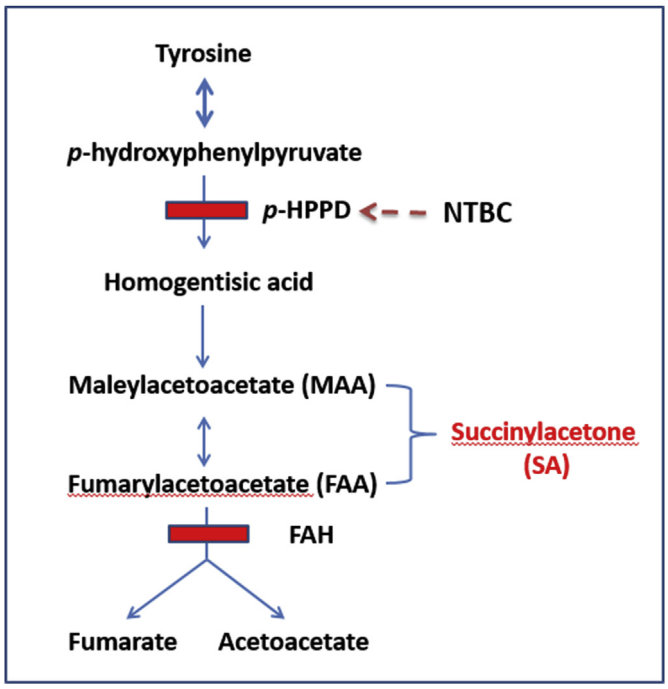

Fig. 3. The tyrosine catabolic pathway. Hereditary tyrosinemia type 1 (HT1) is caused by fumarylacetoacetate hydrolase (FAH) deficiency leading to the accumulation of FAA and MAA, which are further converted to toxic succinylacetone (SA). Nitisinone (NTBC) inhibits parahydroxyphenylpyruvate dioxygenase (*p*-HPPD), thus suppressing the synthesis of not only homogentistic acid, but also MAA and FAA and ultimately toxic SA.

al., 2010, 2014; Cox et al., 2015). Eliglustat is recommended as first-line treatment for eligible patients with GD type 1 (Balwani et al., 2016; Belmatoug et al., 2017).

Niemann-Pick C (NPC) is a primary cholesterol storage disorder resulting in the accumulation of cholesterol and glycolipid in cell. The pathogenesis is similar to the glycosphingolipidoses, like GD. SRT with miglustat has been investigated in NPC patients (Lachmann et al., 2004). The clinical studies have supported a role for miglustat in stabilizing patients with NPC (Patterson et al., 2010; Daniotti et al., 2011; Fecarotta et al., 2015) and approval was granted for the management of NPC in several countries, but not in the United States. A recent report showed treatment with miglustat in two patients with NPC did not prevent the neurological decline even when started very early before the onset of neurological symptoms. This failure raised the question about its efficacy in NPC (Di Rocco et al., 2015). Further study of safety and efficacy of SRT is warranted because it is still unclear what the long-term consequences of decreased substrate biosynthesis are and how perturbations of specific pathways may alter normal physiology and proper biologic function over time (Macauley, 2016).

5. Product supplementation

The pathogenesis of some IEM results from an insufficiency of production or a defect in recycling of something essential. Patients with PKU cannot synthesize tyrosine from phenylalanine because of PAH deficiency. Therefore, non-essential tyrosine becomes an essential amino acid. Supplemental tyrosine is recommended to avoid tyrosine deficiency if blood tyrosine concentrations are consistently below the normal range (Singh et al., 2016). The same concept applies to the administration of L-arginine or L-citrulline in acute hyperammonemia crisis and chronic management of UCDs. These amino acids reactivate the urea cycle and reduce protein catabolism secondary to low L-arginine levels (Haberle et al., 2012). Another successful example is biotin supplementation in patients with biotinidase deficiency due to a defective ability to recycle the essential vitamin biotin. If untreated, patients with profound biotinidase deficiency usually develop significant neurological symptoms and skin abnormalities, and sometimes even lead to coma or death. We now detect this condition by newborn screening. Biotin supplementation completely prevents the manifestations of the disease (Wolf, 2017).

6. Enzyme therapy

Since many IEMs are caused by enzyme deficiency, treatments targeted at supplying the missing enzyme have been investigated over several decades. Here we review two types of enzyme-focused treatment strategies in IEMs: ERT and enzyme substitution therapy. ERT is a treatment which directly replaces the deficient enzyme to improve the body's physiological metabolic processes, predominantly used in LSDs. Enzyme substitution therapy is a treatment which introduces a new enzyme to bypass the physiological defect and convert accumulated substrate to a harmless product using an alternative metabolic process.

6.1. Enzyme replacement therapy

Hurler and Hunter syndromes are lysosomal storage diseases caused by deficiencies of different enzymes: α-iduronidase and iduronate-2-sulfatase, respectively. In 1968, a seminal study demonstrated that the biochemical defect of cultured skin fibroblasts from patients with Hurler or Hunter syndrome was corrected if cells with these two different defects were mixed with each other, or with normal cells (Fratantoni et al., 1968). These experiments demonstrated that lysosomal enzymes are secreted by cells and can be taken up and targeted to the lysosomes of neighboring enzyme-deficient cells. This unique physiologic mechanism was exploited to develop several treatment strategies for LSDs including ERT, hematopoietic stem cell and bone marrow transplantation (HSCT/BMT) (Solomon and Muro, 2017).

The principle of ERT is to provide an exogenous functional enzyme that will be taken up by the patient's deficient cells and targeted to the lysosomes to reduce substrate accumulation. The successful treatment of GD with ERT experienced three decades of dedicated research (Barton et al., 1991; Ries, 2017). ERT products are administered by intravenous infusion. Currently, FDA-approved ERTs exist for GD, Fabry disease, Pompe disease, Mucopolysaccharidosis (MPS) type I, II, IV-A and VI, and lysosomal acid lipase deficiency. ERT products are in clinical trials for MPS VII (Sly syndrome), MPS-III B (Sanfillippo syndrome), Niemann-Pick disease type B, and Neuronal Ceroid Lipofuscinosis 2 (CNL2). The ERT strategy is under investigation for other IEMs, such as homocystinuria caused by loss of cystathionine B-synthase (CBS). PEGylated CBS ameliorates homocystinuria in a murine model (Bublil et al., 2016). A modified PEGylated human truncated CBS (PEG-CBS) will soon move to a phase I clinical trial (Kruger, 2017).

Although ERT offers opportunities to reduce the morbidity and mortality of many LSDs, there are several caveats to this approach. First, ERT for LSDs necessitates weekly or biweekly infusions costing from $50,000–$200,000/year. ERT is both a tremendous burden of time and cost for the patient. Second, peripherally administered enzymes do not cross the BBB and therefore cannot treat LSD associated CNS pathology. Lastly, there are often immune responses that accompany the delivery of ERT that need to be addressed (Macauley, 2016). Many refinements to ERT are in development including novel delivery approaches to bypass glycosylation-dependent targeting and uptake mechanisms to

overcome the BBB for the treatment of the neurological manifestations of some LSDs (Prince et al., 2004; Lu et al., 2010; Ries, 2017). In addition, adjunctive immune modulation therapy improves immune tolerance or reduces antibody production (Kishnani and Beckemeyer, 2014; Giugliani et al., 2017).

6.2. Enzyme substitution therapy

ERT with modified human PAH protein has been investigated for decades, but sensitivity due to plasma proteases and potential immunogenicity precludes it as an effective treatment option (Gamez et al., 2004). Enzyme substitution with a non-human phenylalanine ammonia lyase (PAL) is an alternative treatment targeted at the enzyme level. PAL is an enzyme widely found in plants, some yeast and fungi. It converts phenylalanine to ammonia and *trans*-cinnamic acid, which is further metabolized to hippurate and excreted in urine (Hoskins et al., 1984). Since PAL is not a human enzyme, potential immunogenicity still exists and needs to be overcome. The addition of polyethylene glycol polymers to recombinant PAL to modify the protein surface, so-called PEGylation (PEG-PAL), attenuates the immunogenicity and increases protein stability (Gamez et al., 2007; Ho and Christodoulou, 2014). However, while PEG-PAL reduces phenylalanine, it does not produce tyrosine like the missing enzyme PAH. Tyrosine therefore becomes an essential amino acid and supplementation is important. A phase III clinical trial of PEG-PAL is currently underway.

7. Cell or organ transplantation

7.1. Hematopoietic stem cell and bone marrow transplantation

Hematopoietic stem cell and bone marrow transplantation (HSCT/BMT) allow healthy donor cells to colonize the enzyme-deficient bone marrow of a recipient providing a constant source of enzyme replacement through the principle of cross-correction. Over the past 25 years, this approach has been attempted for patients with a wide range of different LSDs, including MPSs, metachromatic leukodystrophy (MLD), Krabbe disease, X-linked adrenoleukodystrophy (X-ALD), α-mannosidosis, fucosidosis, and progressive GD type 3. Success varies from disease to disease (Miano et al., 2001; Mynarek et al., 2012; Ito and Barrett, 2013; Chiesa et al., 2016). In some LSDs, HSCT/BMT succeeds in replenishing deficient enzymatic activity, but the timing of therapeutic intervention and severity of disease progression greatly affect its efficacy. For example, HSCT/BMT for Krabbe disease is successful only if patients are treated before the onset of symptoms or if they have a milder form of disease (Escolar et al., 2005; Duffner et al., 2009; Wasserstein et al., 2016). In other diseases, such as Hurler syndrome, HSCT/BMT successfully treats some aspects of the disease, like cardiac and pulmonary dysfunction, while others remain largely untouched, such as skeletal deformities (Aldenhoven et al., 2015). The explanation for this phenomenon is likely two-fold: first, many clinical features of LSDs are not reversible (neurodegeneration, skeletal deformities, etc.) where the damage from the disease is too severe to regain normal function even after therapy is initiated. Second, although BMT can act as a depot for lysosomal enzyme production, this does not guarantee that all organ systems have adequate access to the deficient enzymes in order to regain proper function. Most notably, this phenomenon plagues the brain where peripherally targeted enzymes do not cross the BBB in adequate concentrations to treat CNS pathology. Lastly, the effectiveness of HSCT/BMT is also hindered by the adverse effects associated with the severe conditioning regimens necessary for transplantation or the onset of graft-versus-host disease (Macauley, 2016).

7.2. Liver transplantation

Many enzymatic reactions of intermediary metabolism occur primarily in the liver, the main site of pathology in many IEMs and a principal target of therapeutic strategies. Liver transplantation (LT) can replace the missing enzyme and is often curative for some liver-based IEMs, such as most UCDs (Morioka et al., 2005). In other disorders where extrahepatic enzyme expression contributes to disease phenotypes, such as propionic aciduria (PA) and methylmalonic aciduria (MMA) (Barshes et al., 2006; Kasahara et al., 2006), LT can decrease the frequency of metabolic decompensations associated with hyperammonemia, but does not completely prevent other manifestations of disease such as metabolic stroke. Patients with PA and MMA still require ongoing supplementary dietary management even after LT. Nonetheless, some IEMs can still be cured with LT even though there is significant extrahepatic enzyme deficiency, as the transplanted liver can provide sufficient metabolic correction without additional therapy. Maple syrup urine disease (MSUD) caused by deficient branched-chain α-ketoacid dehydrogenase complex (BCKAD) provides an excellent example of this important principle. The skeletal muscle represents 50%–60% of BCKAD oxidative capacity on a whole body basis in humans and the liver accounts for 9%–13% (Suryawan et al., 1998). The unrelated donor liver, presumed non-carrier of MSUD, can replace 9%–13% of BCKAD activity and is sufficient to correct the accumulation of harmful metabolites and compensate for lack of muscle enzyme activity. Interestingly, such adequate extrahepatic enzyme activity in non-MSUD patients allows the use of MSUD livers as domino grafts in the setting of a shortage of donor livers (Badell et al., 2013; Mohan et al., 2016; Yasui et al., 2016). For autosomal recessive IEMs, obligate carriers have at least 50% reduced enzyme activity in liver compared to unrelated cadaveric livers, and therefore carriers parents are not suitable donors for their affected children, especially in IEMs with significant extrahepatic enzyme activity deficiency such as MSUD. Theoretically, obligate carrier parent liver donor would restore only 4%–7% of whole body enzyme activity in the MSUD recipient, and may be insufficient to compensate for extrahepatic deficiency and ensure good metabolic control post LT. However, in cases of donor liver shortage, obligate carriers for IEMs with low or absent extrahepatic enzyme activity deficiency can replace up to 50% enzyme activity and still be considered (Kasahara et al., 2014). In spite of the success of LT, surgical related complications and post-transplant care need to be considered. Close perioperative monitoring and well-organized multidisciplinary care are of paramount importance (Oishi et al., 2016).

8. Induction of the residual enzyme

8.1. Pharmacological chaperone therapy

Pharmacologic chaperones (PCs) are small molecules that selectively bind and stabilize misfolded enzymes to improve their function. The use of PCs in some LSDs can facilitate the proper trafficking of mutated enzyme from the endoplasmic reticulum to lysosomes, where the acidic environment leads to the dissociation of PC and allows the enzyme to metabolize the accumulated toxic substrate (Matalonga et al., 2017). PCs have a number of advantages over ERT. Firstly, oral dosing instead of intravenous infusion has an enormous impact on quality of life. Due to their small size, PCs exhibit easier diffusion and hence broad bioavailability with enhanced drug penetration into tissues (including the brain). PCs are non-immunogenic. Lastly, the enhancement of endogenous enzyme activity by PCs is more physiologic and avoids significant fluctuation of enzyme activity associated with weekly or biweekly

ERT. The safety profiles of some PCs were shown to be acceptable, even before their use for LSDs. The efficacy of PCs is predicated on the presence of some endogenous enzymes, and therefore only a select group of patients with certain amenable missense mutations will be responsive to pharmacological chaperone therapy (PCT). PCs are not suitable for all patients.

The PC migalastat has been studies in patients with Fabry disease caused by α-Galactosidase A (α-Gal A) deficiency. A validated *in vitro* assay in HEK293 cells to identify the α-Gal A mutants amenable to migalastat treatment has been performed (Benjamin et al., 2017). A randomized phase III clinical trial comparing efficacy of migalastat to ERT in Fabry patients with amenable mutations demonstrated comparable effects on renal function over the 18-month study period. In addition, migalastat significantly decreased the left ventricular mass index in affected patients compared to those who were on ERT (Hughes et al., 2017). Another study on migalastat treatment of 6-month duration in eight adult males with Fabry disease demonstrated effective GL3 clearance from renal podocytes, an important and relatively ERT-resistant glomerular cell (Mauer et al., 2017). These outcomes suggest that the broad tissue and cell distribution of the small molecule migalastat leads to better clinical outcomes. It is promising that migalastat may offer the first of its class oral alternative to ERT for Fabry patients with amenable mutations. Multiple PCs have been evaluated for the treatment of GD. The PC shows promise in treating patients with GD type 3. A pilot study showed that high-dose ambroxol improves or arrests progression of neurological symptoms such as dystonia and gait disturbances (Bendikov-Bar et al., 2013; Narita et al., 2016). The future of PCs in the treatment of LSDs is an exciting area that holds great hope for patients.

8.2. Enzyme cofactors

Enzymatic cofactors are bound to the enzyme during catalysis and are, in effect, a type of chaperone. Increasing the amount of a natural cofactor of an enzyme might help stabilize misfolded mutant enzyme, enhancing its catalytic potential and alleviating disease burden. This principle applies in treating some forms of PKU. Tetrahydrobiopterin (BH4) is the natural cofactor of PAH, the defective enzyme in most cases of PKU (Pey et al., 2004). Pharmacologic BH4 supplementation is effective in almost half of PKU patients (Muntau et al., 2014) and selectively used for BH4-responsive patients with PKU in clinical practice.

Some IEMs are directly caused by cofactor deficiency due to defects in their synthesis. In this case, replacement of the missing cofactor is the preferred treatment approach, such as hydroxycobalamin intramuscular injection in defects of cobalamin metabolism, and biotin in biotinidase and multiple carboxylase deficiencies. A comprehensive drug list, including cofactors and vitamin supplements, and their dosages in treating IEMs were reviewed (Alfadhel et al., 2013).

9. Gene therapy

While an understanding of the pathophysiology of IEMs leads to the development of various treatments with a different focus on substrate, product or enzyme, the goal of most current treatments is to ameliorate disease symptoms, not effect a cure. IEMs are single gene disorders and, in principle, the replacement of the mutated gene would provide a definitive cure. However, gene therapy has its hurdles: the BBB, the immune response, cellular toxicity, and potential oncogenesis. All these hurdles have limited its clinical application in human beings in the past.

Several inherited metabolic diseases have been the targets of gene therapy investigations. For example, gene therapy by *ex vivo* transplantation of genetically modified hematopoietic stem cells (HSCs) and AAV-mediated *in vivo* gene therapy directly delivering to the CNS have been conducted in clinical or preclinical settings (Ginocchio and Brunetti-Pierri, 2016). In a recent report, a lentiviral-based *ex vivo* gene therapy for metachromatic leukodystrophy (MLD), caused by arylsulfatase A (ARSA) deficiency, has demonstrated efficacy in the first three patients treated in the pre-symptomatic phase (Biffi et al., 2013). These patients have sustained above-normal ARSA activity in cerebrospinal fluid samples, and MLD disease progression appears arrested. This treatment is promising only for pre-symptomatic patients, not for those who already have disease symptoms. Unfortunately, most new MLD cases are from families with no prior family history of MLD, and genetic testing for MLD is not yet included in the newborn screening. Hence, most children with severe forms of MLD would not be diagnosed at the pre-symptomatic phase of the disease, making it unlikely for this therapeutic option to be currently effective for many MLD patients. However, X-ALD, another potentially devastating childhood neurodegenerative condition, was recently added to the newborn Recommended Uniform Screening Panel (RUSP). This allows identification of the pre-symptomatic at-risk patient. A single-group, open-label, phase 2–3 safety and efficacy study of Lenti-D gene therapy in 17 boys with early-stage cerebral ALD was conducted by infusing Lenti-D lentiviral vector-transduced HSCs. The interim data from median 29.4 months follow up suggest such *ex vivo* gene therapy may be a safe and effective alternative to allogeneic stem-cell transplantation in cerebral X-ALD and long-term follow up is currently undergoing (Eichler et al., 2017).

One way to bypass the BBB is to administer gene vectors directly into the CNS. The preclinical animal study of late infantile neuronal ceroid lipofuscinosis (LI-CLN2) by direct administration of AAVrh.10hCLN2 to the CNS of rats and nonhuman primates showed significant CLN2 expression in the CNS and demonstrated an acceptable safety profile (Sondhi et al., 2012). According to these promising animal study results, the clinical trial to assess safety of a gene transfer vector (rh.10) for children with LI-CLN2 (NCT01161576 and NCT01414985) and with early-onset forms of MLD (NCT01801709) is ongoing.

While gene replacement strategies are moving into a variety of phases of clinical development, the much-celebrated CRISPR/Cas9 system for gene editing is becoming the next generation of potential gene therapy for IEMs (Schneller et al., 2017). The success of the CRISPR/Cas9 mediated correction of type 1 tyrosinemia in mice is a major proof of principle (Yin et al., 2014). As CRISPR technology improves, genome editing will offer great promise to advance the future of personalized therapy for patients with IEMs, especially those in need of improved therapies. However, major technological limitations, such as off-target effects, and ethical issues, must be addressed before any clinical application.

10. Concluding remarks

The last decade has brought a greater understanding of the pathophysiology of many IEMs, leading to an astonishing array of treatments that we could not even imagine a few years ago. With advances in early detection via newborn screening or whole exome (genome) sequencing, early treatment can be offered to patients before the onset of disease manifestations for the optimal outcome. In some IEMs, like LSD, combined therapeutic approaches increase therapeutic efficacy. Further research is needed into disease pathophysiology, combination therapies, and optimal therapeutic

timing. Because of the rarity of individual IEM, multicenter clinical trials will continue to be necessary to provide evidence-based new and effective therapies in the near future.

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