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Galactosemia: The Good, the Bad, and the Unknown

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α-D-Galactose is metabolized in species ranging from *E. coli* to mammals predominantly via a series of sequential reactions collectively known as the Leloir pathway. Deficiency of any one of these enzymes in humans results in a form of the inherited metabolic disorder, galactosemia, although the symptoms and severity depend upon the enzyme impaired, and the degree of functional deficiency (Tyfield and Walter, 2002, The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw Hill.). Studies of these enzymes, and the disorders associated with their loss, have led to a much deeper appreciation of the intricate and interwoven levels of regulation that govern their normal function. These insights have further identified likely mediators of outcome severity in patients, and have enabled a rational approach to the development of novel strategies of intervention. J. Cell. Physiol. 209: 701–705, 2006. © 2006 Wiley-Liss, Inc.

The focus of this article will be a brief review of galactosemia, the potentially lethal metabolic disorder that results from impaired metabolism of galactose. Galactosemia has been the principle topic of research in my laboratory for the past 15 years. First, however, I would like to share with the reader some of the lessons I learned from Art Pardee, who was my postdoctoral mentor at the Harvard Medical School and Dana-Farber Cancer Institute from 1988 to 1991. Although my field of study has changed markedly from the cell-cycle regulated gene expression I studied in Art's lab, the lessons I learned from Art have proved universal, and so I offer them here in part as a tribute to Art, and in part also in hopes of passing them on to other young scientists who may not have enjoyed the benefit of learning them directly from Art. These are not didactic lessons taught in a classroom, or procedures demonstrated at the laboratory bench, but rather life lessons taught by example.

The first lesson is the often-quoted golden rule: '*Do unto others as you would have them do onto you*.' While many people recite this rule, few people live it as consistently and generously as Art, especially when dealing with junior colleagues, students, or trainees. The second lesson is '*Don't be afraid to take calculated risks*,' but make sure you have a safety net. In the contemporary academic setting, this lesson applies to research projects, funding sources, and even hiring practices. Finally, Art taught that '*Science is exhilarating, and it makes for a wonderful career, but your family and friends are your life*.' That means learning to juggle, multitask, and compartmentalize so as to limit research endeavors and career responsibilities that could otherwise consume all of your waking hours. Thank you, Art, for sharing these lessons, and so many more.

REGULATION AND METABOLIC DISEASE

When we speak of regulation and combinatorial control in contemporary biomedical settings, the topic of discussion is often gene expression, development, cell signaling, or cancer. Each of these fields no-doubt offers case after case of intricate molecular switches and cascades of regulation, but the same can be said for a field more commonly considered straightforward, namely that of the 'single gene' metabolic disorder. The more we learn of these disorders, the more it becomes clear that intricate cascades of regulation and combinatorial control operate here as well, overseeing the interplay of enzymes and metabolic pathways under normal conditions, and mediating pathophysiology and the severity of patient outcome under abnormal conditions. Identifying the players and inter-relationships not only teaches us about normal metabolism, it further empowers a rational approach to the development of novel and potentially more effective treatments.

GALACTOSE METABOLISM AND GALACTOSEMIA

α-D-Galactose is metabolized in species ranging from *E. coli* to mammals predominantly via a series of sequential reactions collectively known as the Leloir pathway. The three enzymes that catalyze these reactions are galactokinase (GALK, EC 2.7.1.6), which phosphorylates α-D-galactose (gal) to produce galactose 1-phosphate (gal-1P), galactose-1-phosphate uridylyltransferase (GALT, EC 2.7.7.12), which transfers UMP from UDP-glucose (UDP-glc) to gal-1P, thereby releasing glucose 1-phosphate (glc-1P) and producing UDP-galactose (UDP-gal), and finally UDP-galactose 4′-epimerase (GALE, EC 5.1.3.2), which interconverts UDP-gal and UDP-glc (Fig. 1, Holden et al., 2003). Deficiency of any one of these enzymes in humans results in a form of the inherited metabolic disorder, galactosemia (Tyfield and Walter, 2002).

The most common and clinically severe form of galactosemia is *classic galactosemia* (OMIM 230400), which affects about 1/30,000 to 60,000 live-births, and results from profound impairment of the GALT enzyme (Tyfield and Walter, 2002; Zaffanello et al., 2005). Although typically asymptomatic at birth, patients with classic galactosemia develop escalating symptoms following exposure to a milk-based diet. In the absence of intervention, these symptoms, which include vomit-

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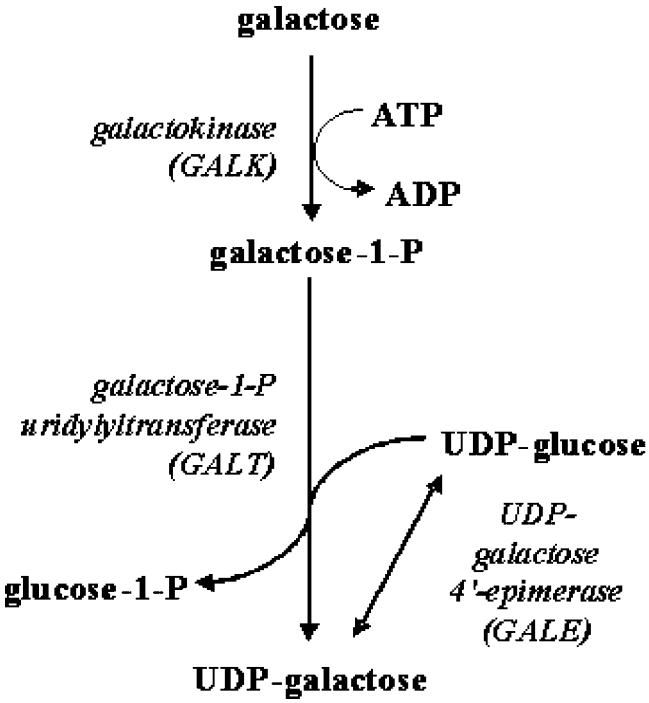

Fig. 1. The Leloir pathway of galactose metabolism.

ing, diarrhea, cataracts, hepatomegaly, and *E. coli* sepsis, can lead to neonatal death. Life-long dietary restriction of galactose, the current standard of care, relieves or prevents these acute and potentially lethal symptoms; however, many patients with classic galactosemia go on to develop serious long-term complications (Holton et al., 2000). The most common problems include speech and/or cognitive disabilities in 30–50% of all patients, and primary or premature ovarian failure in almost 85% of females (Waggoner et al., 1990; Antshel et al., 2004). Other complications include ataxic neurologic disease, delayed growth, and decreased bone density (Tyfield and Walter, 2002).

In contrast to classic galactosemia, *galactokinase deficiency* (OMIM 230200) is very rare (<1:100,000 live births) (Levy, 1980). Infants with GALK deficiency who consume a normal milk-based diet accumulate abnormally high levels of galactose in their bloods and tissues, and like patients with classic galactosemia, often present with cataracts that self-resolve upon dietary intervention. Unlike patients with classic galactosemia, however, patients with GALK deficiency who remain on galactose restricted diets experience no known long-term complications (Tyfield and Walter, 2002). This point is extremely important, because it provides compelling evidence that it is not the accumulation of galactose, but rather gal-1P, or some metabolic derivative of gal-1P, that leads to the complications, beyond cataracts, observed in treated patients with classic and/or epimerase-deficiency galactosemia. Data from yeast (Douglas and Hawthorne, 1964; Ross et al., 2004) and patient cell studies (Ross and Fridovich-Keil, unpublished) further support this conclusion, as explained below.

The third and least well-understood form of galactosemia is *epimerase (GALE) deficiency galactosemia* (OMIM 230350) (Tyfield and Walter, 2002; Openo et al., 2006). Human GALE catalyzes not only the interconversion of UDP-gal and UDP-glc, but also the interconversion of UDP-N-acetylgalactosamine (UDP-galNAc) and UDP-N-acetylglucosamine (UDP-glcNAc) (e.g., Piller et al., 1983; Schulz et al., 2004). Originally described as a 'peripheral' and clinically benign condition in which GALE deficiency is restricted to the circulating red and white blood cells (Gitzelmann, 1972; Gitzelmann and Steimann, 1973; Gitzelmann et al., 1976), GALE deficiency was later demonstrated to exist also in an extremely rare but clinically severe 'generalized' form, characterized by profound enzyme impairment in multiple tissues, with symptoms reminiscent of classic galactosemia (Holton et al., 1981; Walter et al., 1999). Most recently, through work in our laboratory and others, GALE deficiency has been defined as a continuous disorder, with a spectrum of enzyme impairment and corresponding metabolic compromise impacting a variety of tissues in affected individuals (Schulpis et al., 1993; Quimby et al., 1997; Alano et al., 1998; Shin et al., 2000; Openo et al., 2006).

ALTERNATIVE PATHWAYS OF GALACTOSE METABOLISM

Pathways of galactose metabolism that do not involve all three Leloir enzymes also exist in humans and other species; these include (i) conversion of galactose to UDP-glc by the sequential activities of GALK, UDP-glucose/galactose pyrophosphorylase (UGP), and GALE, (ii) reduction of galactose to galactitol by aldose reductase, and (iii) oxidation of galactose to galactonate, presumably by galactose dehydrogenase (Fig. 2, reviewed in Tyfield and Walter, 2002). Under normal conditions, these three alternative pathways are thought collectively to metabolize only trace quantities of galactose. In the absence of functional GALK, GALT, or GALE, however, as intracellular galactose or gal-1P levels rise, approaching or exceeding the K_m parameters of the relevant enzymes, these alternate pathways may

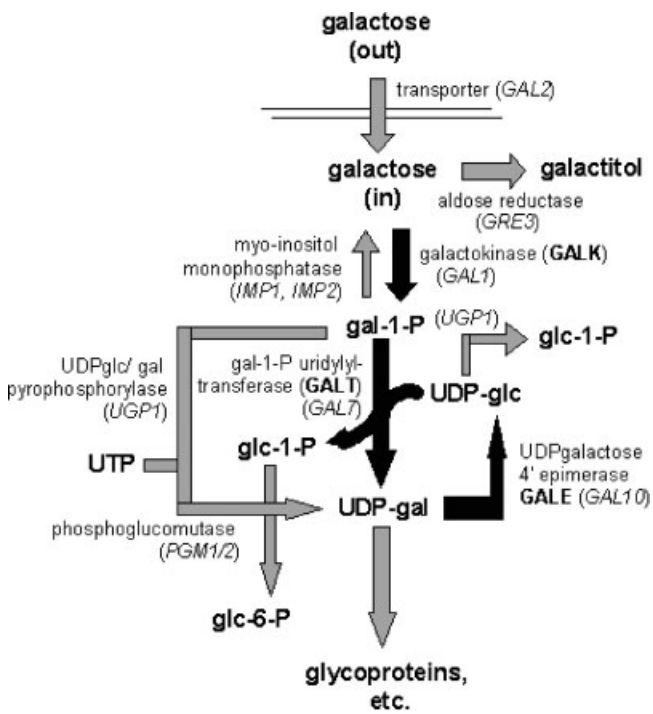

Fig. 2. Alternate pathways of galactose metabolism in humans. The three steps that constitute the Leloir pathway are shaded black in this figure.

become significant. In particular, a flux of galactose through these outlets may limit the accumulation of potentially toxic intermediates (e.g., gal-1P), thereby mitigating negative outcomes. The flow of galactose through these alternate pathways may also result in the accumulation of other end products that are themselves problematic, however, at least in some tissues (e.g., galactitol, see below). These pathways, and the genes and enzymes that comprise them, represent logical candidate modifiers of patient outcome in galactosemia. These non-Leloir enzymes also present potentially novel targets for small molecule therapeutic intervention.

BASES OF PATHOPHYSIOLOGY IN CLASSIC GALACTOSEMIA

Despite decades of study, the underlying basis of most pathophysiology in galactosemia remains unknown (Tyfield and Walter, 2002; Leslie, 2003). What is known is that both untreated and treated patients with galactosemia experience abnormal accumulation and/or depletion of specific metabolites, and that these patients further demonstrate specific abnormalities of glycosylation (Walter et al., 1999; Tyfield and Walter, 2002). Of note, one report from the literature (Charlwood et al., 1998) also demonstrated evidence of aberrant glycosylation in a subset of patients despite prolonged dietary restriction of galactose, offering the possibility that aberrant biosynthesis of glycoproteins and/or glycolipids may contribute not only to the acute, but also to some of the long-term complications experienced by galactosemic patients.

ABNORMAL ACCUMULATION OF METABOLITES

Specific metabolites known to reach abnormal levels in the hemolysates and/or tissues of untreated patients with classic galactosemia include galactose, galactose-1-phosphate (gal-1-P), galactitol, and inositol. Abnormal galactonate also forms, but is excreted in the urine and does not accumulate in tissues (reviewed in Holton et al., 2000; Tyfield and Walter, 2002). Patients with classic galactosemia may also experience a partial depletion of UDP-gal, at least in their red blood cells, although the clinical significance of this finding remains controversial (reviewed in Segal, 1995; Holton et al., 2000; Tyfield and Walter, 2002; Lai et al., 2003).

Like their GALT-impaired counterparts, untreated patients with GALE-deficiency also accumulate abnormally high levels of red blood cell galactose and gal-1P. In addition, these patients also accumulate very high levels of UDP-gal (Holton et al., 1981; Walter et al., 1999; Openo et al., 2006). Considering that gal-1P is a substrate of GALT but not GALE, the fact that it accumulates to abnormal levels in GALE-impaired cells demonstrates the interdependence of enzymes in the pathway. Presumably, gal-1P accumulates in these cells secondary to the accumulation of UDP-gal, which exerts product inhibition on GALT.

TIMING

Although significant environmental exposure to galactose does not begin until after birth, metabolic abnormality in classic galactosemia clearly begins in utero. One study reported elevated galactitol in the amniotic fluid of a galactosemic fetus at 10 weeks gestation, and the elevated levels of galactose, gal-1P, and galactitol measured in the livers of two galactosemic fetuses at 20 weeks gestation were comparable to those found in neonatal infants dying of the disorder (reviewed in Holton et al., 2000). Elevated levels of gal-1P have been detected even in the cord blood of galactosemic infants born to mothers who abstained from galactose consumption during pregnancy (Gitzelmann, 1995), perhaps reflecting the capacity for endogenous production of galactose demonstrated originally by Berry and colleagues (Berry, 1995; Berry et al., 2004).

This observation of metabolic abnormality in galactosemic infants in utero raises the strong possibility that although these patients *appear* phenotypically normal at birth, the foundation of later clinical abnormality may already be set in the form of abnormal myelination in the brain, or abnormal ovarian development, for example. This realization has profound consequences for treatment, suggesting that in order to prevent long-term complications, intervention beyond dietary restriction of galactose may be required initiated before birth.

Following dietary restriction of galactose, patients with classic galactosemia demonstrate marked normalization of their metabolic profiles, although gal-1P often remains outside the normal range (>5 mM untreated, ~0.1 mM treated, undetectable in normal) (Gitzelmann, 1995). Indeed, a number of studies have correlated the presence of elevated gal-1P in patients on dietary galactose restriction with severity of clinical outcome (Kaufman et al., 1988; Ng et al., 1991; Xu et al., 1995b), although there does not appear to be a strict quantitative correlation.

CONNECTING THE DOTS

The biochemical mechanism that logically connects the acute or long-term clinical phenotypes of galactosemic patients with observed metabolic abnormalities remains largely unknown. One exception is the role of galactitol. Long-suspected to underlie cataract formation in untreated patients (Tyfield and Walter, 2002; Leslie, 2003), galactitol was confirmed as the causal agent when a mouse model for GALK-deficiency failed to demonstrate galactose-dependent cataracts until a human gene encoding aldose reductase, the enzyme that forms galactitol from galactose, was crossed into the strain (Ai et al., 2000). Of note, GALT-knock-out mice also fail to recapitulate either the acute or long-term complications observed in human patients, even when exposed to extraordinarily high levels of dietary galactose (Leslie et al., 1996). Wild-type mice express much lower levels of endogenous aldose reductase in the lens than do humans. While that difference clearly accounts for the absence of galactose-dependent cataracts, does it also account for the absence of other symptoms in GALT-deficient mice? The answer remains unknown, but considering that even untreated GALK-impaired patients demonstrate no reported abnormalities beyond galactose-dependent cataracts, it seems unlikely that galactitol alone can account for the non-opthalmological abnormalities associated with untreated or treated classic or epimerase-deficiency galactosemia (Tyfield and Walter, 2002).

In the search for a logical connection between metabolic abnormality and the non-ophthalmologic complications observed in galactosemia, a number of intriguing hypotheses have been raised (reviewed in Tyfield and Walter, 2002; Leslie, 2003). For example, Mayes and Miller (1973) proposed that futile cycles of phosphorylation/dephosphorylation of galactose might deplete affected cells of ATP. Alternatively, Gitzelmann (1995) suggested that elevated intracellular gal-1P might inhibit a number of important enzymes, including glucose-6-phosphatase, phosphoglucomutase,

liver glycogen phosphorylase, UDP-glucose pyrophosphorylase, glucose 6 phosphate dehydrogenase, and at high concentrations, UDP-gal galactosyltransferase. Although the data remain controversial, other reports suggest that elevated gal-1P may also inhibit myo-inositol monophosphatase (Wells et al., 1969; Parthasarathy et al., 1997; Bhat, 2003), the enzyme principally responsible for the production of myo-inositol in many tissues. If true, this inhibition could explain the dramatic loss of both free and lipid-bound myo-inositol observed in brain samples from galactosemia patients (Wells et al., 1965). Most recently, Lebea and Pretorius, (2005) have proposed that depletion of UDP-gal in the cells of patients with classic galactosemia may impede the function of cerebroside galactosyl transferase, which is responsible for galactosylation of cerebrosides. Of course, these possibilities are not mutually exclusive.

Finally, while both the levels and approximate 1:3 ratio of UDP-gal and UDP-glc are very tightly controlled in normal human cells (Segal, 1995), these levels and ratio may be disturbed in both GALT and GALE-deficiency galactosemia. For example, patients with significant GALE-deficiency accumulate strikingly elevated levels of UDP-gal in response to galactose exposure (Walter et al., 1999; Openo et al., 2006). In contrast, patients with classic GALT-deficiency may experience abnormal depletion of UDP-gal and/or UDP-glc, (Xu et al., 1995a, b; Holton et al., 2000; Lai et al., 2003). The possibility that UDP-gal and/or UDP-glc levels or ratios may be abnormal in patient cells again raises the question of logical connection to pathophysiology. Considering that both UDP-gal and UDP-glc serve as important activated sugar donors for glycosyltransferases, the connection to pathophysiology may involve defects in the biosynthesis of glycoproteins and/or glycolipids in the cells and tissues of galactosemic patients (Segal, 1995; Tyfield and Walter, 2002). Indeed, such abnormalities have been found.

ABNORMAL BIOSYNTHESIS OF GLYCOPROTEINS AND GLYCOLIPIDS IN GALACTOSEMIA

Glycosylation, or the addition of specific carbohydrate chains to target macromolecules, is a post-translational modification that mediates the form and function of many proteins and lipids in humans and other species (Freeze and Aebi, 2005). A literature trail extending back 35 years demonstrates clear evidence of abnormal glycosylation in classic galactosemia. In the early 1970s, Haberland and colleagues (Haberland et al., 1971; Witting et al., 1972) demonstrated an abnormal pattern of glycoproteins in the postmortem brain of a galactosemic patient. Twenty years later, four additional reports appeared: one described a deficiency of glycolipids containing galactose or N-acetylgalactosamine, and accumulation of the precursors of these compounds in the postmortem brain of a neonate with galactosemia (Petry et al., 1991), one described abnormalities in the glycosylated serum lysosomal enzymes from patients with galactosemia (Jaeken et al., 1992), and two reported defective galactosylation of complex carbohydrates and glycoproteins in fibroblasts derived from patients with galactosemia (reviewed in Segal, 1995).

More recently, three reports by different groups have both corroborated and extended from these earlier studies. For example, Stibler et al. (1997) demonstrated the presence of carbohydrate-deficient isoforms of serum transferrin in the bloods of patients with classic galactosemia. In particular, these authors found abnormal asialo- and/or disialotransferrin in samples derived from untreated patients; these carbohydrate-deficient isoforms were rarely observed in samples from patients on dietary restriction of galactose. Charlwood et al. (1998) both corroborated those results, and extended from them applying HPLC analysis of transferrin-derived N-linked glycans to explore in greater detail the structural basis of the glycosylation defects in patients. These authors found that the transferrin glycans from untreated patients were more heterogeneous than were their normal counterparts; they contained four major truncated glycans in addition to a smaller amount of the disialylated biantennary complex type (Charlwood et al., 1998). These authors concluded that the truncated glycans were deficient in sialic acid and galactose, and that their structures suggested inadequate galactosyltransferase activity in the biosynthetic tissue, assumed to be liver. Of note, while the serum transferrin glycans largely normalized in patients on dietary restriction of galactose, they did not become completely normal in all patients, even after prolonged treatment. More recent studies of serum transferrin from untreated patients with classic galactosemia (Sturiale et al., 2005) again corroborate the earlier conclusions, but also extend from those conclusions to demonstrate that the glycosylation defects fall into two distinct categories, representing defects of both N-glycan assembly and processing.

CLINICAL RELEVANCE

Two reports within the past decade have suggested a potential mechanism directly linking abnormal glycosylation with the primary or premature ovarian failure seen in treated patients with classic galactosemia. The first, by Prestoz et al. (1997), demonstrated the presence of qualitatively altered FSH isoforms in the sera of three women with profound GALT deficiency. In particular, the abnormal FSH in these women migrated through isoelectric focusing gels to positions representing near-neutral pH (pI 6.4–7); normal FSH has a pI between 4 and 5, in large part due to the acidic nature of the carbohydrate modifications. The elevated pI of the abnormal isoforms suggests they may have lacked at least a subset of their normal glycan chains (e.g., errors of glycan addition). Additional data suggested that the abnormal isoforms of FSH found in these samples were partially deficient in both galactose and sialic acid. Of note, these abnormal isoforms were not detected in samples from any of five healthy women studied, or from one woman with a milder variant of galactosemia associated with residual GALT activity. Finally, a case report published 2 years ago by Menezo et al. (2004) described the successful treatment of a woman with classic galactosemia who experienced menopause at age 19, and who later wished to conceive a child. At age 26, this woman, who demonstrated an endogenous FSH level of 83 U/L, was stimulated with recombinant FSH (rFSH); she conceived and delivered a healthy baby. The ability of recombinant FSH to restore ovarian function in this woman demonstrated that, at least in this case, infertility reflected functional abnormality of the endogenous FSH, rather than a complete lack of ability of the follicles to recognize and respond to normal FSH (Menezo et al., 2004).

Combined, these reports provide compelling evidence that both untreated *and treated* patients with classic galactosemia experience errors in the biosynthesis of their glycoproteins and perhaps also their glycolipids, and that these abnormalities underlie at least a subset of the pathophysiology observed. The implications of these

data, with regard not only to questions of mechanism, but to possibilities of intervention, are profound.

LOOKING AHEAD

One of the principle reasons for studying galactosemia, or any disease, is to optimize treatment. The title of this article is intended to reflect the current status of that quest. The *good* news is that with early diagnosis and simple dietary intervention, galactosemia is no longer a lethal condition. In the US and many other industrialized nations, inclusion of galactosemia in the panel of conditions tested by mandated newborn screening has all but eliminated acute presentation in those populations, and that is a tremendous step forward. The *bad* news is that despite neonatal or even prenatal diagnosis and life long dietary intervention, although the outcome for most patients is clearly normalized, it is not fully normal. The complications experienced by many patients are life-altering; surely we can do better. Finally, the *unknown* refers to the fact that despite decades of study, the underlying mechanism of pathophysiology in galactosemia remains unclear. The goal of current and future research in my laboratory and others is to define that mechanism using both patient studies and model systems, and ultimately to apply that knowledge to develop novel and more effective strategies of treatment.

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