Emerging Concepts of Epigenetics: Background, Significance, and Potential Relevance in Livestock Production[1,2]

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INTRODUCTION

Effective nutritional management during gestation has long been recognized as an important component of sound livestock production practices. Successful neonatal outcomes are essential to efficient livestock production systems, having ramifications for both individual and whole system efficiencies. Developmental programming is the concept that perturbations during critical prenatal or postnatal developmental 'windows' can have lasting impacts on growth and productivity of the offspring throughout life. Fetal intrauterine growth restriction is often associated with an adverse environment during pregnancy or infancy causing programming of organ function and reduced offspring performance, including efficiency of growth and feed utilization, and is consequently a critical issue in livestock production (Wu et al., 2006; Greenwood and Café, 2007; Caton and Hess, 2010; Reynolds et al., 2010).

Epigenetic mechanisms, primarily DNA methylation and histone modifications, have been implicated as the primary mechanism of developmental programming of offspring in utero and postnatally. Changes in gene expression resulting from epigenetics can cause pre- and postnatal alterations that affect the long-term health and performance of the offspring, including their efficiency of feed utilization (Wu et al., 2006). Additional emerging data suggests that some developmentally programmed changes in gene expression, and hence organ function, can even persist transgenerationally. Recent observations and reviews in the area of developmental programming (Godfrey and Barker, 2000; Armitage et al., 2004; Wu et al., 2006; Caton and Hess, 2010) and epigenetics (Ismail-Beigi et al., 2006; Szyf, 2009; Bonasio et al., 2010; Reynolds et al., 2010; Beldade et al., 2011; Migicovsky and Kovalchuk, 2011) have elevated these concepts to the forefront of investigation within numerous research groups and are shaping thought in both the animal agricultural and biomedical arenas.

DEVELOPMENTAL PROGRAMMING

Developmental programming is the concept that adverse events, such as poor nutrition or other types of stress, during critical developmental periods may have life-long impacts on offspring by 'programming' gene expression and hence phenotype. Developmental programming has variously been termed 'fetal programming,' 'the Barker hypothesis,' or 'developmental origins of health and disease,' and is an emerging concept underpinning research in many biomedical and animal agricultural laboratories (Hanson and Gluckman 2005; Wu et al., 2006; Greenwood and Café, 2007; Caton and Hess, 2010; Du et al., 2010; Funston et al., 2010; Reynolds et al., 2010). While not new, this concept has generated great interest among biological scientists based on a series of human epidemiological studies (Barker et al., 1989; Barker 1994; Barker 2004) as well as subsequent follow-up studies using various animal models to not only test the hypothesis, but also to determine the mechanisms responsible (Wu et al., 2006; Caton and Hess, 2010; Ligi et al., 2010; Reynolds et al., 2010).

Many data sets demonstrate a response of offspring growth to maternal factors, including maternal genotype, age, nutrition, and various other 'stressors' (e.g., environmental heat stress, high altitude, behavioral stress, multiple fetuses) in livestock species including cattle (Ferrell, 1991a,b; Ferrell and Reynolds, 1992; Freetly et al., 2000; Wu et al., 2006; Greenwood and Café, 2007; Caton and Hess 2010; Du et al., 2010; Reynolds et al., 1985, 2010). These observations are highly relevant to the current discussion because both fetal and neonatal growth restriction are associated with increased risk of immediate postnatal complications (increased morbidity and mortality) and may also exhibit poor growth and development, with significant consequences

later in life (Barker et al., 1993; Godfrey and Barker, 2000; Barker, 2004; Wu, 2006; Greenwood and Café, 2007; Caton and Hess, 2010; Du et al., 2010; Funston et al., 2010; Reynolds et al., 2010). Moreover, across all livestock species in the U.S., preweaning mortality is as high as 10%, with most occurring in the first week after parturition, indicating that the immediate postnatal period may be particularly sensitive to the negative consequences of developmental programming (Wu et al., 2006; Reynolds et al., 2010), and thus poor herd production efficiency. In cattle, the nonpredator calf death loss for the latest year on record was 5.8% of the calf crop overall (4.5% for beef operations, 7.1% for dairy operations, and 8.7% for mixed operations) across all regions in the U.S. (USDA, 2007). Of these calf death losses, 17.7% were were reported to be due to calving problems but the majority were due to either digestive problems (21.2%) or respiratory problems (31.8%).

Within livestock production systems, ruminants often undergo periods of nutritional stress during pregnancy or lactation because of limited forage quality or quantity, climate-related issues (e.g., drought or harsh winters), production demands (e.g., lactation or growth), and management practices (Wu et al., 2006; Caton and Hess 2010). From an economic standpoint, decreased growth rate and suboptimal carcass composition cost feedlot producers millions of dollars each year (Smith et al., 1995; Gardner et al., 1998). Fetal growth restriction and/or maternal undernutrition can have severe negative impacts on growth efficiency and body composition (Greenwood et al., 1998, 2000; Freetly et al., 2005; Greenwood and Café, 2007; Larson et al., 2009; Meyer et al. 2010a; Neville et al., 2010), even independent of altered birth weight (Gardner et al., 2005; Ford et al., 2007; Martin et al., 2007). Recognizing that permanent changes in postnatal metabolism may be induced by maternal nutritional perturbations presents significant challenges to livestock producers. Because nutritional management decisions are

often based on average body weight, anticipated nutrient density of dietary ingredients, and generalized nutrient requirements, the opportunity for nutrient perturbations exist under well managed production conditions.

EPIGENETICS

The term epigenetics comes from the Greek, epi (besides, upon, over) and literally means in addition to genetics (Jirtle and Skinner, 2007; Bonasio et al., 2010; Feng et al., 2010). It seems clear that the mechanisms responsible for adaptive developmental plasticity and subsequent programming of gene expression in the offspring are not due to genetic mutations but rather must involve epigenetic modifications of chromatin leading to an altered rate of transcription (Ismail-Beigi et al., 2006; Szyf, 2009; Bonasio et al., 2010; Reynolds et al., 2010; Beldade et al., 2011; Migicovsky and Kovalchuk, 2011). Broadly speaking, epigenetics involves gene silencing or activation that occurs independent of changes, or 'mutations,' in the gene's DNA sequence. In other words, epigenetic alterations are reflected by differences in gene expression that do not depend on mutations. Moreover, these epigenetic changes are heritable; that is, they can be transmitted across generations (Ismail-Beigi et al., 2006; Jirtle and Skinner, 2007; Feng et al., 2010; Reynolds et al., 2010; Beldade et al., 2011; Migicovsky and Kovalchuk, 2011). Inheritance of epigenetic status, or 'marks,' has now been well documented and has been termed 'epigenetic memory' (Migicovsky and Kovalchuk, 2011).

It has been suggested that the two primary mechanisms of epigenetic regulation of gene expression are DNA methylation and various histone modifications (Szyf, 2009; Jirtle and Skinner, 2007; Bonasio et al., 2010). DNA is methylated primarily on cytosine residues in 'CG islands' located throughout the regulatory and coding regions of genes. Hypermethylation of

DNA leads to highly condensed heterochromatin, which is unavailable to the transcriptional machinery and therefore transcriptionally silent, and conversely hypomethylated genes are represented by euchromatin, which is transcriptionally active (Szyf, 2009; Jirtle and Skinner, 2007; Bonasio et al., 2010). Histone modifications include acetylation and methylation of the 'tails' of specific histone proteins, which can lead to repression or activation of gene expression (Szyf, 2009; Jirtle and Skinner, 2007; Bonasio et al., 2010). In addition, the systems regulating DNA methylation and histone modifications exhibit cross talk, and tend to reinforce the condensation of decondensation of DNA associated decreased or increased rates of gene expression, respectively (Bonasio et al., 2010).

One of the evolutionary advantages of developmental programming is that it provides a means whereby the genome can respond to the environment in the short-term. That is, changes in gene expression in response to environmental cues, such as maternal nutritional stress during pregnancy or poor milk production or quality postnatally, enable the fetus and neonate to adapt in the short-term, rather than depending on longer-term mechanisms such as gene mutation. These adaptive responses have been termed 'adaptive developmental plasticity,' and from an evolutionary standpoint serve to minimize negative environmental impacts on the individual and thereby protect the population from catastrophic losses in population size and genetic diversity (Beldade et al., 2011). Moreover, although they can be quite stable, epigenetic marks, or status, are also reversible (Szyf, 2009; Jirtle and Skinner, 2007; Bonasio et al., 2010), which is important in terms of managing the consequences of developmental programming.

CRITICAL WINDOWS

Differing offspring responses to nutrient restriction in utero or postnatally are likely due to differing developmental windows of organ systems (Fowden et al 2006; Caton and Hess 2010). Historically, fetal nutrient uptake has been considered a quantitatively important contributor to maternal nutrient requirements only after mid-gestation (Ferrell et al., 1983) because most fetal growth in sheep and cattle occurs during the final third of gestation (Ferrell et al., 1976; Prior and Laster, 1979). However, early and mid-gestation are critical periods of placental growth and establishment of nutrient transferring potential (Fowden et al., 2006).

Birth weight is often used as a gross measure of fetal growth and development, but may not be altered by nutritional insults during gestation, depending on its timing and severity, as well as the age and species of dam. Nutrient restriction in early to mid-gestation beef heifers or cows has had no effect upon fetal or birth weight (Freetly et al., 2000; Freetly et al., 2005; Meyer et al., 2010b). Although maternal nutrient restriction during mid to late gestation (Freetly et al., 2005) or the last trimester of gestation has generally reduced birth weight in beef cattle (Corah et al., 1975; Bellows and Short, 1978; Houghton et al., 1990; Larson et al., 2009), birth weight has not always been affected by late gestational nutrition (Hough et al., 1990; Stalker et al., 2006; Martin et al., 2007). When ewes have been restricted in early to mid-gestation, fetal weight from d 78 to 90 of gestation has been reduced in some studies (Vonnahme et al., 2003; Luther et al., 2007), whereas weight near term has not (Carlson et al., 2009). In general, lamb fetal or birth weight have been reduced with mid- and late gestational nutrient restriction (Luther et al., 2005; Reed et al., 2007; Swanson et al., 2008; Meyer et al., 2010a). Species differences seem to exist, even amongst ruminants, in the sensitivity of fetal weight to nutrient restriction in mid-gestation, which may occur due to species differences in timing of placental development and vascularization (Vonnahme et al., 2007). Overall, severe nutrient restriction for at least the last

one-third to half of gestation is usually required to reduce bovine fetal growth, whereas placental characteristics may be altered by nutrition during early and mid-pregnancy without significantly affecting fetal size (Rasby et al., 1990) or birth weight (Perry et al., 1999; 2002). Additionally, parity influences the effect of nutrient restriction on fetal growth, where primiparous dams appear to be more sensitive than multiparous dams (Redmer et al., 2004; Wallace et al., 2006; Wu et al., 2006; Reynolds et al., 2010).

In addition to placental growth and development, fetal organogenesis occurs during early to mid-gestation, although specific rates and timing of growth vary with each organ system (see Trahair and Sanglid, 2002 for ruminant small intestine developmental windows and Du et al., 2010 for ruminant skeletal muscle and adipose developmental windows). Rapid growth of organ systems in mid- to late gestation precedes maturation of many systems. This maturation occurs immediately before parturition and is often glucocorticoid-dependent (Liggins, 1994). Many organs, especially the gastrointestinal tract, continue with critical development postnatally, giving further possibility for programming by postnatal nutrient intake. Overall, these differential rates of tissue growth, development, and differentiation dictate that multiple 'critical windows' for developmental programming exist. Thus both large reductions in growth caused by late gestational nutrition and more subtle effects on tissue and organ development due to early gestational nutrition may occur. Although some gestational supplements or therapies such as supranutritional Se may improve fetal growth during maternal nutrient restriction (Reed et al., 2007; Meyer et al., 2010a), compromised maternal nutrition during certain periods of gestation appears to have significant impacts on placental and fetal growth and development, as well as postnatal outcomes (Wallace et al., 2006; Wu et al., 2006; Caton and Hess, 2010; Funston et al., 2010; Reynolds et al., 2010).

ROLE OF PROGRAMMING OF SPECIFIC ORGAN SYSTEMS

Examples of tissue and organ system programming due to intrauterine growth restriction or maternal nutrition during gestation can be found throughout livestock and rodent animal literature. An overview of several organ systems, their observed responses to maternal nutrition during gestation in livestock, and possible implications to whole animal production are summarized by Meyer et al., (2012).

Although not greatly studied in livestock species to date, epigenetic mechanisms are likely responsible for many of the reported organ system responses that may affect growth, feed efficiency and production. For example, maternal and postnatal dietary folate has been shown to affect DNA methylation and thus the epigenetic status of growth-related genes in small intestine (McKay et al., 2011). This could be extremely important for efficiency of growth and nutrient utilization because intestinal growth can be programmed in utero or postnatally, and the gastrointestinal tract contributes disproportionately to whole-body energy use.

RELATIONSHIP TO NUTRIENT UTILIZATION

Growth involves changes in both tissue functional and support components including the vascular bed and depends primarily on accretion of cells (increased cell number, termed hyperplasia) and increased cell size (hypertrophy). Because tissue growth involves production of new cells or cell and tissue products, it is energetically and nutritionally costly. Therefore, improvements in the efficiency of gain will likely be best-achieved by increasing the absorption of nutrients in the gastrointestinal tract or by reducing basal metabolic rate. This suggestion seems reasonable because both the absorptive capacity of the gastrointestinal tract and basal

metabolic rate, or maintenance costs, are variable among animals and perhaps amenable to manipulation. Despite this grand theory, supporting studies in cattle are sparse.

The efficiency of energy production for maintenance and growth can be altered by manipulating either mitochondrial number or function. One of the key concepts related to energy utilization is that mitochondrial density, or the number of mitochondria per unit of tissue, is highly correlated with capillary density (Adair et al., 1990). This makes sense, of course, as the oxygen source (the capillary bed) should be closely matched with the oxygen utilizing machinery (the mitochondrion). The mechanism regulating this 'match' involves the cellular oxygen sensing system, which includes the hypoxia-inducible factors as well as the transcriptional coactivator peroxisome-proliferator-activated receptor-γ coactivator-1α, a potent metabolic sensor and regulator, both of which regulate expression of angiogenic factors and their receptors (Pugh and Ratcliffe, 2003; Arany et al., 2008).

Little is known about how nutrient restriction during fetal development influences tissue oxygen consumption and mitochondrial function during postnatal development. Carstens et al. (1987) reported reduced heat production (and thus oxygen consumption) in calves born from heifers that were fed diets restricted in protein. Data on the effects of nutrient restriction on mitochondrial function and biogenesis in rodent models and humans have been inconsistent with some data suggesting increases (Civitarese et al., 2007; Nisoli et al., 2005) and others no change (Hancock et al., 2011) in mitochondrial biogenesis. Additionally, mitochondrial uncoupling of the electron transport chain results in reduced efficiency of ATP production and differences in uncoupling activity between animals could result in differences in energetic efficiency (Harper et al., 2002).

SUMMARY AND CONCLUSIONS

Epigenetic mechanisms, primarily DNA methylation and histone modifications, have been implicated as the primary mechanism of developmental programming of offspring in utero and postnatally. Changes in gene expression resulting from epigenetics can cause pre- and postnatal alterations that affect the long-term health and performance of the offspring. Many data sets demonstrate a response of offspring growth to maternal factors, including maternal genotype, age, nutrition, and various other 'stressors' (e.g., environmental heat stress, high altitude, behavioral stress, multiple fetuses) in livestock species including cattle. Differing offspring responses to nutrient restriction in utero or postnatally are likely due to differing developmental windows of organ systems. Although not greatly studied in livestock species to date, epigenetic mechanisms are likely responsible for many of the reported organ system responses that may affect growth, feed efficiency and production. Additional research is needed to further understand and capitalize upon the role of epigenetics in livestock production systems.

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