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Going Up Inflame: Reviewing the Underexplored Role of Inflammatory Programming in Stress-Induced Intrauterine Growth Restricted Livestock

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Abstract

The impact of intrauterine growth restriction (IUGR) on health in humans is well-recognized. It is the second leading cause of perinatal mortality worldwide, and it is associated with deficits in metabolism and muscle growth that increase lifelong risk for hypertension, obesity, hyperlipidemia, and type 2 diabetes. Comparatively, the barrier that IUGR imposes on livestock production is less recognized by the industry. Meat animals born with low birthweight due to IUGR are beset with greater early death loss, inefficient growth, and reduced carcass merit. These animals exhibit poor feed-to-gain ratios, less lean mass, and greater fat deposition, which increase production costs and decrease value. Ultimately, this reduces the amount of meat produced by each animal and threatens the economic sustainability of livestock industries. Intrauterine growth restriction is most commonly the result of fetal programming responses to placental insufficiency, but the exact mechanisms by which this occurs are not well-understood. In uncompromised pregnancies, inflammatory cytokines are produced at modest rates by placental and fetal tissues and play an important role in fetal development. However, unfavorable intrauterine conditions can cause cytokine activity to be excessive during critical windows of fetal development. Our recent evidence indicates that this impacts developmental programming of muscle growth and metabolism and contributes to the IUGR phenotype. In this review, we outline the role of inflammatory cytokine activity in the development of normal and IUGR phenotypes. We also highlight the contributions of sheep and other animal models in identifying mechanisms for IUGR pathologies.

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Keywords

adaptive fetal programming; developmental origins of health and disease; DOHAD; fetal growth restriction; intrauterine growth restriction; IUGR; low birthweight; metabolic programming

INTRODUCTION

Intrauterine growth restriction (IUGR) frequently results from stress-induced placental insufficiency, which reduces O_2 and nutrients available to the fetus and consequently stunts growth of the highly metabolic fetal muscle tissues (Yates et al., 2018; Pendleton et al., 2021). In livestock, low birthweight due to stress-induced IUGR causes substantial economic losses for the industry due to greater neonatal mortality, less metabolic efficiency, and lower carcass quality (Reynolds et al., 2010; Liu and He, 2014; Ji et al., 2017; Yates et al., 2018). Estimates put low birthweight-related losses at approximately 8% of the potential annual product for US producers and up to 20% of the global annual product (Wu et al., 2006; Flinn et al., 2020). Thrifty metabolic adaptations to muscle, adipose, pancreatic islets, and other tissues cause IUGR-born offspring to be disadvantaged at birth due to insufficient energy stores and poor thermoregulation, which often results in reduced nursing success and a failure to thrive throughout the early neonatal period (Dwyer et al., 2016; Yates et al., 2018). Intrauterine growth restriction-born offspring that survive exhibit reduced feed efficiency, making it cost more to reach proper harvest weight (Bérard et al., 2008; Yates et al., 2018; Gibbs et al., 2020). Thrifty programming also manifests as reduced muscle growth capacity and increased fat deposition beginning at the juvenile age (Greenwood et al., 2000; Yates et al., 2012; Gibbs et al., 2020), which lowers carcass yield and affects meat quality parameters such as tenderness, muscle pH, meat color, and cooking loss (Liu and He, 2014; Matyba et al., 2021). Intrauterine growth restriction also afflicts human pregnancies (Saleem et al., 2011; Nardozza et al., 2017), and global estimates indicate that upward of 53 million infants are born IUGR each year (Sedgh et al., 2014). These babies are at increased risk for perinatal morbidity and mortality (Aucott et al., 2004; Alisi et al., 2011; Alisjahbana et al., 2019) as well as for lifelong health problems such as asthma, type 2 diabetes, cardiovascular disease, obesity, and neurocognitive disorders that begin in early childhood and reduce life expectancy and quality (Nardozza et al., 2017; Darendeliler, 2019; Xing et al., 2020; Briana and Malamitsi-Puchner, 2021).

By the late 1950s, the scientific community had recognized that individuals with metabolic diseases often exhibited physiological indicators of metabolic dysfunction by the time they were neonates (Neel, 1962). However, it was the work of Hales and Barker in the early 1990s and the subsequent publication of their Thrifty Phenotype hypothesis that popularized the idea of a link between fetal developmental programming and lifelong metabolic health (Hales et al., 1991; Hales and Barker, 1992). In the almost three decades since, a number of studies in humans and animal models have advanced this theory with details of how stress before birth causes tissue-specific adaptive programming of growth and metabolism (Morrison, 2008; Posont et al., 2017; Yates et al., 2018; Posont and Yates, 2019; Pendleton et al., 2021). These nutrient-sparing fetal adaptations help to increase the chances for survival *in utero* but also create permanent metabolic changes that are detrimental to

long-term health of the offspring (Sharma et al., 2016a; Kesavan and Devaskar, 2019; Posont and Yates, 2019). Identifying the exact mechanistic facilitators of these changes has been challenging, but one likely potential mechanism that has recently come to light is inflammatory programming (Posont et al., 2018, 2021; Cadaret et al., 2019). This review highlights findings that provide insight for how fetal stress leads to programmed changes in inflammatory pathways that regulate growth and metabolism, with a primary focus on the implications for meat animals.

CAUSES AND PROGRESSION OF IUGR

IUGR Is the Developmental Response to Maternofetal Stress

Clinically, IUGR [alternatively, fetal growth restriction (Nardozza et al., 2017)] is characterized by less growth of the fetus or fetal tissues relative to expected growth potential (Sharma et al., 2016b; Reynolds et al., 2019). It is a pathological condition brought on by fetal nutrient restriction or other stress, although genetic abnormalities can increase the risk (Sharma et al., 2017). In the field of developmental origins of health and disease (DOHaD), IUGR is often used to describe the broader pathological phenotype resulting from chronic fetal stress, which typically (but not always) includes measurable reductions in placental function and birthweight (Sharma et al., 2016b). A number of different maternal conditions can result in placental stunting when they coincide with critical windows for placental growth and development (Sharma et al., 2016b; Yates et al., 2018). In livestock, common factors include environmental stress, illness or forage toxicity, nutritional imbalances, young age of the dam, uterine trauma from previous pregnancies, twin/triplet pregnancies, and side effects from artificial insemination or embryo transfer (Greenwood and Bell, 2003; Greenwood and Cafe, 2007). Such stressors redirect maternal blood flow from the gravid uterus, thus reducing nutritional support for placental hyperplasia and vasculogenesis (Burton and Jauniaux, 2018). Placental functional capacity is determined in large part by the successful establishment of uteroplacental circulation via the rapid development of villous blood vessels beginning around the end of the first trimester and continuing throughout most of the second trimester (Regnault et al., 2003; Burton and Jauniaux, 2018). Indeed, it is during this critical window that the placenta is most vulnerable to insults that may lead to reduction in its vasculature, surface area, and transport proteins needed for maternal-fetal nutrient exchange (Regnault et al., 2005; Burton and Jauniaux, 2018). During such insults, placental tissues are typically characterized by unusually high levels of inflammation, oxidative stress, and apoptotic cells (Cotechini and Graham, 2015; Burton and Jauniaux, 2018).

The diminished maternofetal interface associated with placental insufficiency ultimately reduces O_2 transfer to the fetus, and reductions in placental glucose and amino acid transporters likewise reduce fetal availability of these nutrients (Brown, 2014; Yates et al., 2018; Beede et al., 2019). Indeed, fetal hypoxemia and hypoglycemia in heat stress-induced sheep models of placental insufficiency can exceed 50% reductions near term (Macko et al., 2016; Wai et al., 2018; Stremming et al., 2020), creating a clear need for changes in metabolic processes and growth trajectories (Lackman et al., 2001; Gagnon, 2003). The phenomenon of fetal hypoglycemia can be partially mimicked by sustained maternal

undernutrition, which can decrease fetal growth despite little or no impact on the size or vascularity of the placenta (Lemley et al., 2012; Eifert et al., 2015; Edwards et al., 2020; Contreras-Correa et al., 2021). Interestingly, diminished placental transfer of amino acids due to downsizing of system A and L transporters does not necessarily manifest in reduced fetal blood concentrations (Pantham et al., 2016; Wai et al., 2018), as the IUGR fetus compensates by slowing its protein utilization and accretion rates (Rozance et al., 2018; Wai et al., 2018; Stremming et al., 2020).

The hypoxemic and hypoglycemic conditions resulting from placental insufficiency cause a robust hormone-driven stress response by the fetus. Low blood O_2 concentration detected by O_2-sensitive K^+ channels on the chromaffin cells of the adrenal medulla stimulates secretion of the catecholamines, norepinephrine, and epinephrine (Adams and McMillen, 2000), inducing the hallmark hypercatecholaminemia that progressively worsens over the third trimester of pregnancy. Catecholamines act as strong inhibitors of insulin secretion, which together with hypoglycemia results in a chronic state of fetal hypoinsulinemia (Chen et al., 2017; Limesand and Rozance, 2017). Fetal hypoxemia also leads to an increase in circulating inflammatory cytokines (Krajewski et al., 2014; Visentin et al., 2014), which will be discussed in detail in later sections. Additional inflammatory components such as chemokine C-C motif ligand 16 (CCL16) and acute phase protein C-reactive protein (CRP) have also been found to be increased in IUGR fetuses (Makikallio et al., 2012; Visentin et al., 2014).

IUGR Impairs Growth Capacity and Metabolic Function

In most cases, the fetus can survive unfavorable conditions created by placental insufficiency by altering the development of several growth and metabolic processes in a way that reduces nutrient demands (Gagnon, 2003). First, the combined endocrine response to low fetal blood O_2 content causes a redirection of blood flow away from skeletal muscle and other less vital tissues to maintain support for the brain, liver, adrenals, and pancreas (Gagnon, 2003; Poudel et al., 2015). Indeed, greater vascular resistance can reduce blood flow to muscle-dense areas such as the hindlimb by as much as 45%, which in turn reduces O_2 delivery by up to 40% (Rozance et al., 2018). Secondly, hypoinsulinemia reduces glucose utilization by insulin-sensitive muscle tissues (Davis et al., 2020). Interestingly, this can lead to transient enhancement of insulin sensitivity in the early neonatal period as a compensatory response (Soto et al., 2003; Ong et al., 2004). However, this wanes relatively quickly (Mericq et al., 2005), exposing underlying impairments in insulin action (Jensen et al., 2002).

Poor Skeletal Muscle Growth Leads to Asymmetric Body Composition—The reappropriation of nutrients away from skeletal muscle in the IUGR fetus causes the development more conservative muscle growth rates that are apparent in late gestation but also persist throughout the lifetime of the animal. Indeed, IUGR fetal sheep and rats were found to have smaller cross-sectional areas for all muscle fiber types (Yates et al., 2016; Cadaret et al., 2019a), indicating that less muscle hypertrophy was occurring during gestation. Intrinsic functional deficits in muscle stem cells called myoblasts are a major underlying factor for impaired muscle growth capacity (Yates et al., 2014; Soto et al., 2017; Posont et al., 2018). In ruminants and humans, muscle hyperplasia is completed early in

the third trimester, and subsequent muscle growth is the result of myofiber hypertrophy (Maier et al., 1992; Wilson et al., 1992). Indeed, postnatal muscle growth results from the accumulation of new nuclei within muscle fibers via fusion of myoblasts, which increases capacity for fiber protein synthesis (Allen et al., 1979; Davis and Fiorotto, 2009). Some fetal myoblasts form quiescent populations between the sarcolemma and the basal lamina of muscle fibers. These latent myoblast populations are called satellite cells and can later be activated to facilitate further muscle growth (Davis and Fiorotto, 2009; Yin et al., 2013). Before fusing, myoblasts undergo several cycles of proliferation followed by terminal differentiation, both of which are rate-limiting functional steps for muscle growth (Allen et al., 1979; Allen and Boxhorn, 1989). However, myoblasts from IUGR fetal sheep and rats were found to exhibit reduced proliferation and differentiation capabilities (Yates et al., 2014; Soto et al., 2017; Posont et al., 2018; Cadaret et al., 2019a), leading to reduced muscle mass at birth and throughout postnatal life, as illustrated in Figure 1.

Offspring born with low birthweight due to IUGR initially continue to exhibit slower postnatal growth. For example, lambs born IUGR due to maternal heat stress or maternofetal inflammation remained about 20% smaller at 30 days of age, with comparable reductions in average daily gain (Cadaret et al., 2019b; Yates et al., 2019; Posont et al., 2021). As IUGR-born offspring reach the juvenile stage, many begin to exhibit postnatal catch-up growth, whereby their bodyweights equalize with uncompromised herdmates. Indeed, bodyweights and average daily gain for lambs born IUGR due to maternal heat stress were reduced by only about 12% by 60 days of age (Gibbs et al., 2020), and IUGR-born beef cattle were about 8% lighter at 30 months of age (Greenwood et al., 2005; Greenwood and Cafe, 2007). However, this does not equate to recovery of muscle growth, and thus body composition remains impaired; 60-day old IUGR lambs had smaller loin eye areas, reduced muscle protein, and greater fat-to-protein ratios (Gibbs et al., 2020), and 30-month old IUGR beef cattle had smaller carcass weight, ribeye area, and *longissimus* muscle weight, resulting in less retail yield (Greenwood and Cafe, 2007). Estimates from these cattle indicate that each 1-kg reduction in birthweight equated to a 4.4-kg reduction in slaughter weight (Robinson et al., 2013; Greenwood and Bell, 2019).

Nutrient-Sparing Adaptations Reduce Muscle Glucose Metabolism—In concert with more conservative muscle growth, the IUGR fetus undergoes a glucose-sparing shift in muscle metabolism characterized by reduced oxidation and greater glycolytic lactate production. When IUGR fetal sheep were made hyperglycemic or hyperinsulinemic near term, whole-body glucose oxidation was decreased even though whole-body glucose utilization remained unchanged (Limesand et al., 2007; Brown et al., 2015). Subsequent sheep studies confirmed that the reduction in glucose oxidation rates were muscle-specific and persisted after birth (Cadaret et al., 2019b; Yates et al., 2019; Gibbs et al., 2021; Posont et al., 2021). Four-fold greater circulating lactate concentrations together with greater hepatic expression of gluconeogenic genes in IUGR fetal sheep (Brown et al., 2015) indicate that lactate produced in greater amounts by IUGR skeletal muscle supports hepatic glucose production. This process, called the Cori cycle, benefits the nutrient-restricted IUGR fetus by engaging an otherwise inactive source for glucose (Thorn et al., 2009; Davis et al., 2021). However, it is important to note that the reduction in glucose oxidation arises from

a programmed change in mitochondrial functional capacity that does not appear to be reversible. Although pyruvate dehydrogenase functional activity was increased in IUGR fetal sheep muscle (Pendleton et al., 2019), mitochondrial O_2 consumption and electron transport chain Complex I activity were impaired (Pendleton et al., 2020). Gene expression for isocitrate dehydrogenase, mitochondrial pyruvate carrier, and other integral components of mitochondrial oxidative metabolism were also reduced in IUGR muscle, whereas gene expression for lactate dehydrogenase B (converts pyruvate to lactate) was increased 2.5-fold (Pendleton et al., 2020). It is worth noting that reduced glucose oxidation rates do not appear to be offset by compensatory amino acid oxidation (Pendleton et al., 2021). In fact, oxidation rates for the representative amino acid, leucine, were slightly reduced in IUGR fetal sheep (Brown et al., 2012; Wai et al., 2018). Moreover, impaired glucose oxidation coincided with reduced proportions of oxidative myofibers in hindlimb muscles of IUGR fetal sheep (Yates et al., 2016).

Insulin Signaling Is Impaired in IUGR Skeletal Muscle—Growth and metabolic deficits in IUGR skeletal muscle are at least partially a product of disruptions in insulin signaling through Akt-mediated pathways. Insulin is a primary promotor of muscle growth, as it enhances protein synthesis (Davis and Fiorotto, 2009) and is a well-established stimulator of proliferation and differentiation in adult myoblasts (Allen et al., 1985; Sumitani et al., 2002). More recent studies found that hyperinsulinemia also increases myoblast function in fetal sheep (Brown et al., 2016b; Soto et al., 2017). Additionally, skeletal muscle is the primary tissue for insulin-mediated glucose uptake from the blood (Baron et al., 1988; Brown, 2014). This is facilitated when circulating insulin binds to receptors on the muscle fiber surface and initiates rapid mobilization of sequestered glucose transporter 4 (Glut4) to the cell membrane, where it facilitates glucose diffusion into the cell (Kubota et al., 2011). In addition to its effects on glucose uptake, insulin stimulation increased skeletal muscle glucose oxidation rates 1.5- to 4-fold in fetal sheep (Brown et al., 2015; Cadaret et al., 2019) and 2- to 8-fold in growing lambs (Barnes et al., 2019; Cadaret et al., 2019b; Swanson et al., 2020; Posont et al., 2021). However, several studies have indicated that insulin/Akt signaling is impaired in IUGR muscle. Insulin activates Akt by serine^{463} phosphorylation, but the proportion of phosphorylated Akt was reduced in *flexor digitorum superficialis* muscle from IUGR fetal and neonatal sheep (Cadaret et al., 2019; Posont et al., 2021). This deficit was observed at both low and high insulin concentrations and did not coincide with any reduction in insulin receptor content (Thorn et al., 2009; Yates et al., 2019). Intrauterine growth restriction skeletal muscle also exhibited reduced content of the insulin-sensitive glucose transporter, Glut4, before and after birth (Limesand et al., 2007; Yates et al., 2019), likely due to epigenetic mechanisms such as DNA methylation at the Glut4 promoter region or histone modifications (Raychaudhuri et al., 2008; Wang et al., 2016). Like insulin, the influence of IGF-1 is also diminished in the IUGR fetus, as circulating IGF-1 concentrations and skeletal muscle signaling components are reduced (Thorn et al., 2009; Rozance et al., 2018).

Pancreatic Islet Dysfunction Contributes to Metabolic Deficits—Stress conditions resulting from placental insufficiency induce programming in other tissues that further compounds muscle-centric dysfunction. Chief among these affected tissues are pancreatic

islets, which are diminished in both development and functionality (Boehmer et al., 2017). Near term, IUGR fetal sheep islets are reduced in size by 40% (Rozance et al., 2015; Brown et al., 2016a), and β cell mass is reduced by 60% due to a 40–60% reduction in mitosis (Limesand et al., 2005; Brown et al., 2016a). In addition to being smaller, these β cell populations are less productive, as IUGR fetal islets contain only about 20% the amount of insulin found in normal fetal islets (Limesand et al., 2006). Deficits in islet microanatomy are preceded by insufficient islet vascular formation, which is observable shortly after the start of the third trimester (Rozance et al., 2015). Islet under-development may be due in part to less profound HGF paracrine activity originating from islet endothelial cells (Rozance et al., 2015; Brown et al., 2016a), which appears necessary for β cell development and performance (Dai et al., 2005; Johansson et al., 2009). Like muscle, IUGR fetal islets are also less capable of glucose oxidation, which is the impetus for glucose-stimulated insulin secretion (Limesand et al., 2006). These programmed deficits persist in offspring, as islets from IUGR-born lambs maintained substantially reduced insulin content and glucose stimulus-secretion coupling (Yates et al., 2019), leading to impairments in glucose-stimulated insulin secretion that are comparable to the fetus (Cadaret et al., 2019b; Yates et al., 2019). Interestingly, α cell mass is reduced in IUGR fetal islets, but not to the same magnitude observed for β cells. Moreover, their capacity to appropriately secrete glucagon appears to be unaffected (Limesand et al., 2005).

THE ROLE OF INFLAMMATORY CYTOKINES IN IUGR OUTCOMES

Cytokines Regulate Muscle Growth and Metabolism

Cytokines are a broad class of peptide chemical messengers produced by a wide array of cell and tissue types, often in response to the presence of pathogens, toxins, free radicals, and stress (Tracey and Cerami, 1993; Reid and Li, 2001). Among their other immune functions, inflammatory cytokines modify metabolic activity in muscle and other tissues in order to reappropriate O_2, glucose, and protein (Li and Reid, 2001; Cadaret et al., 2017). They are also potent regulators of muscle growth via their complex impact on myoblast function and insulin sensitivity (Otis et al., 2014; Posont et al., 2018). This makes the broad cytokine milieu integral to metabolic homeostasis and, in turn, general metabolic health, as summarized in Table 1.

Tumor necrosis factor α (TNFα) is perhaps the most comprehensively studied inflammatory cytokine. It is produced in greatest quantities by circulating monocytes and their intra-tissue counterparts, macrophages, but is also produced by glycolytic skeletal muscle fibers and fat cells (Tracey and Cerami, 1993; Li and Reid, 2001; Plomgaard et al., 2005; Dyck et al., 2006). Basal circulating TNFα concentrations are typically low but increase rapidly and profoundly when stimulated (Tracey and Cerami, 1993; Li and Reid, 2001). Pathological metabolic states such as excessive fat deposition, insulin resistance, and hyperglycemia are associated with substantially greater production and secretion of TNFα (Saghizadeh et al., 1996; Lo et al., 2007), as is pathological muscle atrophy (Li and Reid, 2001). Most cell types express one or both of two surface TNFα receptor isoforms (TNFR1, TNFR2), and TNFR1 is predominant for muscle (Popa et al., 2007). Once activated by TNFα, the intracellular domain of TNFR1 binds and activates the downstream TNFR1-associated death

domain (TRADD) proteins (Popa et al., 2007), which in turn activate Fas-associated protein with death domain (FADD) pathways and TRAF2/NFκB pathways (Popa et al., 2007). In skeletal muscle, these pathways are most associated with protein catabolism, lipolysis, and metabolic suppression (Cheema et al., 2000; Li and Reid, 2001; Popa et al., 2007). They also decrease synthesis of the myofibril components myosin and actin as well as sarcoplasmic proteins (Cheema et al., 2000; Li and Reid, 2001; Lang et al., 2002). In differentiating myoblasts, TNFα inhibits MyoD expression, which impedes their progression, and in mature fibers it increases protein catabolism, which reduces the content of myosin and other integral proteins for muscle function (Li and Reid, 2001). Both of these outcomes appear to be mediated by canonical NFκB pathways (Li and Reid, 2001; Remels et al., 2015). In mature skeletal muscle, TNFα-activated NFκB pathways increase the proportion of glucose undergoing glycolytic lactate production by increasing activity of HIF-1α, which is concurrent with reduced glycogen synthesis (Boscá and Corredor, 1984; Rhoades et al., 2005; Remels et al., 2015). The effects of TNFα on glucose oxidation rates are more complex, as the cytokine appears to be stimulatory during acute exposure but inhibitory when exposure is sustained (Gao et al., 2012; Cadaret et al., 2017, 2019). In addition to direct effects on muscle growth and metabolism, TNFα also impairs insulin sensitivity. In rats, TNFα diminished the effects of insulin on skeletal muscle glucose uptake by 50% (Youd et al., 2000; Li and Reid, 2001), perhaps by increasing the content of diacylglyceride, a potent activator of the insulin antagonist protein kinase C (Bruce and Dyck, 2004; Dyck et al., 2006). In pancreatic islet cells, TNFα exposure was shown to reduce glucose metabolism in β cells and, in turn, glucose-stimulated insulin secretion (Oleson et al., 2015).

The interleukin IL-6 is produced by leukocytes and muscle cells, often in response to rising TNFα concentrations (Tracey and Cerami, 1993; Haddad et al., 2005). Consequently, circulating IL-6 concentrations follow similar patterns as TNFα during sub-acute and chronic inflammatory conditions (Wolsk et al., 2010). When bound, the soluble IL-6 receptor (IL6R) forms a heterodimer with the downstream messenger gp130 (Wang et al., 2013), which primarily activates the JAK/STAT3 pathway but can also activate PI3K/Akt/mTOR and Ras/Raf/MEK/ERK pathways (Wang et al., 2013; Johnson et al., 2018). Elevated IL-6 activity limits hypertrophic muscle growth by interfering with growth hormone and IGF-I activity and also increases muscle protein catabolism, thus contributing to muscle atrophy (Haddad et al., 2005; Bodell et al., 2009). Although it may increase myoblast proliferation at some concentrations, IL-6 also reduces the progression of differentiation in primary fetal sheep myoblasts (Haddad et al., 2005; Posont et al., 2018). The predominant aspects of metabolic regulation by IL-6 are similar to those of TNFα. First, the nature of its effects on skeletal muscle appear dependent on the magnitude and duration of exposure, as sustained exposure is substantially more detrimental. Additionally, IL-6 is associated with pathological metabolic states, presumably due to its propensity to decrease skeletal muscle carbohydrate metabolism in favor of fatty acid oxidation and to disrupt insulin signaling (Bruce and Dyck, 2004; Wolsk et al., 2010; Knudsen et al., 2017). Finally, IL-6 is detrimental to pancreatic islet function, as overexpression of IL-6 in β cells resulted in alterations to islet structure, increased fibrosis, and decreased insulin production (Campbell et al., 1994).

Additional inflammatory cytokines appear to have roles in muscle regulation but have been less extensively studied. For example, IL-1β is involved in collagen degradation, muscle protein catabolism, and branched-chain amino acid metabolism (Nawabi et al., 1990; Dinarello, 2000; Li et al., 2009). Consequently, it is associated with reduced myofiber width, myofibril construction, and actin content (Li et al., 2009). In islets, IL-1β promotes β cell apoptosis, which impairs glucose-stimulated insulin secretion (Harms et al., 2015; Oleson et al., 2015). IL-18, IL-8, and TWEAK appear to have similar roles in regulating muscle growth and metabolism.

Inflammatory Tone Is Increased in the IUGR Fetus

Studies in a multitude of mammalian species show that IUGR fetuses exhibit greater circulating leukocyte and cytokine concentrations, which correlate closely with hypoxemia (Romero et al., 2007; Guo et al., 2010; Cadaret et al., 2019; Oh et al., 2019). Increased TNFα, IL-6, and IL-18 were observed in cord blood of IUGR infants at delivery and in blood serum at 24 h after delivery (Krajewski et al., 2014; Visentin et al., 2014). In fact, high concentrations of inflammatory cytokines in cord blood are considered reliable clinical markers for diagnosing fetal inflammatory response syndrome (FIRS) (Kemp, 2014). In IUGR fetal sheep, greater circulating TNFα in the mid-third trimester coincided with increased monocytes, granulocytes, and total white blood cells (Cadaret et al., 2019). Similarly, IUGR fetal rodents exhibited elevated blood concentrations of TNFα, IL-6, and IFNγ, as well as greater leukocyte activity (Hudalla et al., 2018; Cadaret et al., 2019a). In addition to circulating concentrations, cytokine expression is elevated in IUGR tissues including lungs, brain, skeletal muscle, and white blood cells (Kemp, 2014; Cadaret et al., 2019a), but not necessarily in pancreatic islets (Kelly et al., 2017).

IUGR Tissues Develop Enhanced Inflammatory Sensitivity

Some rodent models of IUGR indicate that greater circulating cytokine concentrations are maintained into adulthood. Indeed, IUGR-born rat and mice offspring exhibited greater circulating TNFα, IL-6, and IL-1β from birth to adulthood (Desai et al., 2009; Riddle et al., 2014; Chisaka et al., 2016; Oliveira et al., 2017). However, recent findings indicate that enhanced cytokine signaling pathways in muscle and other tissues maintain increased inflammatory tone even when elevated circulating cytokines subside after birth (Cadaret et al., 2019a; Posont et al., 2021). We have postulated that this enhanced responsiveness to cytokines contributes to the persistent dysregulation of muscle growth and metabolic function observed in IUGR-born offspring (Yates et al., 2018; Posont and Yates, 2019). At term, skeletal muscle from IUGR rat pups exhibited greater gene expression for TNFR1, IL6R, and Fn14 (TWEAK receptor) (Cadaret et al., 2019a). Moreover, muscle from IUGR-born mice and rats exhibited greater TNFα and IL-6 gene expression at 2 and 12 months after birth (Sutton et al., 2010; Tarry-Adkins et al., 2016). In sheep, proliferation and differentiation rates of primary IUGR fetal myoblast were reduced when exposed to basal or high TNFα or IL-6 concentrations (Posont et al., 2018). Additional data from these samples indicate increased gene expression for TNFR1 and IL6R in IUGR myoblasts and *semitendinosus* muscle, as well as reduced muscle IκBα protein content and increased c-Fos protein content (Posont, 2019). As neonates, IUGR-born lambs exhibited increased TNFR1 protein content in *semitendinosus* muscle and greater circulating concentrations

of monocytes, granulocytes, and platelets (Posont et al., 2021). Transcriptomics were subsequently performed in muscle samples from these lambs, which indicate that gene expression for numerous components of TNFα, IL-6, IL-1β, and IL-12 pathways were upregulated (Yates et al., 2018; Cadaret, 2019), as summarized in Figure 2. This paralleled similar transcriptomics findings in skeletal muscle from IUGR fetal sheep (Cadaret et al., 2019; Posont and Yates, 2019). Interestingly, IUGR-born lambs also exhibited greater muscle IκBα protein content and a 50% reduction in circulating TNFα, perhaps as a compensatory mechanism for enhanced cytokine sensitivity (Posont et al., 2021). Although additional studies are needed to fully understand the magnitude and nature of inflammatory programming in IUGR skeletal muscle, it is clear that such enhanced activity would help to explain the deficits in myoblast function, muscle growth, body composition, insulin action, and metabolic efficiency described in earlier sections.

Targeting Inflammatory Adaptations May Improve IUGR Outcomes

Inflammatory programming is likely one of several underlying mechanisms for IUGR-associated pathologies, but its ability to be targeted makes it of particular interest. In fact, several studies have provided fundamental evidence that treating IUGR fetuses and IUGR-born offspring with anti-inflammatory nutrients or pharmaceuticals can help to mitigate or improve growth and metabolic deficits. In mice, maternal supplementation of the anti-inflammatory nutraceutical folic acid reduced the frequency and severity of IUGR resulting from maternal inflammation (Zhao et al., 2013). The mice receiving folic acid also exhibited a less severe increase in amniotic concentrations of IL-6 and other cytokines. Although not assessed in muscle, the enhancement of cytokine signaling pathways observed in IUGR placental tissues was mitigated by folic acid (Zhao et al., 2013). In sheep, direct daily infusion of the anti-inflammatory nutraceutical eicosapentaenoic acid (EPA) into the bloodstream of IUGR fetuses during the mid-third trimester of gestation for 5 days resulted in less severe fetal hypoxemia, hypoglycemia, and hyperlactatemia (Beer et al., 2021). In addition, the greater lactate production observed for IUGR fetuses during hyperglycemia was improved substantially, perhaps indicating a less severe metabolic shift to glycolytic lactate production by muscle (Lacey et al., 2021). This coincided with an improvement in fetal growth and body symmetry. EPA infusion also improved whole hindlimb mass as well as loin and *flexor digitorum superficialis* muscle mass in the IUGR fetuses, which is indicative of improved muscle growth during late gestation (Lacey et al., 2021). It is worth noting that growth was not recovered for all muscles, which may have been due to the natural differences in insulin sensitivity and metabolic phenotypes among muscle groups (Kirchofer et al., 2002). After IUGR fetuses had been infused with EPA for 5 days, they exhibited improved basal and glucose-stimulated insulin secretion, indicating partial rescue of pancreatic islet function (Lacey et al., 2021). These fetuses also exhibited improvements in blood pH, HCO_3, Na^+, and Ca^{++} concentrations, which indicate improved fetal health and well-being (Lacey et al., 2021). In addition to nutrient compounds, maternal delivery of anti-inflammatory pharmaceuticals may also represent an effective intervention strategy. A recent clinical study showed that high doses of the non-steroidal anti-inflammatory drug (NSAID) aspirin taken by pregnant women during critical windows of fetal development reduced the frequency of IUGR (Roberge et al., 2017). Of course, the benefits of such drugs must be considered in combination with potential side effects for fetal development.

Inflammatory programming can also be targeted in offspring, which is of particular interest in livestock. Dietary supplementation of the anti-inflammatory nutraceutical curcumin to IUGR-born neonatal pigs and mice mitigated the elevated concentrations of blood TNFα, IL-6, and IL-1β, which improved insulin sensitivity, lipid homeostasis, and neonatal growth (Niu et al., 2019a,b,c).

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IMPLICATIONS

The link between maternofetal stress, IUGR-induced low birthweight, and postnatal deficits in metabolic efficiency and growth potential are well-established in livestock, but scientific advancements regarding the molecular mechanisms underlying this link have been lacking. However, recent studies provide evidence that systemic fetal inflammation and developmental programming that enhances tissue sensitivity to inflammatory cytokines are contributing factors to growth and metabolic deficits, particularly those that are muscle centric. Although inflammatory programming is likely one of many underlying mechanisms, it is of particular interest to the livestock industry because it is both identifiable and treatable. Indeed, there are a number of currently marketed nutritional supplements and pharmaceuticals with anti-inflammatory properties, which could provide producers a number of options for mitigation and treatment strategies. Food animals born with low birthweight due to stress-induced IUGR are persistently one of the greatest barriers to US and global livestock production. Moreover, the emergence of climate change will likely increase the incidence of environmental stress on pregnant animals, creating a greater challenge for sustainable livestock production. As the global population continues to increase, recovering growth, efficiency, and meat production in low birthweight animals through practical management strategies represents one of the most realistic options for increasing meat production without greater land and water resource inputs. Although more work is warranted, early evidence indicates that treatment of enhanced inflammatory tone in IUGR-born animals may be an effective approach.

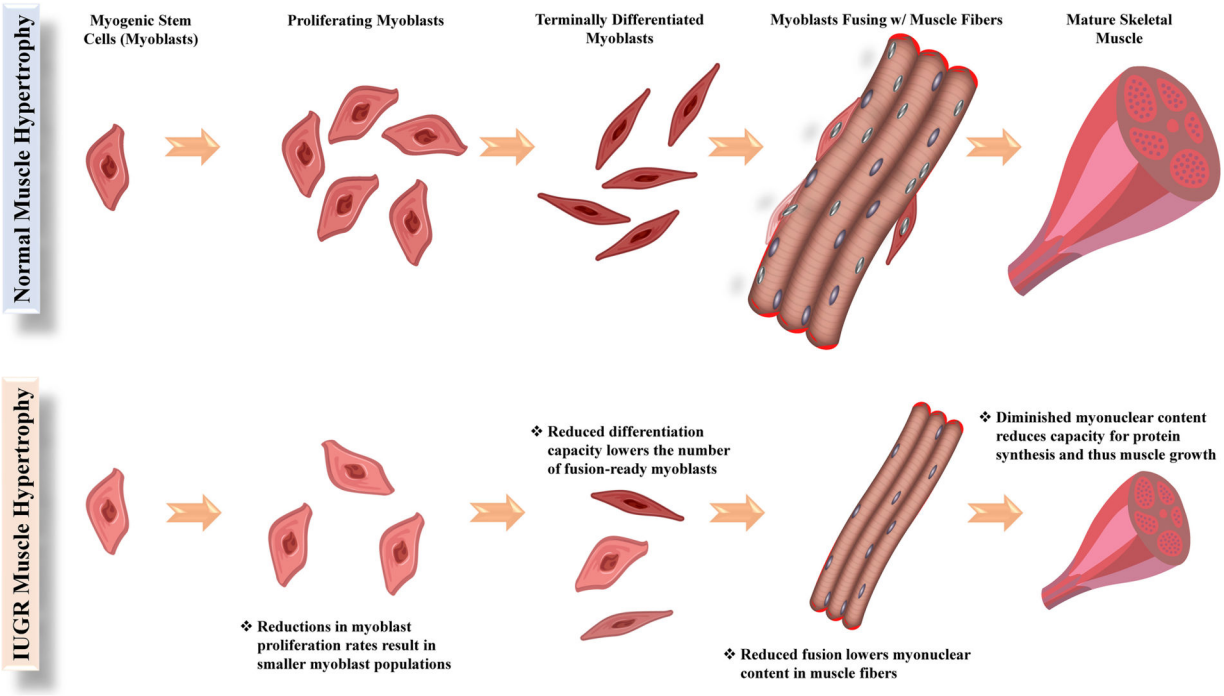

FIGURE 1 |.

Functional steps of myoblasts (muscle stem cells) and their facilitation of hypertrophic growth in normal and IUGR skeletal muscle.

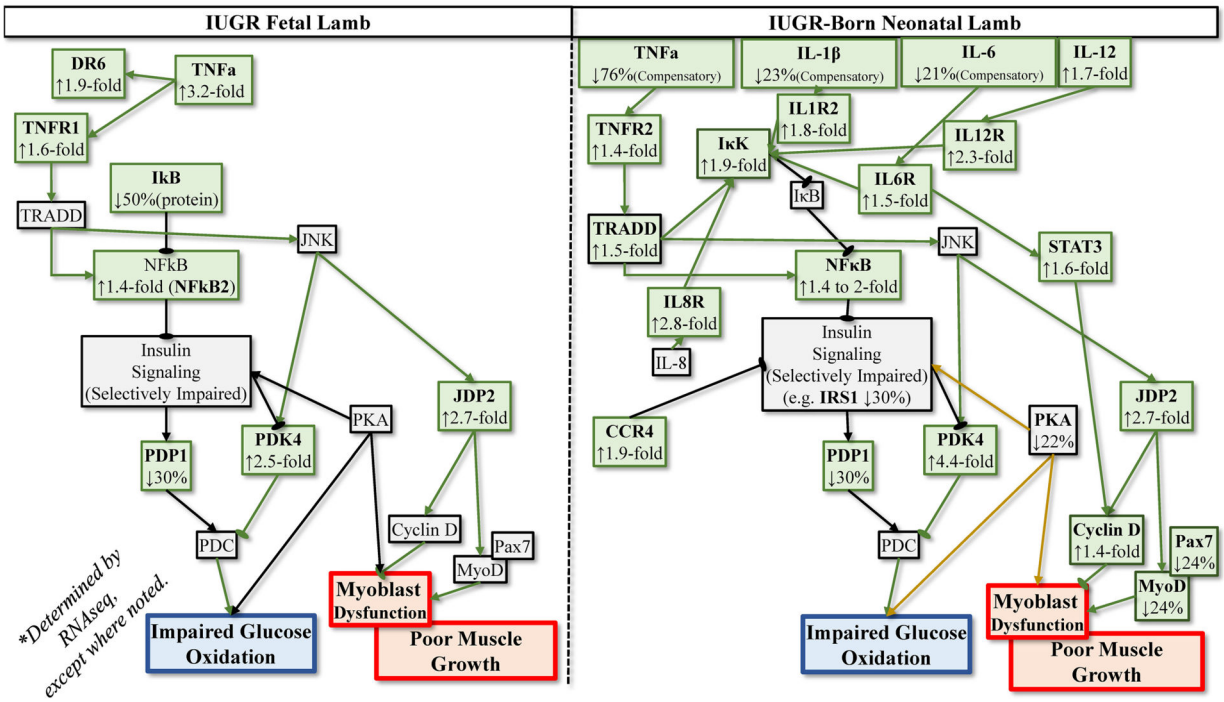

FIGURE 2 |.

Postulated programming of enhanced sensitivity to inflammatory cytokines based on transcriptomics analyses of IUGR semitendinosus muscle from IUGR fetal sheep during late gestation and IUGR-born neonatal lambs at 1 month of age.

TABLE 1 |

Summary of the major effects that key inflammatory cytokines elicit in tissues affecting growth and efficiency in meat animals.

Cytokine	Tissue		
	Skeletal muscle	**Pancreatic islets**	**Other**
TNFα	↓MyoD (Li and Reid, 2001; Alvarez et al., 2020) ↓Myoblast differentiation (Alvarez et al., 2020) ↓Myosin, actin, and sarcoplasmic proteins (Alvarez et al., 2020) ↑Protein catabolism (Cheema et al., 2000; Popa et al., 2007) ↑Glycolysis (Boscá and Corredor, 1984; Rhoades et al., 2005; Remels et al., 2015)	↓Glucose oxidation in β cells (Oleson et al., 2015) ↓Glucose-stimulated insulin secretion (Oleson et al., 2015) ↓Insulin sensitivity (Youd et al., 2000; Li and Reid, 2001)	↑Lipolysis in fat deposits (Cheema et al., 2000; Popa et al., 2007)
IL-6	↓Muscle hypertrophy (Haddad et al., 2005; Bodell et al., 2009) ↓Myoblast differentiation (Haddad et al., 2005; Posont et al., 2018) ↑Muscle atrophy (Haddad et al., 2005; Bodell et al., 2009)	Altered islet structure (Campbell et al., 1994) ↑Fibrosis (Campbell et al., 1994) Impaired insulin signaling (Bruce and Dyck, 2004; Wolsk et al., 2010; Knudsen et al., 2017)	↓GH and IGF-1 secretion and sensitivity, multiple tissues (Haddad et al., 2005; Bodell et al., 2009)
IL-1β	↑Protein catabolism (Nawabi et al., 1990; Dinarello, 2000; Li et al., 2009) ↓Myofiber width (Li et al., 2009) ↓Actin content (Li et al., 2009)	↑β cell apoptosis (Harms et al., 2015; Oleson et al., 2015) ↓Glucose-stimulated insulin secretion (Harms et al., 2015; Oleson et al., 2015)	Collagen degradation, multiple tissues (Nawabi et al., 1990; Dinarello, 2000; Li et al., 2009)