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Review: Link between intestinal immunity and practical approaches to swine nutrition

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Gaining a deeper understanding into the underlying mechanisms associated with intestinal function and immunity during the weaning transition is critical to help shed new light into applied nutrition approaches to improve piglet performance and health during this critical life-stage transition. The transient anorexia triggered at weaning leads to compromised intestinal barrier function and a localized inflammatory response. Considering barrier function, specific nutrient fractions appear to have a significant impact on the development and function of the immune and microbial systems around weaning. Understanding the specific impact of nutrients in the small intestine and hindgut is important for helping to bring more focus and consistency to nutritional approaches to support health and immunity during the weaning transition period. The challenge continues to be how to translate these modes of action into practical and scalable approaches for swine nutrition. We will focus specifically on practical nutritional approaches to influence intestinal immunity through lipid, protein and antioxidant nutrition.

Keywords: swine, nutrition, immunity, intestine, weaning

Implications

The ability to translate the physiological, immunological and digestive changes at weaning into practical nutritional approaches for commercial swine production remains an exciting challenge for our industry. As we continue to gain more insight into the underlying modes of action, a more targeted nutrient approach can be applied to help achieve more targeted and consistent outcomes for the weaned pig.

Introduction

Gaining a deeper understanding into the underlying mechanisms associated with intestinal function and immunity during the weaning transition is critical to help shed new light into practical nutrition approaches to improve piglet performance and health during this critical life-stage transition. Nutrition approaches have focused on achieving heavier weaning weights by providing highly digestible diets to encourage better DM intake as the young pig transitions from milk to solid feed. The benefits of achieving success in the weaning transition are significant. Tokach *et al.* (1992) demonstrated that heavier weaning weights and higher gain during the first-week post-weaning can result in a 10-lb BW advantage at day 56 of age and up to a 10-day marketing advantage. Main *et al.* (2004) demonstrated that the potential improvement of increasing weaning age by 1 day between day 12 and 21 would result in an extra 0.93 kg of day 42 BW and up to 0.47% reduction in wean-to-finish mortality. The economic implications of these aforementioned benefits, among others, are significant to swine producers and will continue to drive urgency to find new ways to achieve these advantages in commercial settings. Intestinal function and immunity during the weaning transition are critical leverage points for the ability of nutrition to influence immediate and longer term performance and health impacts (Jacobi and Odle, 2012). Consequently, there is a need to gain better insights to underlying physiological, nutritional and immunological adaptations occurring in the intestine at weaning to allow for practical application of nutritional approaches to support immunity and intestinal function.

Intestinal immunity during the weaning transition

The development of the gastrointestinal system occurs over several months after birth. Development of digestive functions coincides with the development of the adaptive and innate immune systems. From an immune development

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standpoint, the innate immune system defenses responsible for barrier function are more mature relative to the adaptive immune system given the time needed for lymphocytes to populate secondary lymphoid tissues, mature and expand in order to function properly (Bailey *et al.*, 2005). Piglets are limited in their ability to mount T and B cell responses during the first few weeks of life, and this contributes to an overall immuno-compromised condition (Lalles *et al.*, 2007). Consequently, the young pig is more reliant on innate immunity given the maturity of this system through the first few weeks of life. The intestinal immune system provides protection along the intestinal tract and balances the host response to microflora dynamics and intestinal pathogens. The structure and function relationships of barrier function and intestinal immunity development have been reviewed in detail (Everaert *et al.*, 2017; Moeser *et al.*, 2017). The type and rate of microbial colonization in the intestine and the host's response to their presence play an important role in the establishment of intestinal immunity.

The intestinal microbiome ecosystem is extremely complex and is tightly linked to performance and health. The changes in the microbiome ecosystem in pigs are more variable and less stable relative to adults, which can pose a health and performance risk that may have long-term impacts (Merrifield *et al.*, 2016). The changes in microflora at weaning are broadly characterized by a reduction in obligate anaerobic bacteria (e.g., Clostridia and Bateroidia) and an increase in facultative anaerobic bacteria (e.g., Enterobacteriaceae) which translate to decreased microbial diversity and a pro-inflammatory state within the intestine (Gresse *et al.*, 2017). While certainly not mutually exclusive, changes in the microbiome ecosystem are also influenced by nutritional and husbandry approaches. For example, piglets raised on milk replacers have significantly different microbial ecosystems and functional intestinal immune responses relative to piglets raised with the sow (Lewis *et al.*, 2012). Additionally, while sow genetics can also influence the development of the piglet microbial ecosystem, the age of weaning and time of exposure to solid feed have a greater impact (Bian *et al.*, 2016). Taken together, the microbiome ecosystem is dynamic and we are continuing to learn how this can be impacted by nutrition, genetics and husbandry. This continues to be an area where a deeper understanding of how microbial phenotypes translate to practical outcomes in commercial settings is still needed. While there is progress to begin to understand some relationships, such as linking porcine gut microbial ecosystems and performance (Ramayo-Caldas *et al.*, 2016), there will be a need to understand how specific nutrients and additives, such as prebiotics, probiotics, phytogenics, enzymes, among others, can more consistently make the desired impacts through microbiome mode of action. While not intended to go into full detail in this review, the impact of specific additives on intestinal immunity and microbiome ecosystems has been discussed (Lalles *et al.*, 2007; Jacobi and Odle, 2012; Gresse *et al.*, 2017). Additionally, as the identification of preferred microbiome modifiers is better understood and appreciated we can begin to assess different nutritional approaches to help improve transition from sow milk to dry feed, better productivity and health.

Nutritional implications of an intestinal immune response

Pastorelli *et al.* (2012) completed a meta-analysis to understand the impact of an immune response on feed intake and growth responses. The meta-analysis classified the performance response to immunity according to digestive bacterial infections, poor housing conditions, lipopolysaccharide challenge, mycotoxicosis, parasitic infections or respiratory disease. Digestive bacterial infections had the greatest negative impact on growth response relative to the other categories evaluated. The change in gain was partly explained by a reduction in intake; however, the majority was attributed to reduced feed efficiency and changing maintenance requirements and digestive function during the immune challenge. Intestinal immune responses result in a significant nutritional cost to the animal as shown through reductions in intake and the efficiency in which these nutrients are used for growth. While not a pathogenic challenge, the combination of changes in intestinal architecture, microbial profiles and immune-competence of the pig at weaning initiates an intestinal immune response that can contribute to limitations in performance and health during the weaning transition (Lalles *et al.*, 2007). As we continue to understand the morphological, physiological, endocrine and immune mechanisms that contribute to these phenotypes, we can improve our ability to target nutrition to help mitigate these limitations encountered at weaning. Intestinal barrier function continues to be the focal point for nutritional support given the morphological and endocrine changes that occur during the weaning transition period.

Intestinal barrier function plays a critical role in the overall health and performance of weaned pigs (Moeser *et al.*, 2017). The combined social, microbial and environmental stressors at weaning lead to targeted impacts on barrier function due to reductions in intake. Reductions in intake at weaning are significant and in some instances it may take 10 to 14 days to reach pre-weaning intake levels (Le Dividich and Seve, 2000). The reduction in energy intake at weaning reduces villous height and increase crypt depth, which collectively contributes to reduced enzymatic capacity and absorptive surface area (Le Dividich and Seve, 2000). By providing more energy intake at weaning through supplementation of milk, reductions in villous height can be mitigated, suggesting that feed intake and beneficial intestinal histology have a positive association (Le Dividich and Seve, 2000). Changes in morphology of the intestine occur relatively quickly compared to intestinal barrier function, and this may explain why histological measurements do not always associate well with performance metrics. As noted by Moeser *et al.* (2017) and mentioned earlier with the meta-analysis of digestive bacterial infections, a

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breakdown in intestinal barrier function can have deleterious consequences on health and animal performance.

The weaning process results in increased intestinal permeability due to decreased tight junctions (Moeser *et al*., 2007). This leads to transmigration of luminal antigens, toxins, viruses or even bacteria into the lamina propria. These pathogen-associated molecular patterns are well recognized by cells of the immune system that reside within the lamina propria, and their activation results in the release of pro-inflammatory mediators and signaling molecules to help neutralize and recruit other immune cells into the region (Lalles *et al*., 2007). This results in an inflammatory response, which can further contribute to reductions in intake and reduced growth. The inflammatory response results in a catabolic response and, depending on the severity and time frame of the inflammatory response, a shift in the flux of nutrients away from growth and more toward immune support (Klasing and Johnstone, 1991). Skeletal muscle catabolism helps to support amino acid substrate for the synthesis of acute phase proteins that are an important component of the innate immune response to infection. While the reductions in animal performance during an immune response are largely associated with decreased feed intake, the increase nutrient need for the immune system may help explain why digestive bacterial infections resulted in the greatest reduction in growth relative to other immune challenges (Pastorelli *et al*., 2012). Consequently, nutritional approaches to support barrier function and/or modified inflammatory response can help mitigate the negative impacts of weaning on health and performance.

Weaning stress also results in activation of the hypothalamic-pituitary adrenal axis, resulting in elevated serum corticotrophin-releasing factor (**CRF**) for days post-weaning (Moeser *et al*., 2007). In the intestine, CRF plays a major role in stress-related intestinal disturbances and does so by binding to CRF receptors on epithelial, neuron and immune cells, most notably mast cells (Bonaz and Bernstein, 2013). Mast cell degranulation within the intestine results in inflammatory mediators to help destroy pathogens and signaling molecules, such as chemokines, and other regulators such as interleukins that will help to coordinate the local immune response. In fact, administration of the mast cell stabilizer cromolyn prevented weaning-induced increases in intestinal permeability (Moeser *et al*., 2007) and increased post-weaning growth to 36 days of age by 20% (Mereu *et al*., 2015). These data show the importance of the mast cell in the weaning-induced changes in intestinal barrier function and the potential that can exist when steps in these processes can be ameliorated. Taken together, while there is certainly more knowledge needed in these areas, practical nutrition approaches focused on supporting barrier function have the potential to help mitigate local and systemic inflammatory responses.

Nutritional approaches to support barrier function

As mentioned previously, the transient anorexia triggered at weaning leads to compromised intestinal barrier function and a localized inflammatory response. The absence of food in the intestine leading to these changes in intestinal function and immunity points to the importance of feed intake at weaning. In neonatal pigs, data suggest that a minimum of 40% of total nutrient intake is required to maintain intestinal mucosa and 60% of total nutrient intake is required for increased intestinal growth and proliferation (Burrin *et al*., 2000). Simple measures to help promote intake are a very practical step to help ameliorate these inflammatory responses and improve barrier function (Pluske *et al*., 1997; McCracken *et al*., 1999). As reviewed by Anastasilakis *et al*. (2013), the absence of nutrition stimulus from food in the gastrointestinal tract (**GIT**) results in changes in intestinal immunity. This includes a reduction in intestinal immune cells and imbalances in cytokines, chemokines and other immune markers. Of note, these changes include IL-4, IL-10 and IFNγ leading to a more prominent T-helper 1 phenotype. A subsequent effect of this shift in immune profile is decreased IgA content in intestinal and mucosal tissues. Changes in intestinal microflora also occur as a consequence of no enteral intake. Compared to enteral nutrition, parenteral nutrition changes the intestinal microflora to predominately gram-negative Proteobacteria (Demehri *et al*., 2013), a phylum containing a number of pathogens including *Escherichia* and *Salmonella*. This shift to Proteobacteria is linked to increased toll-like receptor (**TLR**) signaling in the intestine, which can further increase inflammation and decrease intestinal barrier function. Blocking of TLR signaling through the use of MyD88 knock-out mice inhibits the increase in TNFα and IFNγ and mitigates the effect from the shift to Proteobacteria (Demehri *et al*., 2013). Consequently, promoting early intake and weaning and more consistent meal patterns at weaning are important to ensure the presence of feed in the intestine to further mitigate inflammation.

A central focus of nutrition for early intake at weaning continues to be on nutrient use and availability given the importance of animal performance, health and sustainability. Considering barrier function and intestinal immunity, however, what is undigested and how that is influencing microbial changes within the intestine may be just as important. This continues to be an area of opportunity as we understand the impacts of nutrient release into the distal small intestine and hindgut and how these can influence immunity, health and feeding patterns during the weaning transition period. The opportunity continues to be how to translate these into practical approaches for swine nutrition and building health outcome-based diets, such as improved livability and reduced medication need, for pigs during the weaning transition. We will focus specifically on practical nutritional approaches to influence intestinal immunity through lipid, protein and antioxidant nutrition. The impact of carbohydrates on intestinal health has been reviewed (Bach Knudsen *et al*., 2012), and the specific impact of insoluble and soluble fiber fractions on barrier functions continues to be evaluated (Wu *et al*., 2018). From a practical nutrition standpoint, we will assess different approaches to promote

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intestinal barrier function through delivery of lipids as signaling molecules, control of undigested protein and ability to support antioxidant defense during the weaning transition period.

Lipid nutrition

Fat is the primary energy source during the first few weeks of life. Weaning reduces fat calorie intake given the shift to carbohydrate-based ingredients. The impact of fat calorie intake on satiation and meal patterns in piglets is not well investigated. Lipid research for weaned pigs has mainly focused on comparing different types of fats and oils on performance, digestibility and other traits (Cera *et al.*, 1988; Kim *et al.*, 2013), n-3 fatty acids for their anti-inflammatory potential (Carroll *et al.*, 2003) or medium chain fatty acids or triglycerides as readily available source of energy with antimicrobial potential (Hanczakowska, 2017). Less focus has been given to the effect of lipids on gastrointestinal transit and peptide secretion and effect on intake and intestinal health. Several studies investigated the effect of lipid infusion in the pig gastrointestinal tract and its effect on intake and Cholecytokinin (**CCK**). Gregory and Rayner (1987) investigated the effects of stomach, duodenum, jejunum or ileum infusion of intralipid or digestion products on feed intake. When intralipid was infused in the duodenum, it dose dependently decreased feed intake to a greater extent than the energy infused. Infusion of monoglyceride, oleic acid and glycerol also had effects on intake when infused in the duodenum or ileum, but only infusion of monoglyceride decreased the overall energy intake. Further experiments determined that CCK mediated the effects on intake when intralipid or monoglyceride was infused in the duodenum (Gregory *et al.*, 1989b) and that duodenal infusion of intralipid and glucose inhibits gastric emptying (Gregory *et al.*, 1989a). Collectively, the data indicate that lipids influence gastric emptying and that the intestinal location of lipid digestion products can also influence intake and gastrointestinal peptide secretion.

More recent efforts in humans have investigated the effect of lipid gastric emulsion stability and droplet size on gastric emptying, gastrointestinal peptides and satiety. Foltz *et al.* (2009) investigated the effect of feeding a meal that was mixed with fat (i.e., emulsion) or non-mixed (i.e., layered) on intake responses. The layered fat delayed lipid absorption, increased post-prandial CCK and increased satiety. Differences between acid stable and acid unstable emulsions have also been investigated (Marciani *et al.*, 2007 and 2009). Acid unstable emulsions quickly separate in the stomach leading to fat layering and decreased gastric emptying, increased post-prandial CCK and an increased feeling of satiety. These results are in contrast to the results of Foltz *et al.*, 2009. Differences may be attributed to how the meal was delivered and the quantity of fat delivered in the two experiments. Decreasing fat droplet size has similar effects as acid stability on gastric emptying; however, it further increases satiety or decreases subsequent meal size (Hussein *et al.*, 2015). Further investigations into the effect of differences in gastric emptying on gastrointestinal peptides determined that increased gastric emptying from acid-unstable emulsions increases CCK and Glucagon-like peptide-1 (**GLP-1**) while lowering total post-prandial CCK. In contrast, increasing droplet size decreased the initial peak in CCK (Steingoetter *et al.*, 2017). Additionally, acid unstable emulsions and increased droplet size decreased total peptide YY, another peptide involved in regulation of intake.

Glucagon-like peptide-1 along with Glucagon-like peptide 2 (**GLP-2**) is produced by enteroendocrine cells in the intestine and is synthesized from the proglucagon gene and is involved in stimulating intestinal growth, stimulation of digestive activity and nutrient absorption, improvement in intestinal barrier function, regulation of feed intake, improvements in insulin sensitivity and increasing β-cell proliferation (Brubaker and Anini, 2003; Burrin *et al.*, 2003). Fat is a strong stimulator of GLP-1 secretion (Knapper *et al.*, 1995) by products of lipid digestion including fatty acids (Voortman *et al.*, 2012) and monoglycerides (Hansen *et al.*, 2011). While prior data have focused on the effect of lipids regulating intake, in cases of low feed intake, such as weaned pigs, the effect of lipids on gastrointestinal peptide secretion and the impact on intestinal barrier function and potential for immune modulation may be as relevant as the impact on intake. Treatment with GLP-2 decreases serum amyloid A and haptoglobin concentrations in the blood providing evidence that it can reduce inflammation in conditions of low intake (Kvidera *et al.*, 2017). Like GLP-2, there is also evidence of anti-inflammatory effects of GLP-1 for a number of chronic conditions in humans (Lee and Jun, 2016). Translational data in pigs are currently limited; however, these provide new perspectives into lipid nutrition for young pigs to help support intestinal barrier function and immunity through improved feed intake.

Undigested protein

Undigested protein can be defined as the amount of N that enters into the hindgut for use in bacterial fermentation. This N source is in excess of what the pig is able to digest and absorb, either due to poor protein quality and/or limited V_{max} of digestive enzymes and nutrient transporters in the intestine. The excess N available for fermentation in the distal ileum and colon has a negative impact on barrier function and immunity and is a major contributor to post-weaning diarrhea at weaning (Kim *et al.*, 2012). Increasing total N flow into the terminal ileum results in increased NH_3–N content in the ileum and hindgut as well as increased pH (Heo *et al.*, 2010a and 2010b). Increased N availability results in a shift in microbial populations toward more proteolytic populations and increased production of fermentation by-products, such as branched chain fatty acids, ammonia, amines, volatile phenols and indols (Williams *et al.*, 2001). Microbial populations shift from *Lactobaccilus* spp and butyrate producing saccharolytic microbes to more proteolytic spp such as *Clostridium* (Opapeju *et al.*, 2009; Gresse *et al.*, 2017).

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Products of protein fermentation have toxic and pro-inflammatory impacts on the intestinal epithelium. Consequently, undigested protein is a substrate that leads to more toxic compounds in the intestinal lumen during a time when the intestinal tract is immature and more susceptible to the negative impacts of these compounds. To further compound the issue, pathogen challenges, which are common in commercial settings, further exacerbate these responses. A pathogen challenge, such as enterotoxigenic *Escherichia coli*, increased total N flow to the distal ileum, further increases pH and has more of an impact on intestinal structure, such as villous height and associated impacts on nutrient digestion and absorption potential (Heo *et al*. 2009 and 2010b; Pluske *et al*., 1997). In addition, toxins produced by pathogens such as *E. coli* can also disrupt water regulation and absorption and reabsorption of minerals, which contributes to post-weaning diarrhea (Sun and Kim, 2017). These impacts, both undigested protein and pathogen infection, lead to an inflammatory response in the intestine that can have systemic implications and may further reduce performance (Pieper *et al*., 2012). There is an opportunity, therefore, to apply nutritional approaches to mitigate the negative impacts of undigested protein on intestinal barrier function in order to support a smooth transition through weaning.

Reductions in dietary CP levels in post-weaning diets have long been advised (Nyachoti *et al*., 2006; Kim *et al*., 2012). Interestingly, while digestive enzymes of the weaned pig are compromised at weaning, the apparent ileal digestibility is not impacted by CP level or during an *E. coli* infection, suggesting that V_{max} for these digestive processes has been achieved at even 20% to 40% reduction in dietary CP levels. Total N flow to the terminal ileum in either low- or high-CP diets did differ, however, which was mainly due to similar intake across these diet types (Heo *et al*. 2009 and 2010b). These data suggest that high-CP diets, such as in excess of 23% CP as fed in these studies, under health and low disease pressure may not be detrimental; however, from a commercial perspective where disease challenge is high the ability to reduce total N flow through lower CP diets can help support reduced post-weaning diarrhea (Kim *et al*., 2012). Lowering the dietary protein content with balanced AA might reduce the formation of microbial metabolites and consequently reduce the incidence of diarrhea. Htoo *et al*. (2007) showed no effect on piglet performance and fecal score, ileal ammonia and ileal amine content when the protein level of the diets was lowered from 24% to 20% with the same levels of standardized ileal digestibility (**SID**) AA and energy.

While there continues to be a need to gain better insight into amino acid availability and nutrition across life stages and feedstuffs, more focused attention on amino acid needs for the intestine are somewhat limited. The long-standing practical nutrition principle is to utilize more expensive specialty proteins in piglet feeds and to maintain the proper amino acid ratios (Goodband *et al*., 2014). There continues to be interest in evaluating amino acid ratios for optimal intestinal barrier function at weaning. Specific attention has been focused on tryptophan given the further metabolism of this amino acid to functional metabolites that can have immune-regulatory properties, such as regulation of T cell function and response. Results with tryptophan are somewhat unclear, as Le Floc'h *et al*. (2009) reported lower plasma Trp levels suggesting that Trp availability was limited for growth and other metabolic functions. Capozzalo *et al*. (2012) discovered that Trp:Lys ratios in excess of growth resulted in improved feed efficiency in either the presence or absence of an enterotoxigenic *E. coli* infection; however, there was no immune challenge by Trp:Lys interaction. Optimal Thr:Lys ratios have also been evaluated in piglets given the importance of this essential amino acid for intestinal use and barrier function (Stoll *et al*., 1998). Wang *et al*. (2010) demonstrated that true ileal digestibility Thr levels of 0.37% or 1.11% were least effective for villous architecture and concentrations of ileal acidomucins and duodenal sulfomucins. The optimal ratio of Thr:Lys for supporting intestinal barrier function was concluded to be 0.89% for weaning piglets, which was above the optimum level of 0.74% for growth performance (Wang *et al*., 2010). Dispensable amino acids also play an important role in intermediary nitrogen metabolism through production of conditionally essential amino acids (e.g., arginine), energy metabolism intermediates (e.g., tricarboxylic acid (**TCA**) cycle intermediates) and also purines and pyrimidines. Collectively, these positively impact energy status in the intestine, which can lead to enhanced integrity and function (Burrin and Stoll, 2009). Amino acids that seem to be of particular importance are glutamine, glutamate, proline, aspartate, ornithine and citrulline, which is due in large part to their connectivity via inter-organ amino acid metabolism. Of particular importance is the ability of these amino acids to positively regulate AMP-activated protein kinase (**AMPK**), which is the master regulator of cellular energy status. Glutamate, glutamine and aspartate are primary energy substrates for the intestine and have been shown to modify AMP:ATP ratios in the intestine, which can influence AMPK signaling pathways. The ability to fully leverage these insights is somewhat limited today, mainly due to commercial limitations associated with synthetic amino acid price and sourcing along with analytical limitations of the availability of these amino acids in different raw materials. Most ideal protein studies have assessed the appropriate ratio to lysine to other indispensable amino acids, but have not determined the optimal ratio of indispensable to dispensable amino acids. The ratio of indispensable to dispensable amino acids at a given dietary protein level is also important and is determined by the ratio of lysine to protein (Li *et al*., 2001). Although an average total lysine:CP ratio of 6.8% is often cited, a higher lysine:CP ratio can be used in the diet because the lysine released during normal muscle protein breakdown is conserved and recycled with greater efficiency than other amino acids (Nemechek *et al*., 2011). Ratliff cited by Nemechek *et al*. (2011) suggested that the total Lys:CP ratio should not exceed 7.1%.

Crude protein and amino acid digestibility of raw materials is another important factor contributing to fermentable

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protein and associated challenges to the **GIT** during the weaning transition. The current approach is to use a similar standardized ileal digestibility value for all life phases. Li *et al.* (1993) indicated that the ileal amino acid digestibility increases with age and that weaned piglets may have a reduced capacity for CP and amino acid use. This is also supported by reduced pancreatic and brush border enzymes around the time of weaning. Consequently, the use of SID values for growing pigs may not be adequate for the weaned pig and this may have implications on the amount and variability of undigestible protein. Urbaityte *et al.* (2009) determined standardized ileal CP and amino acid digestibilities for protein supplements using 15-day-old (BW 4 ± 0.5 kg) ileal cannulated barrows. Compared to tabular grower-finisher values from National Research Council (**NRC**), SID values for indispensable amino acids were 2 to 19 percentage points lower for extruded soybean meal and 2 to 12 percentage points lower for high-protein soybean meal. These indicate that for some ingredients there is a large difference in SID values, which will result in a larger impact of fermentable protein on intestinal health and immunity. For some high-quality protein ingredients, the ileal digestibilities are relative similar or close to what is recommended in either the NRC or Centraal Veevoeder Bureau (**CVB**) standards. In this case, the use of high-quality protein as proposed by Goodband *et al.* (2014) to help mitigate nutritional challenges to the intestine are well supported.

Antioxidant nutrition

Weaning and weaning-associated intestinal inflammation generate large amount of reactive species. Jejunum reactive oxygen species increase threefold, and thiobarbituric acid-reactive substances increase 50% in 28-day-old weaned pigs compared with pre-weaning pigs (Wei *et al.*, 2017). Similar results were reported by Zhu *et al.* (2012) in that the concentrations of nitric oxide and hydrogen peroxide were significantly increased after weaning. Nitric oxide released into the GIT lumen is rapidly transformed into nitrate, which confers a growth advantage for *E. coli* (Gresse *et al.*, 2017). Zeng *et al.* (2017) remarked that perturbations of the microbiota are commonly observed in diseases involving inflammation in the GIT, with the inflamed microenvironment being particularly conducive to overgrowth of *Enterobacteriaceae*, which acquire fitness benefits while other families of symbiotic bacteria succumb to environmental changes. A recent study by Wei *et al.* (2017) reported an increased concentration of reactive oxygen species in the intestine coupled with an expansion of the *E. coli* population 7 days after weaning. Overgrowth of *E. coli* induces further inflammation and activation of the immune system, which in turn generates more free radicals, and undermines its functions (Catoni *et al.*, 2008). Free radical overproduction could overwhelm antioxidant systems and deplete *in vivo* antioxidants such as vitamin E and enzymes. Kim *et al.* (2016) reported that plasma vitamin E was dramatically decreased from around 3.0- to 2.0-mg/l post-weaning and was further decreased with *E. coli* challenge. Dietary supplementation of 200 IU/kg of vitamin E is not sufficient to restore plasma vitamin E to pre-weaning status of 3 mg/l.

Another consequence of weaning is dramatic reduction of energy intake. Piglets consume around 1200 kJ/BW 0.75/day from sow milk (Pluske, 1993). A significant percentage of pigs do not eat anything during the first 24- to 72-h post-weaning. During this period, body tissue is mobilized to maintain body temperature and essential biological function. Excess tissue mobilization and catabolic status increase free radical production (Bernabucci *et al.*, 2005). This has been described in sows (Zhu *et al.*, 2012), dairy cows (Castillo *et al.*, 2005) and rats with a glucocorticoid-induced catabolic metabolism (Orzechowski *et al.*, 2002). Insufficient energy intake in weaning pigs results in intestine villous atrophy and impaired barrier function. Intestinal inflammation generates great amount of reactive oxygen species (**ROS**), as indicated previously. It is critical to improve early feed intake to prevent excess body metabolism during the first few days post-weaning, to maintain intestinal integrity and antioxidant balance. Wijtten *et al.* (2011) reported a linear correlation between villous height and DM intake. Piglets had higher DM intake with longer villous and better barrier function (Pluske *et al.*, 1997).

To protect the cells against potentially damaging effects of radicals, cells possess antioxidant networks that include antioxidant enzymes, such as superoxide dismutase and gluthatione peroxidase, vitamins and non-proteins (coenzyme Q, glutathione). During the weaning period, antioxidant systems are overwhelmed due to intestinal inflammation, pathogenic bacterial overgrowth and catabolic metabolism. Results clearly indicated that intestinal dysfunction after weaning is associated with unbalanced antioxidant systems as indicated by reduced super oxide dismutase (**SOD**), glutathione peroxidase (**GPX**) and increased ROS in the intestines and the blood. There is much interest in the use of assessing antioxidant status (Buchet *et al.*, 2017) and compounds (Zhu *et al.*, 2012) to mitigate this problem of antioxidant imbalance. Dietary polyphenols have been shown to play important roles in human health by lowering risks of many chronic diseases including cancer, cardiovascular disease, chronic inflammation and many degenerative diseases (Milner, 1994). Others, such as flavonoids, have direct effects on a variety of immune and inflammatory cell functions (Catoni *et al.*, 2008). Diets supplemented with grape polyphenol extraction at 100 or 150 mg/kg increased serum IgG, IgM, C4 and IL-2 concentrations (Shi *et al.*, 2003). Combination of vitamin E and C, polyphenols and fermented components effectively improved jejunum and colon antioxidant status (GPX, SOD, total antioxidant (**T-AOX**)) in weaning pigs (Xu *et al.*, 2014). In addition, intestinal microflora balance is restored with more *Lactobacillus* and *Bifidobacterium* and reduced *E. coli* in both the jejunum and the colon compared to weaned controls. Interestingly, a positive correlation of antioxidative status with potential beneficial bacteria and negative correlation

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with *E. coli* was reported. These results suggest that intestinal ROS strongly impacts microflora balance which in return impacts intestinal inflammation and antioxidant balance. By scavenging free radicals, or preventing oxidative chain reactions, dietary antioxidant supplements have been shown to improve antioxidant status, immunity as well as restore intestinal microflora balance.

In conclusion, antioxidant balance is a critical aspect of intestinal immunity and microbial balance in weaning pigs. There is a strong relationship between ROS production, microflora population and intestinal immune function. Dietary antioxidants such as vitamins and polyphenols can be used to scavenge ROS and prevent oxidation stress, which consequently improve microflora balance and digestive health.

Conclusions

Practical nutrition approaches to support intestinal immunity should focus on ways to mitigate the inflammatory response. This requires consideration of not only the nutrient needs for animal performance, but also balancing the nutrient needs impacting the intestinal immune system to ensure resilience and health-based outcomes through the weaning transition. While genetic advancements and husbandry practices will no doubt play a significant role in this advancement, practical nutrition approaches will also be important to ensure that the right intestinal and microbial outcomes are achieved. As discussed in this review, the ability to not only stimulate feed intake post-weaning but rather the intake of specific nutrient fractions that have a more profound impact on achieving health outcomes in weaning is needed. Looking beyond lipids as an energy source and as a regulator of intestinal growth and maturity will cause us to view fat source, quality and application differently. Furthermore, considering what is undigested, in the case of protein, and how this shapes the microbiome and health in the young pig brings a different perspective on how to evaluate protein quality and relative value of protein rich ingredients for young animal feeds. Finally, the weaning-induced increase in reactive oxygen species, as well as the plasma reductions in vitamin E at weaning, points to an opportunity to consider other sources of antioxidant defense and supplementation. Taken together, there continues to be a need to gain more of an understanding of how to feed the immune system to achieve the desired outcomes in commercial swine production systems. By gaining a deeper insight into the physiological, immunological and digestive changes occurring in the intestine at the time of weaning a more targeted nutritional approach can be achieved.

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None.

Ethics statement

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