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Original

The Role of Aryl Hydrocarbon Receptor-Microbiota Interactions in the Litter and Pre-Fattening Pigs' Health

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ABSTRACT

Background: the presence of an ever-growing number of gastrointestinal pathogens is causing economic losses to the swine industry. The prophylactic and therapeutic uses of antibiotics are not the solution. **Aim**. To analyze the interactions between the aryl hydrocarbon receptor (AHR) and the microbiota (enhanced through probiotic use), which have improved the health and production indicators of pigs (piglets and pre-fattening). **Development:** Enteropathies (colibacillosis and salmonellosis) are a significant and frequent cause of mortality of piglets and pre-fattening pigs in intensive breeding systems. The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor that is widely expressed in immune, epithelial, endothelial, stromal cells, and tissue. It regulates the microbe-host symbiosis by ligand activation in the diet. The AHR-IL-22 axis (aryl-hydrocarbon receptor-interleukin-22 axis) in the intestine plays an important role in the defense of the host against microbial pathogens while providing resistance to these diseases. **Conclusions**: the AHR receptors are important in the restoration of damage possibly caused by pathogens or an inappropriate diet in postweaning pigs, by re-establishing and creating stability in the intestinal microbiota; the utilization of probiotics, may lead to favorable responses of the production and health indicators of piglets and pre-fattening pigs.

Keywords: Pigs, gastrointestinal diseases, microbiota, probiotics, aryl hydrocarbon receptor (Source: *MeSH*)

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INTRODUCTION

The swine industry is one of the most promising sectors to meet the growing needs of foods demanded by humans. The production tren increased until 2016, then it was followed by a 0.9% decline in the annual growth rate. This setback was the result of economic losses associated with respiratory and gastrointestinal pathogens whose occurrence is growing. Other reasons have also affected this sector, often related to deficient management. Their identification is essential to adopt measures that reduce the negative impact they cause (Rodríguez *et al*., 2020).

Enteropathies (colibacillosis and salmonellosis) are a significant and frequent persistent cause of mortality of litter and pre-fattening pigs in intensive breeding systems (Barreto, Rodríguez and Campal, 2020b). The utilization of antibiotics for prophylaxis and treatment aggravates this problem, since they affect the intestinal microbiota, which is deficient in the litter, then altered after weaning (Rodríguez *et al.,* 2020; Barreto, and Rodríguez, 2021). This choice threatens consumer health and the environment; it also triggers the selection and propagation of antibiotic-resistant strains (Espinosa *et al*., 2019). Only the treatments that stabilize a normal microbiota are effective. In this sense, the utilization of prebiotics, probiotics, and efficient microorganisms (EM) (Barreto, Rodríguez, and Campal, 2020b).

The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor that is widely expressed in immune, epithelial, endothelial, and stromal cells, and tissue. One of the most relevant related functions is their role as a central sensor of several diet components. This interaction conditions intestinal homeostasis and favors the host-biota synergy, while stimulating a more effective local immune response (Stockinger *et al*., 2014; Mahringer *et al.,* 2018; Avilla *et al*., 2020).

The AHR-IL-22 axis (aryl-hydrocarbon-interleukin-22 axis) in the intestine plays an important role in the defense of the host against microbial pathogens. AHR signaling via IL-22 inhibits inflammation and colitis in the gastrointestinal tract of mice. The modulation of AHR pathways is an attractive therapeutical strategy (Monteleone *et al*., 2011; Murray *et al*., 2016; Boule *et al*., 2018; Cervantes-Barragan, and Colonna, 2018; Ehrlich *et al*., 2018). The evidence indicates that the indoles derived from the intestinal microbiota can alter the response to acute stressing factors. Indole derivatives may activate AHR to produce IL-22, pointing to an epithelial repair program (Powell *et al*., 2020), which along with the utilization of prebiotics and probiotics, could be useful to treat and control gastrointestinal diseases in pigs.

This paper aims to analyze the interactions between the aryl hydrocarbon receptor (AHR) and the microbiota (enhanced through probiotic use), which have improved the health and production indicators of pigs (litter and pre-fattening animals).

DEVELOPMENT

Swine production demands veterinary specialists with knowledge and practical skills to perform the task properly. Some farms, seeking higher yields, fail to meet the minimum basic requirements

in terms of facility, balanced diet, and zootechnical veterinary management (Barreto *et al.*, 2020a), which are associated with mortality losses and have a considerable negative impact (Barreto, Rodríguez, and Campal, 2020b; Rodríguez *et al.*, 2020). Consequently, they diminish the possibility of meeting the production parameters set for the pig industry at the end of the production cycle.

Pig enteropathies

Enteropathies are very frequent, they constitute a serious health problem for breeding and pre-fattening farms, with a significant influence on mortality as one of its first causes. In that context, multiple enteropathogens to which these animals are exposed since they are born, find the space to affect the most sensitive categories. Two of the main bacterial agents involved are *Escherichia coli* pathotypes (some of them zoonotic), and *Salmonella.* The enterotoxigenic *E.coli* (ETEC) pathotype causes enormous economic losses; the Shiga toxin-producer *E.coli* (STEC) pathotype causes post-weaning diarrhea, though hybrid strains have been isolated (ETEC/STEC), both from newborn and post-weaning diarrhea. The ETEC strains cause most cases and outbreaks of colibacillosis in intensive swine systems worldwide (Barreto *et al.*, 2020a; Guillén, and Ríos, 2020). Therefore, this *Escherichia* species is among the 40 pathogens that affect pigs with a gastrointestinal syndrome that targets suckling and weaned pigs (Barreto, Rodríguez, and Campal, 2020b; Guillén, and Ríos, 2020).

Moreover, septicemic salmonellosis in pigs is mostly caused by *Salmonella* serovar Choleraesuis, and by *Salmonella* serovar Typhimurium to a lesser extent; both types are zoonotic. In diarrheal manifestations, their order is generally inverted. They are also a significant cause of losses in swine production derived from treatments and failure to meet the sales agreements (Pastrana, Mogollón, and Rincón, 2014; Barreto, Rodríguez, 2012; Barreto *et al*., 2020a).

Salmonella is one of the most frequent causes of pig gastroenteritis in industrial countries. This agent gets in contact with consumers through the meat and derivatives, producing zoonosis. For years, pig products have been a significant source of salmonellosis in Camagüey. Pigs might be infected by an enormous quantity of serovars, but they may be clinically affected by *S.* Choleraesuis, *S.* Typhisuis, and *S.* Typhimurium (Rodríguez *et al.*, 2011; Barreto, and Rodríguez, 2012; Pastrana, Mogollón, and Rincón, 2014).

For years, the tendency to prevent these problems has been antibiotic supplementation in the diet (feeds) or direct administration to the animals. However, the utilization of antibiotics for prophylaxis and growth promoters, or as therapy, does not solve the problem. On the contrary, it alters the intestinal microbiota, which is critical for the development and later health state of the animals (Barreto, Rodríguez, and Campal, 2020b). Prebiotic and probiotic use, both commercially or as mixtures, such as efficient microorganisms (EM), or multipurpose autochthonous microorganisms (MAM), contribute to the development of microbiota in young animals, and its re-establishment following weaning stress (Barreto *et al*., 2015).

AHR and swine enteropathies

A receptor is a molecule or polymeric structure located on the surface or within a cell that recognizes and joins an endogenous compound. The binding sites are tridimensional structures that form sacs or sluts on the surface of proteins that enable specific interactions with compounds known as ligands, which are complementary molecules at the protein-biding site. The receptors have an effector system (also denominated as signal transduction pathways) (Rang *et al*., 2016; Riviere and Papich, 2018; Katzung and Trevor, 2019; Visovsky *et al.*, 2019).

An agonist is a substance that acts by activating or unblocking cellular receptors that cause changes and actions in the body's cellular function (response) (Rang *et al.*, 2016, Riviere and Papich, 2018; Katzung and Trevor, 2019; Visovsky *et al.*, 2019), therefore acting as receptors.

In the last 15 years, AHR has been reported to be involved in several physiological processes, such as cellular homeostasis, cell proliferation and differentiation, embryogenesis, carcinogenesis, inflammation, and host immunity (Rademacher *et al*., 2018). Recent studies reveal the molecular functions of AHR in the immunological system during the balance state, and during infection and inflammation (Zhu *et al.,* 2018). The intestine's capacity to regenerate through stem cell proliferation and differentiation of crypt stem cells continues to be critical in the repair of damaged epithelium and enabling pathogen response (Powell *et al*., 2020).

AHR resides in the cytoplasm, and upon binding to the ligand, it moves to the nucleus where it heterodimerizes with the AHR nuclear translocator (ARNT). The AHR trimer: ligand: ARNT binds the dioxin-response elements (DRE) of xenobiotic-response elements (XRE) in the regulatory regions of AHR target genes that include cytochrome P450-dependent Cyp1a1 monooxygenase activity, AHR repressor (AHRR), and IL-22 interleukin (Figure 1).

Reports have also been made of non-canonic AHR signaling pathways, whether at the genomic level by association with other transcription factors, such as the nuclear enhancer of kappa light chains of activated B-cell (NF-κB) or at the non-genomic level (for instance through the release of c-SRC kinase tyrosine) (Gutiérrez-Vásquez *et al.,* 2018; Lamas *et al.,* 2018; Wang *et al*., 2020). Apart from xenobiotics (including the 2,3,7,8-tetrachlorodibenzo-p-dioxin AHR prototype agonist (TCDD)), diet-derived AHR ligands have been identified, many of which are sub-products from tryptophan (Trp) metabolism (Hubbard *et al.,* 2015; Wang *et al*., 2020).

The trp metabolism in the intestinal microbiota generates AHR agonist ligands that sustain the development and maintenance of intestinal type 3 innate lymphoid cells. AHR signaling is also necessary for the maintenance of IL-22 expression by intraepithelial lymphocytes. IL-22 participates in the healing of wounds in the mucosa, and the production of anti-microbial peptides by intestinal epithelial cells. The AHR-IL-22 axis plays an important role in the defense of the host against microbial pathogens while providing resistance to these diseases (Cervantes-Barragan and Colonna, 2018; Ehrlich *et al*., 2018; Boule *et al.,* 2018) (Figure 2).

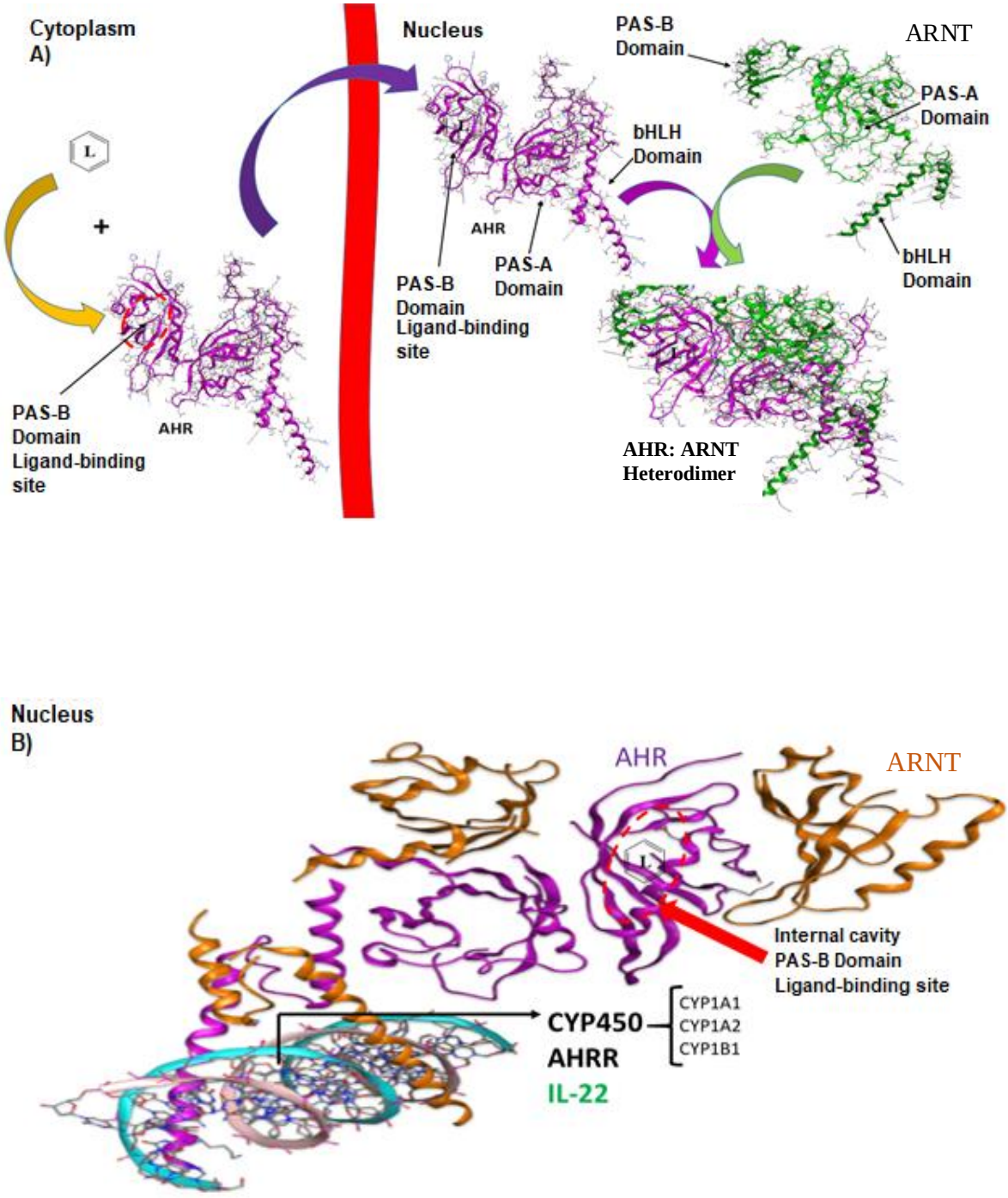

Figure 1. Sketch representation of the structural architecture of AHR and ARNT monomer interaction for the formation of the region associated with dimerization and ligand binding of the functional AHR heterodimer: ARNT modele by SwissModel (A), gene activation and protein synthesis following the binding to the DRE or XRE (B). L: AHR ligand.

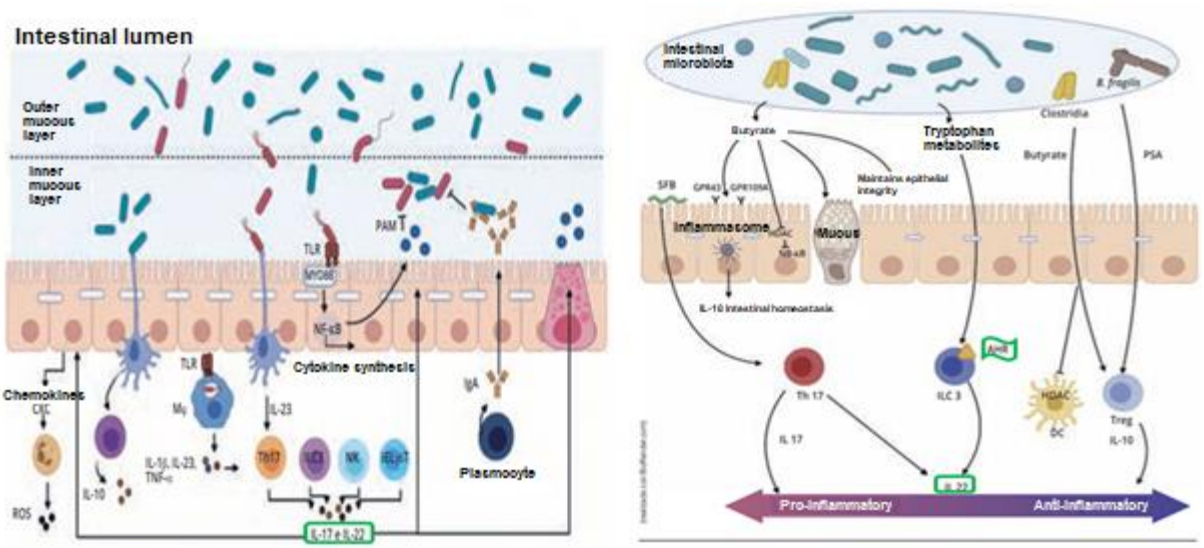

Figure 2. Sketch representation of receptor and ligand mediation in the modulation of the intestinal inflammatory response (Source: Czerucka, 2021).

The key role of AHR intestinal microbiota and immunity.

The gastrointestinal tract (GIT) has developed defense mechanisms against adverse environmental agents to which it is exposed orally (allergens, pathogens, etc.). The intestinal microorganisms influence the development and function of the immunological system. The rupture of this balance with the host may lead to immunological deregulation and contribute to the occurrence of chronic inflammatory and immune disorders (Álvarez *et al*., 2021). AHR is involved in the regulation of pro-inflammatory and tolerance responses, since AHR stimulates IL-22 production in intestinal immune cells (Bessede *et al*., 2014), and inhibits the inflammation induced by the experimental colitis, thus suggesting that AHR plays a key role in addressing the intestinal inflammation (Basson *et al.*, 2021) (Figure2). The suppressor effect is exerted through the production of anti-inflammatory cytokine IL-10 via AHR-associated c-SRC (Zhu *et al*., 2018).

Why are IL-17 and IL-22 important?

IL-22 is necessary for intestinal homeostasis. It is quickly induced in the intestinal mucosa as a response to IL-23, and the AHR activation to restore pathogen-caused damages or inappropriate post-weaning diets. IL-22 has been demonstrated to play a protective role in the infection caused by some pathogens, including vancomycin and *Plasmodium chabaudi resistant Klebsiella pneumoniae, Citrobacter rodentium*, and *Enterococcus.* One of the mechanisms through which IL-22 enhances the function of the mucosa barrier through the induction of antimicrobial proteins at that level. A function that partially explains its role in blocking intestinal niche commensals. For instance, in mice, IL-22 treatment reduced *Escherichia coli* abundance, regardless of the dose, which correlated to the drop observed in the serum endotoxin levels (Basson *et al.*, 2021).

The main function of IL-17 (also induced in IL-23 response) is to participate in the recruitment of neutrophils on the site of infection through chemokine induction CXC (they have an intermediate amino acid between the first two of four cysteines, like CXCL1 and CXCL8) (Soler, 2021), and by improving granulopoiesis, which explains their protective role during infection by a variety of pathogens (Figure 2).

Diet tryptophan ligands and metabolites that interact with AHR

The AHR ligands are classified into two physiological classes: xenobiotic and endobiotic. The xenobiotic ligands are compounds present in an organism where they do not originate. Their presence in the organism is foreign or from an outer source (Xeno). The common sources of xenobiotic ligands include dioxins and their congeners. On the contrary, the term endobiotic is used to indicate any AHR ligand that is easily produced by a particular biological system, including the gastrointestinal tract. Some widely studied endogenous ligands are 6-formylindolo[3,2-b]carbazole (FICZ), 2-(1H-indole-3-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), indigo, indirubin, and bilirubin (Avilla *et al.,* 2020).

The high-affinity prototype AHR agonist, xenobiotic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), shows a 10-fold affinity greater than the mouse AHR, compared to that of humans. On the contrary, the indole metabolites derived from the diet have a greater affinity to human AHR, possibly due to evolution (Hubbard *et al.*, 2015; Murray *et al*., 2016; Lamas *et al.*, 2018).

Among the endogenous AHR ligands, there are several tryptophan metabolic products, such as indirubin, kynurenine, and **6-formyl**-indolo[**3**, **2-b**]**carbazole** (**FICZ**). In addition to the tryptophan metabolites, in the 1980s, Lumichrome, a riboflavin metabolite, was identified as endogenous AHR ligands in rats. Besides, the products from heme degradation, bilirubin, and its metabolic precursor, biliverdin, are recognized as endogenous AHR ligands for directly active AHR transformation and the transcription of CYP isoenzymes. In a mouse model with hyperhomocysteinemia, it was found that lipoxin A4 (a metabolite from the arachidonic acid) increases AHR activity remarkably, and upregulates CD36 expression. These metabolites, along with tryptophan metabolites, have an important impact on homeostasis, by regulating AHR activity (Kawajiri and Fujii-Kuriyama, 2017; Hattori *et al.*, 2018; Larigot *et al.*, 2018; Wang *et al*., 2020; Furue *et al*, 2021; Goya-Jorge *et al.*, 2021; Kou, 2021).

The Trp is an essential amino acid obtained from the diet. The intestinal microbiota (*Lactobacillus reuteri* and *Allobaculum*) might catabolize tryptophan in indole derivatives, which are AHR agonists. In response, IL-22 production increases the protection against colon inflammation (colitis), since the bacterial enteropathogens are unable to degrade these derivatives (Marsland, 2016) (Figures 2 and 3).

AHR agonists derived from Trp

The Trp-derived AHR ligands include compounds like FICZ (6-formyl-indolo[3,2-b]carbazole), which is a very potent endogenous agonist ligand but requires the Tryptophan amino acid (Trp)

from the diet. It results from the Trp conversion by UV-dependent photo-oxidation or H_2O_2-mediated oxidative stress (Wincent *et al*., 2009). The next endogenous AHR agonist ligand identified was indirubin (2- (2-oxo-2,3-dihydro-1H-indol-3-ylidene)-1H-indol-3-one), but its synthesis requires tryptophan (Trp) from the diet. It results from Trp metabolism by the intestinal microbiota commensals and the host's hepatocytes. Indirubin was demonstrated to be more potent to activate human AHR than 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the prototype AHR agonist. Human AHR is also a more powerful agonist than murine AHR (Adachi *et al.*, 2001; Hubbard *et al.*, 2015). The third compound of this group is the ITE (2-(1H-indole-3-carbonyl)-thiazole-4-carboxylic acid methyl ester). The hypothesis is that it derives from the gastric conversion of glucobrassicin, a family of highly concentrated metabolites in cruciferous vegetables (broccoli, and Brussels), or from a condensation reaction between two amino acids, tryptophan, and cysteine. ITE is a potent AHR agonist, both *in vitro* and *in vivo*, and unlike 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), it does not induce toxicity (Henry *et al*., 2010; Hubbard *et al.*, 2015; Lamas *et al*., 2018). Lastly, the L-kynurenine (Beta-Antraniloil-L-Alanine) was the first subproduct of Trp metabolism, generated through the enzymatic kynurenine pathway. The L-kynurenine mode of action in AHR is still unclear. It could be a low-affinity AHR pro-ligand that transforms slowly into high-affinity compounds that act as AHR agonists at subnanomolar concentrations (Bessede *et al*., 2014; Hubbard *et al.*, 2015; Seok *et al.*, 2018; Wang *et al*., 2020) (Figure 3).

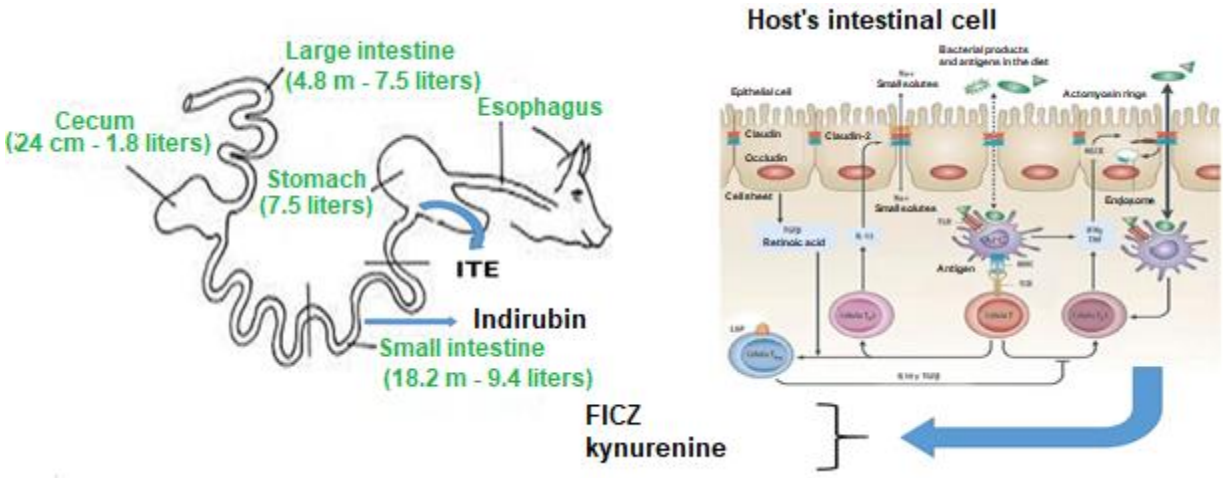

Figure 3: Formation signaling of tryptophan-derived metabolites (Sources: www.elsitioporcino.com; nutriNews, the journal of animal nutrition).

The convenient solution to restore the damage caused by pathogens or inappropriate diets consists in administering an adequate microbiota through the diet while lactating. Then, try to re-establish it at weaning, using liquid nutritional formulations that favor a quick re-establishment of microvilli, which is aided by prebiotics and probiotics; they offer feasible choices to any farm engaged in suckling and pre-fattening pigs (Barreto, Rodríguez, and Campal, 2020b).

A prebiotic is a substrate selectively used by microorganisms present in the host, and it offers benefits to health. This concept would apply to different substances, including carbon hydrates, polyunsaturated fatty acids, etc. (Álvarez *et al.*, 2021). In turn, probiotics are defined as living microorganisms that confer benefits to the health of the host when administered in the proper amounts. The microorganisms sold as probiotics include yeasts (*Saccharomyces, Kluyveromyces*), and bacteria of different genera (*Lactobacillus, Streptococcus, Enterococcus, Pediococcus, Bifidobacterium, Propionibacterium, Bacillus*), with proven benefits to particular health conditions (for instance, acute diarrhea) (Álvarez *et al.*, 2021).

Probiotics should have scientifically proven properties, such as 1) inhibition of intestinal and extra-intestinal pathogens; 2) inhibition of toxins derived from pathogens and feeds; 3) increase in nutrient uptake; and 4) the production of substances with bioactive effects on the host (Delgado, Barreto, and Rodríguez, 2014). Adequate nutrition supplemented with Trp-rich nutrients or derivatives previously mentioned has a stabilizing role in the microbiota and enhances the immune response against diseases caused by pathogenic agents in these stages of development and growth when they act on AHR. The utilization of prebiotics and MAM will improve the health and productive yields of the animals.

CONCLUSIONS

The AHR receptors are important in the restoration of damage possibly caused by pathogens or inappropriate diet in pigs after weaning, by increasing IL-22 and enabling the re-establishing and stability in the intestinal microbiota, which along with the utilization of probiotics, may lead to favorable responses of the production and health indicators of the litter and pre-fattening pigs.

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AUTHOR CONTRIBUTION

Author participation was as follows: Conception and design of research: OGCG, HdCRT, GBA, redaction of the manuscript: OGCG, HdCRT, GBA.

CONFLICT OF INTERESTS

The authors declare the existence of no conflicts of interest.