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Amino acid metabolism-mediated immune cell fate and function in pigs

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Review

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Abstract

Amino acids are fundamental to sustaining life. They are crucial for intracellular processes, such as energy metabolism, biosynthesis of nucleotides, and maintenance of oxidative homeostasis. These processes ensure the proper functioning of cells (including immune cells) and organs. Many studies have demonstrated that immune cells, as key players in immune regulation, have distinct amino acid demands, and their rapid growth and activation are shaped by amino acid availability in their microenvironment. In particular, the proliferation, maturation, and functional responses of innate immune cells are closely linked to amino acid metabolism. The transport, sensing, and mobilization of amino acids drive metabolic reprogramming to support these processes. Therefore, this review focuses on the influence of amino acids on the fate and function of immune cells across development, homeostasis, activation, and effector phases, highlighting the underlying mechanisms. It provides a scientific basis for improving disease resistance and production efficiency in animals.

Introduction

Amino acids are essential components that not only condense into peptides and proteins but also maintain the homeostasis of the immune system. Their influence on immune cell fate and functionality is multifaceted (Tomé 2021). On the one hand, amino acids provide the essential structural components and energy sources required for immune cell proliferation, differentiation, and functioning. On the other hand, immune cells have specific demands for amino acids. Processes like amino acid mobilization, uptake, and sensing drive metabolic reprogramming in immune cells, which affects their fate and functionality (Hope and Salmond 2021; Pearce and Pearce 2013). Studies have revealed that metabolic pathways of various immune cell types during origin, proliferation, differentiation, maturation, activation, and senescence differ significantly from those in resting states. For example, during an immune response to infections or environmental changes, immune cells transition into a highly active state characterized by elevated expression of amino acid transporters (Song et al. 2020). T cells serve as a representative example. When they become activated, they rapidly proliferate and upregulate the transcription and translation of key immune-related genes. This heightened activity accelerates amino acid metabolism to support the synthesis of essential macromolecules like proteins and nucleotides (Kaech et al. 2002).

Emerging research has revealed the link between dysregulated amino acid metabolism and various pathological conditions, such as metabolic disorders and immune dysfunction. In animal husbandry, amino acids are important feed components for livestock and poultry, effectively regulating immune dysfunction triggered by external or internal factors, thereby influencing disease resistance and survival rates (Bai and Plastow 2022). This is especially relevant under policies restricting antibiotic use and in the context of African swine fever, where amino acids, as key nutritional regulators, have become increasingly important in improving health and immune function in livestock such as pigs. Previous studies have suggested that serine and glutamine can influence the porcine T cells activity, improving host defense against pathogens (Chen et al. 2020; Ma et al. 2022; Ren et al. 2018; Shan et al. 2022; Yu et al. 2022; Zheng et al. 2023a). Research on amino acid metabolism pathways further highlights their role in regulating redox balance, gene expression in immune cells, and lymphocyte proliferation (Han et al. 2021; He et al. 2023; Muri and Kopf 2021; Zhang et al. 2020). For example, arginine supports the growth and proliferation of immune cells while contributing to the synthesis of key immune mediators, such as nitric oxide and cytokines, which are vital for modulating inflammation

and controlling autoimmune disorders (Martíi Líndez and Reith 2021). These findings illustrate the dynamic interplay between amino acid metabolism and immune cells, driven by signal transduction and metabolic reprogramming, which adapts to physiological and pathological conditions in animals. This provides an essential theoretical foundation for an in-depth understanding of how amino acid metabolism affects the immune cell fate and function and also opens new ways for the development of nutritional strategies to enhance animal immunity. Therefore, this review aims to focus on three key areas: (1) the mechanisms by which immune cells sense and selectively utilize amino acids; (2) the influence of amino acids on metabolic reprogramming in immune cells; and (3) the impact of amino acids on the function and fate of immune cells. Finally, we discuss future directions for research on how amino acid metabolism impacts immune cells, aiming to establish a theoretical basis that fosters integration between immunology and nutrition and expands the existing nutritional theories on amino acids.

Sensing and uptake of amino acids by immune cells

Mechanisms of amino acid sensing in immune cells

Rapamycin, a compound isolated from soil, exhibits antifungal and antitumor properties (Ghoname et al. 2022). In mammals, the mammalian target of rapamycin (mTOR) is a conserved serine/threonine kinase that senses environmental changes to regulate eukaryotic cell metabolism and growth (Mota-Martorell et al. 2020). This kinase forms two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The primary difference between these complexes lies in their unique scaffold proteins, with mTORC1 showing higher sensitivity to macrolide drugs like rapamycin (Fu et al. 2023). Activation of mTORC1 involves key metabolites, such as amino acids, glucose, and nucleotides, through signaling pathways involving small GTPases, such as Ras homolog enriched in brain (RHEB) GTPases (Kim and Kim 2016; Nguyen et al. 2017; Zhu and Wang 2020). At the molecular level, the Rag complex, consisting of heterodimers formed by RagA or RagB with RagC or RagD, collaborates with the Ragulator complex, which acts as a guanine nucleotide exchange factor for RagC or RagD. Together, these complexes facilitate the lysosomal translocation of mTORC1, a critical step that enables its activation by RHEB on the lysosomal surface (Groenewoud Marlous and Zwartkruis Fried 2013; Lama-Sherpa et al. 2023; Sancak et al. 2010; Tsujimoto et al. 2023). The regulatory mechanism of the Rag complex is further refined by the GTPase activating protein activity toward Rags 1 (GATOR1), which specifically targets RagA and RagB, modulating their activity (Shen et al. 2019). Its localization to the lysosomal membrane is mediated through its interaction with the Rag complex. This process is further regulated by the KICSTOR complex, a key assembly that includes SZT2, and by the GTPase activating protein activity toward Rags 2 (GATOR2) complex, which acts upstream to fine-tune the Rag complex activity (Cui et al. 2023; Valenstein et al. 2024; Zhao et al. 2023).

Some studies have demonstrated that immune cells sense amino acids through mTORC1, which relies on vacuolar-type ATPase on lysosomes (Wang et al. 2021d). Under conditions of sufficient amino acid availability, the vacuolar-type ATPase activates the guanine nucleotide exchange function of Ragulator, facilitating nucleotide exchange and activating Rag GTPases (Brady et al. 2016; Hertel et al. 2022). The activated Rag GTPases then recruit mTORC1 to the lysosomal membrane, positioning it near RHEB, which triggers mTORC1 activation (Carroll 2020; Gan et al. 2019; Sancak et al. 2010, 2008). Following its activation, mTORC1 localizes to the lysosome, where it phosphorylates 4EBP1. This phosphorylation event releases eIF4E, which initiates protein synthesis (Battaglioni et al. 2022; Clemens et al. 2013; Grosso et al. 2011; Wang et al. 2022). GATOR2 can inhibit GATOR1, but when arginine or leucine is present, the cellular arginine sensor for mTORC1 (CASTOR1) or Sestrin can bind GATOR2 in response to arginine or leucine, which relieves this inhibition (Jiang et al. 2023). Additionally, some studies have shown that a sensor of S-adenosylmethionine (SAM) (a metabolic product of methionine) upstream of mTORC1 (SAMTOR) can suppress mTORC1 by interacting with GATOR1, and binding of SAM to SAMTOR destroys this interaction (Kitada et al. 2020). Amino acids such as arginine and methionine play important roles in activating mTORC1 across various T-cell subsets (Abdullah et al., 2022). Key transporters, including L-type amino acid transporter 1 (LAT-1/SLC7A5) and SLC1A5, are critical for initiating mTORC1 signaling in naive, activated, and regulatory T cells (Tregs) (Grosso et al. 2011; Huang et al. 2020; Yang et al. 2022). During the first division of $CD8^+$ T cells, the asymmetric distribution of amino acid transporters changes how much mTOR accumulates in proximal and distal daughter cells, which eventually determines whether $CD8^+$ T cells become memory cells or effector cells (Arsenio et al. 2014, 2015; Cai et al. 2022; Chen et al. 2023; Pollizzi et al. 2016). Additionally, the Rag complex is indispensable for detecting amino acid levels and has been found to suppress regulatory T-cell function (Delmonte et al. 2020; Shi et al. 2019; Thangavelu et al. 2022; Zhu et al. 2024). Thus, immune cells sense environmental amino acid levels by regulating mTORC1 activity, reshaping their fate and functionality.

Immune cells also sense amino acids through general control nonderepressible 2 (GCN2), which detects tRNA that is not fully loaded with amino acids (Kim et al. 2020). Under normal conditions, tRNA that carries amino acids accumulates at ribosomes during protein translation, ensuring that the growing peptide chain receives enough amino acids (Englander et al. 2015). When amino acids are scarce, uncharged or unloaded tRNA accumulates in the cell. This accumulation leads to an overall slowdown in protein translation to save energy and resources, accompanied by a selective reduction in the translation of mRNAs that restore cellular homeostasis (Darnell et al. 2018). Excessive accumulation of uncharged tRNAs interacts with GCN2, causing a structural rearrangement that triggers downstream signaling pathways (Wu et al. 2019). Upon activation, GCN2 phosphorylates eIF2α at serine 51, which disrupts the assembly of the eIF2/tRNAiMet/GTP ternary complex, a crucial step in initiating protein translation (Kedersha et al. 2002) (Fig. 1). Previous studies have suggested that GCN2 activation negatively affects T-cell proliferation and Treg differentiation (Rashidi et al. 2020; Sonner et al. 2016; Zheng et al. 2023b). Studies on amino acid deprivation, such as those using indoleamine 2,3-dioxygenase to degrade tryptophan, have revealed that indoleamine 2,3-dioxygenase increases IL-10 production while reducing IL-12 expression in macrophages via a GCN2-dependent mechanism that inhibits protein synthesis (Battu et al. 2017; Yan et al. 2010). During apoptosis or exposure to apoptotic antigens, macrophages suppress IL-12 mRNA expression while increasing IL-10 transcript translation (Filardy et al. 2010). Additionally, the amino acid starvation response activated by halofuginone can suppress IL-1β production in macrophages through GCN2 activation (Battu et al. 2018). Collectively, immune cells can sense amino acids through both the GCN2 and mTORC1

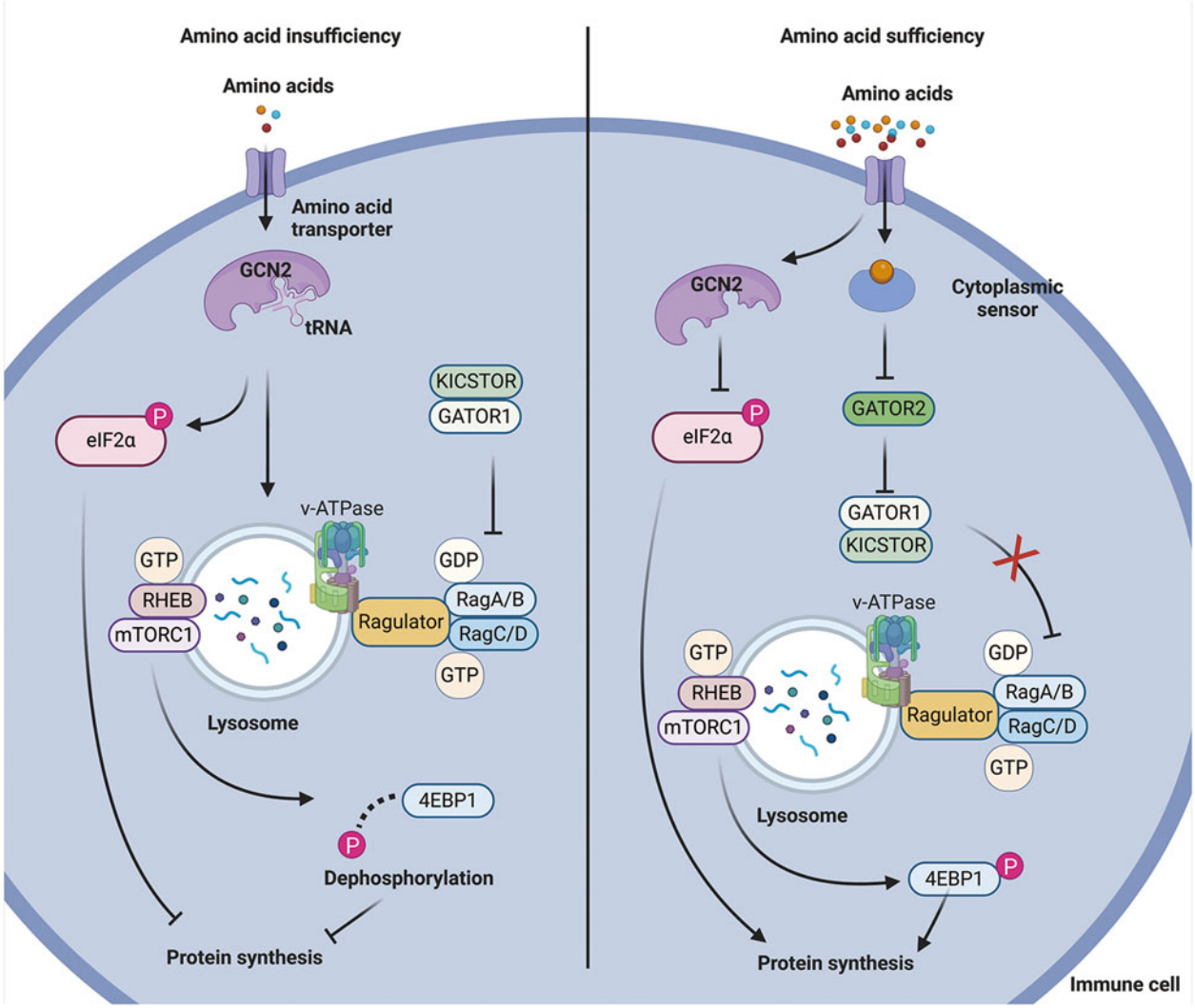

Figure 1. Mechanism of amino acid sensing by immune cells. When amino acid levels are low, uncharged tRNA activates GCN2, which interferes with the recruitment of mTORC1 substrates and blocks protein synthesis. In contrast, when amino acid levels are sufficient, cytoplasmic amino acid sensors inhibit GATOR1 through GATOR2, ultimately activating mTORC1 and promoting protein synthesis.

pathways, which allows them to regulate their fate and function based on amino acid availability.

Mechanisms of amino acid mobilization and uptake in immune cells

Amino acid mobilization and uptake are critical regulatory points that impact the significantly influence immune cell function and fate. These cells primarily acquire amino acids through transporters that move amino acids from the microenvironment into the cells (Almeida et al. 2016; Ma et al. 2024; Tae et al. 2023; Yang et al. 2023). Activation of the T-cell receptor (TCR) has been shown to trigger metabolic reprogramming in T cells, leading to changes in glycolysis, oxidative phosphorylation, and fatty acid β-oxidation pathways (Cammann et al. 2016; Marelli-Berg et al. 2012; Patsoukis et al. 2016; Xuekai et al. 2024). These metabolic changes rely heavily on amino acid availability and the corresponding transporters. The large amino acid transporter 1, also referred to as SLC7A5, forms a heterodimeric complex with the transmembrane protein CD98 (also known as SLC3A2) to transport large hydrophobic amino acids (Bröer et al. 2019). This transporter facilitates the uptake of seven essential amino acids, excluding lysine and threonine (Brunocilla et al. 2023). T-cell activation dramatically increases the expression of the LAT-1/CD98 complex, supporting antigen recognition and rapid clonal expansion (Cantor and Ginsberg 2012; Hayashi et al. 2013). Some studies have found that $CD4^+$ T cells with a knockout of the *Slc7a5* gene exhibit impaired antigen responses, with an inability to proliferate or differentiate into Th1 and Th17 subsets (Sinclair et al. 2013; Yeramian et al. 2006). These findings suggest the critical role of LAT-1 not only in early T-cell activation but also in guiding T-cell differentiation. In animal models of lupus and psoriasis induced by imiquimod (a TLR7 agonist), the absence or inhibition of LAT-1 significantly reduces IL-17 secretion and suppress the expansion of γδ T cells and $CD4^+$ T cells (Zhang et al. 2021b). Other amino acid transporters, such as SLC7A7, which forms complexes with CD98, are responsible for the transport of lysine, arginine, and other amino acids, highlighting the diversity and complexity of amino acid transporters in immune function regulation (Dai et al. 2021). Once amino acids

enter immune cells, the cells can recycle certain chemical groups to synthesize new amino acids (Yang et al. 2023). Lysosomes within immune cells also contain amino acid transport mechanisms as part of the self-protection system during starvation (Wang et al. 2021a). These lysosomal transporters are also crucial for immune functions such as the production of type I interferons in dendritic cells and immunoglobulin G synthesis in B cells (Akkaya et al. 2017; Jiang et al. 2018; Li et al. 2022; Montoya et al. 2002).

The asymmetric distribution of amino acid transporters is crucial in determining T-cell fate (Arsenio et al. 2014). When interacting with antigen-presenting cells, SLC7A5 displays a notable asymmetric distribution (Kedl et al. 2000). This distribution results in differing amino acid concentrations and metabolic activities between proximal and distal T-cell subsets, ultimately influencing immune cell function and fate (Pollizzi et al. 2016). In proximal daughter cells, high SLC7A5 expression promotes increased amino acid uptake, particularly glutamine, which supports rapid proliferation and high energy demand (Huang et al. 2023). Increased glutamine enhances glycolysis, providing abundant energy and carbon sources for biosynthesis. Additionally, glutamine contributes to α-ketoglutarate production, accelerating the tricarboxylic acid (TCA) cycle and enhancing metabolic activity and energy generation (Oh et al. 2020). Enhanced glycolysis and metabolic activity activate the c-Myc and mTORC1 signaling pathways, laying the molecular foundation for proximal daughter cells to differentiate into effector T cells. In contrast, distal daughter cells with lower SLC7A5 expression exhibit reduced amino acid uptake and metabolic activity, resulting in weaker metabolic activity. While this situation does not favor rapid cell proliferation, it does help the cells conserve energy and resources, preparing them for future reactivation and rapid responses. Consequently, these distal daughter cells tend to develop into memory T cells that survive long-term and can respond quickly when they encounter the same antigen again (Kaech and Cui 2012; Montacchiesi and Pace 2022; Pollizzi et al. 2016; Verbist et al. 2016). Overall, the uptake of amino acids and the asymmetric distribution of their transporters are decisive factors in T-cell function and fate, affecting both immediate immune responses and long-term functionality and survival.

T-cell development

The development of T cells occurs primarily in the thymus. Hematopoietic stem cells derived from the bone marrow differentiate into common lymphoid progenitor cells, which migrate to the thymus and further develop into progenitor T cells (Karsunky et al. 2008). These progenitor cells undergo TCR rearrangement and selection processes, giving rise to mature conventional αβ T cells as well as unconventional subsets such as γδ T cells, natural killer T cells (NKT), mucosal-associated invariant T cells, and thymic-derived regulatory T cells (tTreg) (Hoebeke et al. 2007; Liu et al. 2015). T-cell maturation progresses through distinct developmental stages, including double-negative (DN) and double-positive (DP) phases. The DN stage is further classified into DN1, DN2a, DN2b, DN3a, DN3b, and DN4 phases (Guha et al. 2020; Wang et al. 2021b; Yui et al. 2010). The transition from DN2 to DN3 determines whether pro-T cells differentiate into αβ or γδ T cells (Ciofani and Zúñiga-Pflücker 2010). Pre-TCR and Notch signaling in DN3a cells are crucial for β-selection and the subsequent development of conventional αβ T cells (Ciofani and Zúñiga-Pflücker 2010). Conversely, DN2 and DN3 cells exposed to elevated interleukin-7 (IL-7) signaling pathways are driven towards the γδ T-cell lineage (Saba et al. 2011). DP cells have the potential to differentiate into unconventional subsets, such as iNKT and tTreg cells (Wang et al. 2021c; Winter and Krueger 2019) (Fig. 2). In pigs, the composition of T-cell subsets differs significantly from other mammals. Some studies have shown that during late gestation in sows, the population of γδ T cells in embryonic blood and peripheral lymphoid tissues increases sharply, far exceeding the number of $CD4^+CD8^-$ and $CD4^-CD8^+$ T lymphocytes. This αβ-to-γδ T-cell ratio is distinct from what is observed in other mammals (Augustyniak et al. 2023; Bianchi et al. 1992; Le Page et al. 2022; Schalk et al. 2019). Some T cells in pigs may originate outside the thymus (Licence and Binns 1995). Previous studies identified mitotic T cells in the gastrointestinal epithelium of pigs, referred to as intraepithelial T cells (IEK) (Wiarda et al. 2020). Currently, research on unconventional T cells in pigs remains limited. Further studies on these cells could enhance our understanding of their roles in amino acid metabolism, disease prevention, and vaccine responses.

Immune cell metabolism

Once immune cells mature, they leave the thymus. When T cells are in a resting state and have not been activated by receptor engagement or cytokine signals, their metabolic demands remain low. They rely mainly on fatty acid β-oxidation and TCA cycle. The maintenance of this resting metabolic state in T cells requires external signals such as IL-7. When T cells encounter an antigen, they undergo dynamic metabolic, differentiating into effector T cells in a process known as metabolic reprogramming. The activated T cells switch their primary energy source from oxidative phosphorylation to glycolysis (Almeida et al. 2016; Kempkes et al. 2019). Although glycolysis produces less ATP per cycle compared to oxidative phosphorylation, it can generate ATP at a faster rate, work effectively in low-oxygen or acidic environments, and provide higher biosynthetic efficiency to help maintain redox balance (Choudhury 2021; Lees et al. 2017; Wang et al. 2020). Metabolites produced during glycolysis feed into the pentose phosphate pathway, which contributes to amino acid and nucleotide biosynthesis and generates nicotinamide adenine dinucleotide phosphate for reducing power (Ge et al. 2020). During the later stages of immune responses, a small subset of antigen-specific T cells persists as long-lived memory T cells (Xu et al. 2016). These memory T cells are characterized by an increased mitochondrial mass, which enhances their spare respiratory capacity and prepares them for rapid responses upon re-exposure to antigens (Li and Zhang 2020). Therefore, amino acid metabolism is an integral component of T-cell metabolism, providing intermediates that support these metabolic pathways and determining immune cell functionality (Almeida et al. 2016; Kelly and Pearce 2020; Wang and Zou 2020) (Fig. 3).

In addition to the metabolic distinctions between effector and memory T cells, various T-cell subsets exhibit unique metabolic characteristics. The differentiation of Th1, Th2, Th17, and Tregs is heavily influenced by cytokines such as interferon-γ (IFN-γ), interleukin-4, interleukin-6, and transforming growth factor-β, respectively (Barnes and Powrie 2009; Liu et al. 2015; Li et al. 2014, 2007a; Maloy et al. 2003; Marie et al. 2005; O'Shea et al. 2009; Tang et al. 2020). While Th1, Th2, and Th17 cells primarily rely on glycolysis for energy and biosynthesis, Tregs employ a mixed metabolic approach that integrates glycolysis, fatty acid oxidation, and oxidative phosphorylation (Kempkes et al. 2019; Ma et al. 2024) Interestingly, shifting the metabolic balance can alter

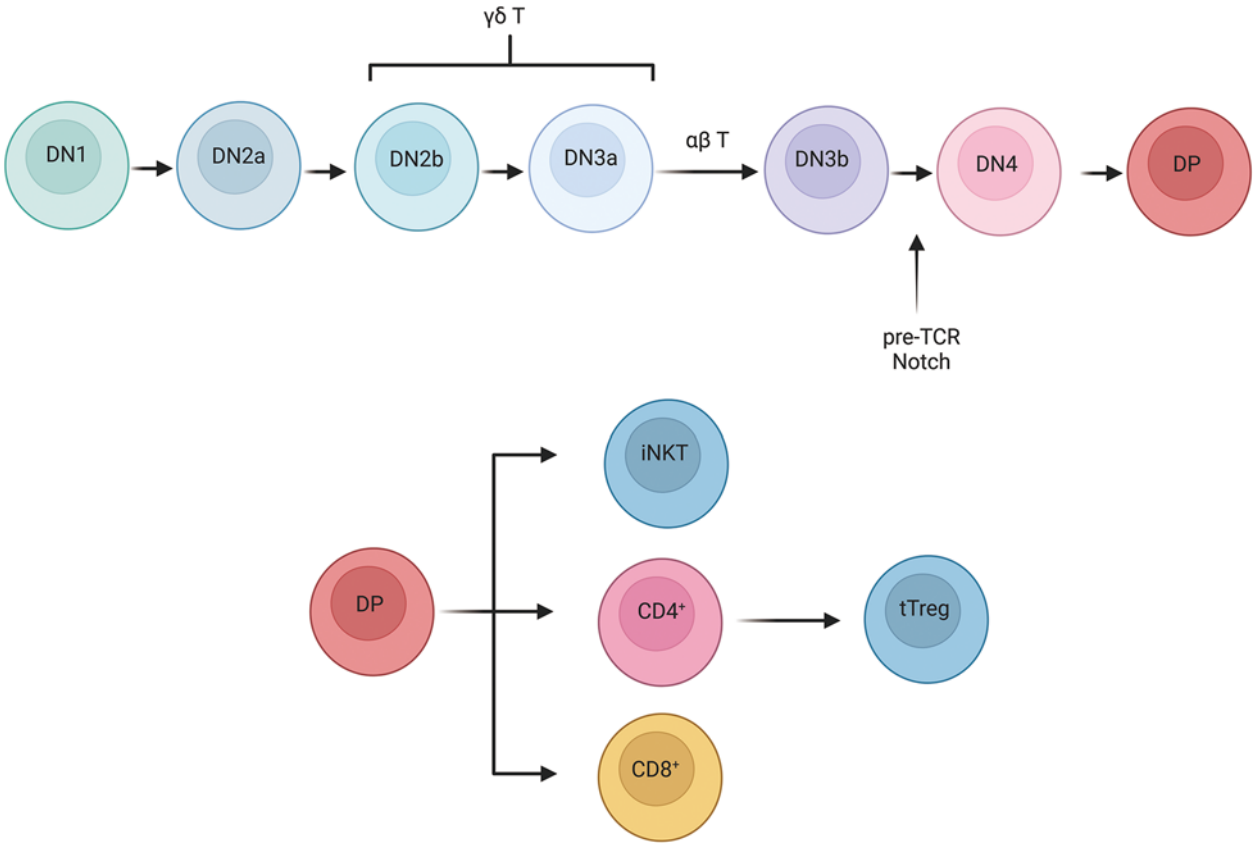

Figure 2. Development of T cells. T-cell development proceeds through a series of stages. DN1 cells can differentiate into B cells, myeloid cells, and innate T cells, while DN2b and DN3a cells can give rise to γδ T cells. At the DN3 stage, the pre-TCR complex-formed by TCRβ, pTα, and CD3 molecules-promotes β selection and drives the transition from DN3 to DN4. Both the pre-TCR and Notch signals are crucial for β selection and for the shift from the DN to the DP stage. After positive selection in the thymic cortex and negative selection in the thymic medulla, DP cells eventually differentiate into $CD4^+$ T cells, $CD8^+$ T cells, or iNKT cells.

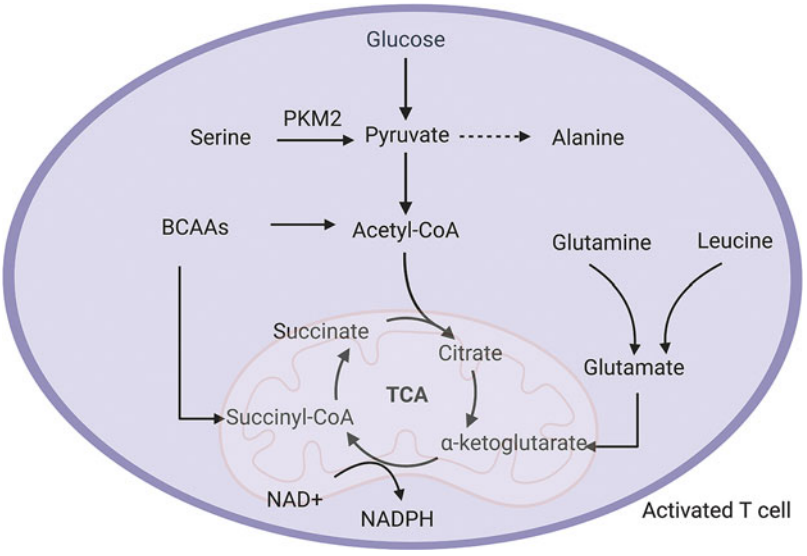

Figure 3. Amino acid metabolism in activated T cell. Serine is required for the production of cytokines in activated T cells with the help of the key glycolytic enzyme PKM2. Although pyruvate can be used to make alanine, activated T cells reduce the synthesis of alanine from pyruvate in order to conserve pyruvate metabolism and convert it into acetyl-CoA for TCA cycle activity. Branched-chain amino acids (BCAAs) provide the TCA cycle with the intermediate product CoA. Glutamine and leucine also contribute to the TCA cycle via glutamate to α-ketoglutarate.

T-cell differentiation. Inhibiting glycolysis during Th17 differentiation has been shown to favor the generation of Tregs (Barbi et al. 2013; Shi et al. 2011; Sun et al. 2017; Zhang et al. 2021a). Similarly, the addition of exogenous fatty acids to T-cell cultures significantly suppresses the production of cytokines associated with Th1, Th2, and Th17 cells, while having minimal impact on Tregs. Notably, this suppression of effector T cells by fatty acids cannot be reversed by the addition of cytokines that typically promote their differentiation (Allen et al. 2014; Michalek et al. 2011). Moreover, suppressing mTOR signaling to enhance fatty acid oxidation increases the number of memory T cells (Chi 2012; Pearce et al. 2009; Waickman and Powell 2012). These findings underscore

the fundamental metabolic differences between effector T cells and Tregs. Therefore, the study on amino acid metabolism-mediated T-cell fate and function has emerged as a hot and active topic in the present and future.

The impact of amino acid metabolism on immune cell fate and function

Glutamine metabolism-mediated immune cell fate

Glutamine and its metabolism are critical for the proliferation, differentiation, and activation of T cells by providing essential energy (Carr et al. 2010; Yaqoob and Calder 1997). Some studies have shown that in glutamine-free media, T cells predominantly differentiate into Tregs rather than Th17 cells, and prolonged glutamine deprivation exacerbates this effect (Edwards et al. 2021). Immune T cells rely on SLC38A2 to transport extracellular glutamine into the cell. Without this transporter, Th17 differentiation is significantly reduced, whereas the formation of Tregs remains unaffected (Zheng et al. 2023b). Within immune cells, glutamine metabolism requires the catalytic activity of glutaminase-1 (Gls1) to convert glutamine into glutamate. Th17 cells exhibit higher Gls1 expression levels than other T-cell subsets, with elevated intracellular levels of glutamate and α-ketoglutarate (a glutamate metabolite) (Kono et al. 2018). Previous studies have suggested that Gls1 deficiency reduces α-ketoglutarate levels, affecting chromatin states and gene expression, further inhibiting mTORC1 and IL-2 signaling, thereby impairing Th17 differentiation while promoting Th1 cell formation (Johnson et al. 2018; Lin et al. 2024). The dependence of Th17 cells on glutamine has been further demonstrated in Gls1-deficient mice. Inhibition of Gls1, either through pharmacological means or siRNA-mediated approaches, significantly reduces Th17 differentiation *in vitro* (Kono et al. 2018).

Glutamine also influences the activation, proliferation, and development of other immune cells. In M1 macrophages, it enhances the production of α-ketoglutarate, a key metabolite that drives the synthesis of IL-1β and supports inflammatory responses (Kolliniati et al. 2021; Palmieri et al. 2020). In M2 macrophages, glutamine contributes to the TCA cycle, supporting anti-inflammatory responses (Gupta and Sarangi 2023; Jha et al. 2015; Liu et al. 2017; Zhao et al. 2020b). Additionally, glutamine is vital for the activation and functionality of NKT cells and B cells. NKT cells use glutamine to synthesize glutathione and hexosamines, while B cells depend on it for antibody production (Jiang et al. 2018; Loftus et al. 2018). Overall, glutamine serves as a versatile metabolite that sustains the functionality and metabolic adaptability of diverse immune cell populations.

Branched-chain amino acids metabolism-mediated immune cell fate

In addition to glutamine, branched-chain amino acids (BCAAs) contribute to the TCA cycle and are involved in various biosynthetic processes. Through the generation of intermediates such as acetyl-CoA and succinyl-CoA, BCAAs provide essential substrates for the TCA cycle (Bo and Fujii 2025; Dimou et al. 2022; Neinast et al. 2019). During immune cell activation, neutral amino acid transporters, particularly SLC7A5/CD98, are significantly upregulated, serving as crucial mediators during pathogen infections and immune responses. In T cells, infections trigger elevated expression of SLC7A5, a process further maintained by IL-2 to ensure a constant supply of BCAAs (Almutairi et al. 2019; Kang et al. 2024; Sinclair et al. 2013). The inhibition of SLC7A5 has been shown to significantly reduce IFN-γ and IL-17 production, impairing the differentiation of Th1 and Th17 cells, while having minimal impact on the Tregs (Hayashi et al. 2013; Song et al. 2020). Loss of SLC7A5 in T cells also impairs mTORC1 and Myc-dependent glycolysis, affecting T-cell activation and proliferation (Marchingo et al. 2020). In macrophages, lipopolysaccharide (LPS)-induced inflammatory responses also activate BCAA transporters, with leucine transported by SLC7A5 being essential for glycolysis (Yoon et al. 2018). Similarly, CD98 expression is closely linked to the proliferation of immune cells and cytokine production. Plasma cells with high CD98 expression demonstrate stronger immune responses, longer lifespans, and increased antibody production (Cantor et al. 2009, 2011; Jensen et al. 2017; Nguyen et al. 2021; Robinson et al. 2022). The enzyme BCAA aminotransferase 1 (BCAT1) is integral to BCAA metabolism, catalyzing the conversion of BCAAs into branched-chain keto acids, which serve as precursors for TCA cycle entry. Inhibition of BCAT1 effectively reduces glycolysis and oxidative phosphorylation, thereby reducing the production of anti-inflammatory metabolites (Papathanassiu et al. 2017). These metabolic pathways not only drive short-term immune responses but also underpin the adaptive immune responses required for prolonged antigen exposure.

Serine metabolism-mediated immune cell fate

Serine regulates immune cell metabolic reprogramming, influencing their fate and function. It interacts with pyruvate kinase M2 (PKM2), enhancing glycolytic flux to provide energy for immune cells (Chaneton et al. 2012). Previous study has suggested that PKM2 activation in lipopolysaccharide-induced macrophages drives a shift toward glycolysis and speeds up IL-1β production (Bahiraii et al. 2022; Palsson-mcdermott et al. 2015; Xie et al. 2016). In $CD4^+$ T cells, activation of the TCR promotes the nuclear translocation of PKM2, increasing glycolysis and facilitating differentiation into Th1 and Th17 subsets. Inhibiting PKM2 nuclear translocation can limit the differentiation of these cells and reduce cytokine production, which helps slow the progression of multiple sclerosis (Angiari et al. 2020; Puckett et al. 2021; Traba et al. 2021). Additionally, limiting serine intake can reduce PKM2 activity, thereby lowering macrophage activation in atherosclerosis and decreasing LPS-induced IL-1β production (Liu et al. 2021; Shirai et al. 2016; Tabas and Bornfeldt 2020). Similar findings from our lab have demonstrated that LPS-treated piglet serum exhibits elevated IL-1β levels, which are reduced by dietary serine supplementation (Zhou et al. 2017). In a dextran sulfate sodium-induced colitis model, our study also indicated that adding serine lowered the levels or activity of proinflammatory cytokines in mice (Zhang et al. 2018). Additional research highlights the role of phosphoglycerate dehydrogenase (PHGDH), a rate-limiting enzyme in the serine de novo synthesis pathway, in macrophages. Inhibiting PHGDH increases NAD^+ levels and enhances the activity of NAD^+-dependent SIRT1/3, which promotes IL-1β production. PHGDH also supports Toll-like receptor 4 transcription via H3K9/27 acetylation and activates the NLRP3 inflammasome by facilitating acetylation of inflammasome components (Wang et al. 2024). Lack of serine can suppress IL-1β production in macrophages by inhibiting mTOR signaling (Chen et al. 2020; Shan et al. 2022). Moreover, our team was the first to discover that adding appropriate amounts of serine to sow diets during late pregnancy and lactation significantly increased antibody levels in both sows and piglets, raised the positive rate of $CD4^+/CD8^+$ cells, improved

the growth performance of nursing piglets and the reproductive performance of sows, and enhanced immunity in both sows and piglets (He et al. 2020). This suggests that serine may be a promising new feed additive for improving swine immunity. Additionally, serine supports mitochondrial metabolism through serine hydroxy methyltransferase 2 (Shmt2), essential for mitochondrial translation and respiration. Shmt2-deficient models exhibit severe respiratory defects (Tani et al. 2018). Serine-derived one-carbon units are crucial for nucleotide synthesis and methionine cycling, particularly in proliferating tissues. In Shmt2 null Jurkat cells, supplying one-carbon units can fix defects in mitochondrial respiration and translation, especially under low-glucose conditions, highlighting the vital role of this pathway in adjusting metabolic states (Minton et al. 2018). Moreover, serine is indispensable for T-cell proliferation and differentiation. The serine *de novo* synthesis pathway supports purine synthesis and one-carbon metabolism, while activated T cells upregulate key enzymes in this pathway to regulate immune responses and metabolism directly (Ma et al. 2017). In models of *Pasteurella multocida* infection, serine levels in the lungs significantly decrease. Supplementing serine in these mice reduces bacterial colonization and inflammatory responses, further demonstrating its critical role in immune regulation (He et al. 2019).

Sulfur-containing amino acids metabolism-mediated immune cell fate

Methionine plays multiple roles in regulating immune cell function and fate, primarily through its involvement in methylation processes. By providing SAM, methionine drives the methylation of biomolecules, which can promote or inhibit transcription by changing how DNA is accessed by transcriptional machinery. During T-cell activation, both repressive and activating histone methylation events occur frequently, facilitating transcriptional remodeling (Henning et al. 2018; Sinclair et al. 2019). Additionally, RNA methylation, particularly N6-methyladenosine modification, plays a pivotal role in maintaining T-cell homeostasis. The absence of this modification leads to defects in mRNA stability, splicing, and translation initiation, ultimately impairing T-cell proliferation and differentiation (Frye et al. 2018; Galloway et al. 2021; Li et al. 2017). Beyond transcriptional regulation, methionine metabolism has a profound impact on immune memory formation and function. The methylation of histones, RNA, and other cellular components relies on the availability of SAM. For example, Th17 cells starved of methionine or subjected to methionine cycle inhibition exhibit reduced H3K4 methylation, leading to decreased IL-17 production, while methionine restriction in Th1 cells similarly reduces IFN-γ expression. Additionally, dietary methionine restriction has been shown to reduce the number of IL-17- and IFN-γ-producing cells, thereby influencing immune responses in conditions such as experimental autoimmune encephalomyelitis (Roy et al. 2020).

Methionine not only participates directly in methylation reactions through its metabolite SAM but also supports immune cell function and proliferation through byproducts such as S-adenosylhomocysteine and further metabolic pathways. β-glucan-trained human peripheral blood mononuclear cells exhibit increased H3K4 trimethylation at cytokine and immune signaling gene promoters, enhancing cytokine production upon *Candida albicans* re-exposure (Quintin et al. 2012). Similarly, memory $CD4^+$ T cells show enriched histone marks associated with cytokines such as IL-17 and IFN-γ and transcription factors like T-bet, establishing a "primed" chromatin state that enables rapid cytokine production upon stimulation (Durek et al. 2016; Schmidl et al. 2018). Methionine transport is critical for these processes. Following antigen stimulation, T cells upregulate methionine transporters, including SLC7A5, to meet the increased demand for methyl donor production and protein synthesis, which are essential for T-cell differentiation and function. The balance between SAM and its byproduct, S-adenosylhomocysteine, also modulates histone methylation levels. Accumulation of S-adenosylhomocysteine due to disruptions in methionine metabolism can inhibit histone methylation, further suppressing immune gene expression. This metabolic-epigenetic interplay ensures that immune cells efficiently integrate nutrient availability with functional adaptation, reinforcing the role of methionine metabolism in maintaining long-term immune memory (Kelly and Pearce 2020).

Cysteine, another sulfur-containing amino acid, is vital for maintaining redox balance and methylation regulation. It serves as a key precursor for glutathione (GSH), one of the body's main antioxidants that control reactive oxygen species levels and preserve intracellular redox balance. In immune cells, methionine metabolism can generate cysteine. Beyond the regulatory roles methionine plays, cysteine also modulates immune cell responses through specific mechanisms: (1) antioxidant and cellular protection: Upon activation, T cells, B cells, and macrophages upregulate GSH synthesis, with cysteine providing the sulfur atom essential for this process. For example, LPS-stimulated macrophages produce high ROS levels, which are neutralized by GSH to prevent oxidative damage. (2) sulfur metabolism and translational support: Cysteine also contributes to iron-sulfur cluster synthesis, vital for mitochondrial electron transport chains and various metabolic enzymes. These clusters play a vital role in sustaining energy production and metabolic activity in T cells and macrophages (Fig. 4). Additionally, cysteine plays a role in post-translational modifications. The sulfur from cysteine is critical for tRNA thiolation, which facilitates efficient translation, particularly for proteins required in immune activation. Furthermore, iron-sulfur clusters derived from cysteine support mitochondrial metabolism and electron transport chain function, ensuring energy production for highly active immune cells. Therefore, sulfur-containing amino acids play indispensable roles in regulating oxidative stress, cellular metabolism, epigenetic control, and long-term immune memory.

Arginine metabolism-mediated immune cell fate

Arginine influences protein structure modifications and immune cell activity regulation through its metabolism. In the presence of SAM, arginine generates polyamines, highlighting the interdependence and centrality of arginine and SAM in immune cell metabolism (Puleston et al. 2019). Polyamine production signals sufficient nutrient supply, coordinates biosynthesis, and supports immune cell proliferation. Polyamines participate in producing rare amino acid derivatives critical for the post-translational modification of eukaryotic translation initiation factor 5a (eIF5a), a key regulator of translation elongation and termination (Pelechano and Alepuz 2017; Schuller et al. 2017). Inhibition of the polyamine-eIF5A-taillessin pathway suppresses oxidative phosphorylation-dependent M2 macrophage polarization, leading to a shift towards glycolysis-dependent M1 polarization (Puleston et al. 2019).

Other amino acids metabolism-mediated on immune cell fate

During immune cell proliferation and differentiation, nucleotides synthesis relies on amino acids such as aspartate and glycine.

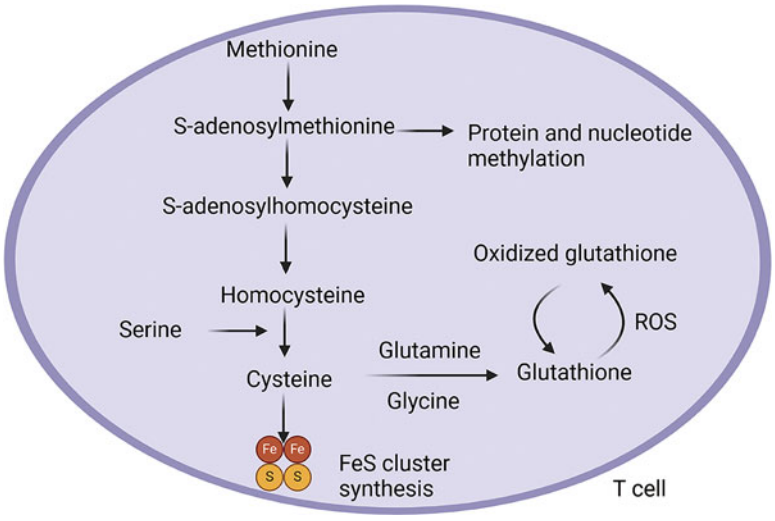

Figure 4. Sulfur-containing amino acids maintain redox status homeostasis in T cells. In T cells, methionine can be converted into cysteine. During this process, the intermediate S-adenosylmethionine donates methyl groups that modify immune effector proteins and nucleic acids, promoting cytokine gene expression in T cells and supporting innate and adaptive immune memory. Serine can also be transformed into cysteine, which contributes to the synthesis of the antioxidant glutathione and the formation of iron-sulfur (FeS) clusters.

Aspartate and serine-derived glycine provide carbon backbones for nucleotide formation (Lane and Fan 2015). Glycine plays a particularly critical role in the early stages of T-cell activation (Ma et al. 2017). Although glycine can convert to alanine, T cells typically use alanine for protein synthesis rather than glycolysis (Ron-Harel et al. 2019). Tryptophan's metabolic product, melatonin, can influence macrophage M1/M2 polarization (Xia et al. 2019). Additionally, melatonin regulates the activation and differentiation of T cells (Th17, Treg, and memory T cells) by activating calcineurin and the ERK1/2-C/EBPα signaling pathways (Ren et al. 2017a). Gamma-aminobutyric acid promotes the differentiation of intestinal Th17 cells and the expression of IL-17 during *E. coli* infection (Ren et al. 2017b). These functions, along with the broader immunomodulatory roles of amino acids, have been extensively summarized in previous reviews (Bhandage and Barragan 2021; Castellano and Molinier-Frenkel 2020; Liao et al. 2022; Stone and Williams 2023; Tantawy and Naguib 2019; Yang et al. 2023; Zhao et al. 2020a).

Challenges and practical considerations in pig farming

Despite the potential benefits of amino acid supplementation in improving immune function and growth performance in pigs, several challenges must be addressed for successful application in pig farming. Amino acid bioavailability is a key determinant of immune cell function and fate, as immune cells require optimal amino acid availability to support proliferation, cytokine production, and immune signaling pathways (Yang and Liao 2019). The absorption efficiency of amino acids depends on feed formulation, processing methods, and the presence of anti-nutritional factors. Arginine and glutamine play essential roles in immune regulation, supporting T-cell activation and macrophage function, but their bioavailability is highly dependent on feed processing and dietary composition (Fanimo et al. 2006; Sá et al. 2020; Wu et al. 2018). Feed formulation influences amino acid digestibility through ingredient selection, balancing essential and non-essential amino acids to meet metabolic demands (Buraczewska et al. 1999). Processing methods, such as extrusion and pelleting, can enhance amino acid bioavailability by breaking down cell walls and denaturing anti-nutritional proteins, but excessive heat treatment may degrade heat-sensitive amino acids like lysine and methionine (Ohh et al. 2002). Anti-nutritional factors, such as tannins and phytates in plant-based feedstuffs, can inhibit amino acid absorption by forming complexes with proteins, reducing enzymatic hydrolysis and intestinal uptake (Woyengo and Nyachoti 2013). Plant-derived protein sources contain fiber and phytates, which can lower amino acid digestibility and reduce their availability to immune cells, thereby impairing immune function (Myrie et al. 2008). Pigs (13-35 kg) fed a low-protein diet (13.9% crude protein) also impair T-cell activation and proliferation, suggesting that protein restriction can compromise immune resilience (Peng et al. 2016).

Amino acid metabolism also interacts with other nutrients, influencing immune homeostasis and inflammatory responses. Amino acid antagonism is a significant factor influencing nutrient bioavailability and immune regulation. For instance, excessive lysine intake can interfere with arginine absorption by competing for the same transporters, potentially reducing nitric oxide production and impairing macrophage-mediated immune responses (Li et al. 2007b). Similarly, an imbalance in BCAAs, particularly excessive leucine, can suppress isoleucine and valine uptake. Valine deficiency can reduce lymphocyte proliferation and hinder the growth of lymphoid tissue (Wang et al. 2023). Deficiencies in key vitamins, such as vitamin B6, which is involved in amino acid metabolism, can impair amino acid transamination processes, leading to reduced protein synthesis and weakened immune responses (Li et al. 2019).

Although amino acid fortification enhances immune resilience and growth performance in pigs, its cost-effectiveness remains a significant consideration. While synthetic amino acid supplements can improve the bioavailability of nutrients, they can increase feed costs, so the cost-effectiveness must be carefully evaluated (Ju et al. 2008). Future research should focus on optimizing dietary formulations that balance immune support with economic feasibility to maximize health and productivity outcomes in pig farming. Addressing these challenges through optimized feed strategies and targeted research will improve the practical implementation of amino acid-based nutritional interventions in pig farming, ensuring that immune cell function and fate are optimally regulated to improve disease resistance and overall health outcomes.

Gut microbiota, amino acid metabolism, and immune cell function in pigs

Gut microbes not only utilize dietary amino acids for microbial protein synthesis but also influence host amino acid availability through protein degradation and nitrogen recycling (Dai et al. 2011; Macfarlane and Macfarlane 2012). Specific commensal bacteria, such as *Bacteroides, Clostridium, Lactobacillus*, and *Streptococcus*, contribute to protein fermentation and enhance amino acid bioavailability by synthesizing essential amino acids that the host cannot produce (Dalmasso et al. 2008). In the small intestine, microbial protein synthesis is predominant, whereas in the large intestine, amino acid catabolism dominates, generating various metabolites such as ammonia, short-chain fatty acids and biogenic amines. These metabolites not only impact on intestinal health but also modulate host immune responses (Blachier et al. 2007; Collins et al. 2012).

Tryptophan is metabolized by gut bacteria into indole derivatives, such as indole-3-aldehyde, which activate the aryl hydrocarbon receptor in immune cells. Aryl hydrocarbon receptor activation induces IL-22 production, which enhances mucosal immunity and maintains gut homeostasis by promoting epithelial barrier integrity (Zelante et al. 2013). Additionally, Tryptophan metabolism leads to the formation of kynurenine, a metabolite that modulates immune responses by interacting with dendritic cells and macrophages, affecting cytokine secretion and T-cell differentiation (Ma et al. 2018). Glutamine is a critical amino acid for immune cells and intestinal barrier function. Gut bacteria metabolize glutamine into glutamate, which influences the gut-microbiome-immune axis by supporting intestinal epithelial renewal and regulating immune responses (Blachier et al. 2009). Arginine metabolism by gut microbiota also plays a key role in immune modulation. Certain bacteria convert arginine into ornithine and nitric oxide, both of which contribute to macrophage activation and pathogen clearance. Nitric oxide, produced by inducible nitric oxide synthase, is essential for immune defense, as it enhances macrophage antimicrobial activity and controls inflammatory responses (Kan et al. 2015). However, when gut microbiota composition is imbalanced, amino acid metabolism can generate harmful metabolites that impair immune function. For example, the overgrowth of proteolytic bacteria, such as certain *Clostridium* species, can lead to excessive production of ammonia and hydrogen sulfide, which negatively affect intestinal epithelial integrity and immune homeostasis (Blachier et al. 2007). However, there is currently little understanding of the basic mechanisms of the interactions between amino acids, the microbiome and immune cells. Future research should clarify their relationship in order to improve pig health and productivity.

Conclusion and perspectives

In recent decades, the relationship between amino acid metabolism and T-cell development and function has gained increasing attention. Although significant progress has been made, many fundamental issues remain unresolved. A deeper understanding is needed to elucidate how amino acid metabolism shapes the fate and function of immune cells across different mammalian species, particularly in livestock and poultry, where research remains relatively limited. While numerous studies have explored the impact of amino acids on T-cell activity and differentiation, the role of amino acid metabolism in maintaining or reprogramming effector cells is still not fully understood. Some studies have confirmed that dietary amino acids must be digested in the intestine and then undergo intracellular transformations before the body can utilize them. Simply adding amino acids to the diet may not allow them to be directed to specific sites to exert their corresponding effects. Immune cells exhibit distinct responses to amino acid perturbations, emphasizing the need to decode metabolic requirements in various tissues and physiological contexts. Another major challenge is converting our knowledge of how amino acids affect immune cell fate and function into precise and targeted therapies. Future studies targeting amino acid-specific signaling pathways in immune cells under different conditions will facilitate the development of targeted metabolic strategies for combating pathogens, tumors, and related diseases.

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