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Genetic determinism of fatty acid composition in liver, muscle, backfat and plasma and its link to immunocompetence and performance in pigs

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Fatty acids are a diverse group of lipid molecules that play essential roles in energy metabolism, cellular differentiation and signalling mechanisms. The objective of this study was to explore the genetic determinism of fatty acid composition across backfat, liver, muscle and plasma and its association with immunocompetence and performance traits in pigs. Fatty acid profiles were analysed in 432 commercial Duroc pigs. High heritability was found for most fatty acids in backfat and for long-chain polyunsaturated fatty acids in liver, while muscle and plasma showed medium to low heritabilities. Strong genetic correlations were observed between the relative abundance of γδ T cells and cytotoxic T cells with the lipid profiles of backfat and muscle, with opposite patterns between these cell types. Muscle unsaturated fatty acids were positively correlated with phagocytosis capacity and red blood cell traits, and negatively with plasma cortisol. Acute phase proteins showed similar correlations with liver lipids but opposite with some plasma fatty acids. Lean meat and fatness traits were particularly associated to the backfat fatty acid composition, showing opposite correlation patterns, while pH was strongly correlated with the liver fatty acid profile. These results demonstrated the specific lipid profiles of backfat, liver, muscle and plasma, their genetic determinism, and their relationships with immunity and production traits.

Keywords Fatty acid profiles, Heritability, Genetic correlations, Immunity, Pig

Fatty acids (FA) are a diverse group of hydrocarbon chains of varying length and can be divided into three main groups (saturated, monounsaturated, and polyunsaturated) based on the number of double bonds in their structure. From the production point of view, fatty acid composition affects the organoleptic attributes of pork, such as tenderness, juiciness, and overall palatability, and influences the nutritional quality of the meat[1,2]. Higher content of saturated fatty acids, such as myristic (C14:0) or palmitic (C16:0), increases fat firmness and improves the oxidative stability of the meat but is associated with an increased risk of cardiovascular diseases in humans[3,4]. Polyunsaturated fatty acids such as linoleic acid (C18:2n6) have the potential to improve human immune system by improving beta-cell function and reducing insulin resistance[5]. Due to that, genetic selection of the intramuscular FA content and composition has been promoted to improve meat quality while reducing unwanted saturated fat and, thus, obtaining a healthier product[6–8].

Physiologically, fatty acids play crucial roles in cellular differentiation, signalling, and metabolic homeostasis. Differences in chain length and degree of unsaturation are reflected in the diverse, and sometimes opposing, roles of these metabolites[9,10]. In recent years, increasing efforts have been made to study the importance of lipid

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species and their metabolic interactions and pathways in the proper activation and modulation of the immune response[11,12]. Chen et al.[13] showed that theaflavin disruption of African swine fever virus replication may be caused by the downregulation of several lipid metabolic pathways. Moreover, the replication of pathogens such as PRRS virus and porcine parvovirus has been proved to be mediated by lipid metabolism and lipid droplet formation[14,15]. Fatty acids are essential components of cell membranes, where they play a key role in maintaining membrane integrity and fluidity. Lipids are heterogeneously distributed along the plasma membrane and are susceptible to alterations in cellular activity[16]. It has been proved that lipid metabolism is highly involved in the activation and differentiation of immune cells[17–19]. For instance, the activation, differentiation, and proliferation of T and B lymphocytes are influenced by the choice of metabolic pathway and their interaction with circulating FAs[20–22]. In general terms, saturated fatty acids and unsaturated omega 6, such as linoleic, γ-linolenic (C18:3n6) and arachidonic (C20:4n6) acids, promote the proliferation and activation of the pro-inflammatory response in T cells, while the omega-3 unsaturated FAs reduce proliferation and promote polarization into anti-inflammatory T cell subsets[23,24]. B cell survivability is dependent on the correct activation and regulation of mitochondrial OXPHOS and TCA metabolic pathways[25,26]. Additionally, lipoxins, resolvins, protectins and maresins, which are derived from polyunsaturated fatty acids, increase B cell differentiation towards antibody secretion[26,27].

Eicosanoids are endogenous bioactive lipid mediators synthesized from the oxidation of arachidonic acid and the omega 3 eicosapentaenoic (EPA; C20:5n3) and docosahexaenoic (DHA; C22:6n3) acids, playing a role in regulating various inflammatory and homeostatic processes[28,29]. Higher intake of omega-3 fatty acids has been proved to improve the general immune response of pigs, and even increase the quality of sows' colostrum resulting in a better growth performance of piglets[29,30]. Saturated fatty acids, such as palmitic acid, have been proved to promote the inflammatory response of macrophages, dendritic, and mast cells by activating nuclear factor kappa B signals through the TRL4 ligand[31] or, as recently suggested, by directly altering the cellular lipidome and, thereby affecting their phenotype[32].

In recent years, the introduction of immune markers and health-related traits into selection indices has been proposed as a promising method to enhance the immunocompetence of pig populations[33,34]. Therefore, considering the significant role of long chain fatty acids both as immunomodulators and as an energy store, selecting for specific FA profiles could improve the immune response in pigs, as well as backfat and intramuscular lipid profiles. Furthermore, the identification of FAs as biomarkers associated with health-related traits and pork quality, could facilitate more targeted breeding strategies, enhancing overall herd resilience and health without impairing production traits.

The goal of this study is to unravel the genetic determinism of the fatty acid profile in plasma and three different porcine tissues from a commercial Duroc population, as well as to explore their link to the immunocompetence, welfare and productivity of the pigs.

Results

Descriptive statistics and phenotypic correlations of the lipid profiles

The lipid profile of backfat, liver, muscle, and plasma samples was previously analysed in a commercial Duroc population[35]. In this study, compositional data comprising 15 fatty acids and 11 indices, although γ-linolenic and n3-docosapentaenoic (n3-DPA; C22:5n3) acids were not detected in the plasma samples, were used for further analysis. Cofactor analyses revealed differences between sexes and batches in the FA composition of backfat, liver and muscle, whereas plasma FA profile only showed differences across batches. Also covariation with backfat thickness was observed for FA composition of backfat.

Estimated pairwise phenotypic correlations ($\mathbf{r_p}$) between all FA and indices within plasma and tissues (Fig. 1) revealed differences in the map of associations in plasma and the three analysed tissues. The lipid profile of muscle presented the highest number of correlations above the threshold (rp > |0.2|). Two opposed groups of highly linked FA were observed: one conformed by polyunsaturated FA (both N3 and N6 FA), positively correlated with each other, and a second group formed by the palmitic, palmitoleic (C16:1n7) and oleic (C18:1n9) acids, jointly with the global content of MUFAs and SFAs. In muscle, the relative abundance of stearic (C18:0) and myristic acid did not correlated relevantly with other FA. These opposed correlation patterns in muscle were also reflected in the respective indices: PUFA, the unsaturation index (UI), and the average chain length (ACL) followed the pattern of the first group, whereas SFA and MUFA showed the pattern of the second group. The backfat lipid profile showed similar but weaker associations between several PUFAs, oleic and palmitic, but stearic was very negatively associated to MUFA content (particularly 18-carbon MUFAs). In liver, the cluster of SFAs and MUFAs positively correlated between them gathered the myristic, palmitic, palmitoleic, cis7-hexadecenoic (C16:1n9) and oleic acids. This group of lipids was negatively associated to stearic, dihomo-γ-linolenic (C20:3n6), arachidonic, n3-DPA and DHA. Finally, few and weak phenotypic correlations between lipids were observed in plasma.

Phenotypic correlations of FA profiles across plasma and tissues were also estimated (Supplementary Table S1). Relative abundance of a particular FA in plasma or in one specific tissue was not necessarily correlated with its abundance in other tissues or in plasma. However, relevant associations were found between the FA profile of liver and backfat. A strong correlation pattern was found for the abundance of cis-vaccenic (C18:1n7) acid in liver, positively correlating to the abundance of all four MUFAs, α-linolenic (C18:3n3) and γ-linolenic, and negatively to palmitic and stearic in backfat. The relative abundance of stearic acid in muscle also correlated with the backfat lipid profile, showing positive correlations with the abundance of palmitic and stearic acids in backfat, and negatives with MUFAs content, specially the oleic and cis-vaccenic acids. Fewer and lower phenotypic correlations were observed in the rest of across-plasma and tissue comparisons, especially for those correlations involving the plasma profile.

The phenotypic relationships between FAs content in the backfat, liver, muscle and plasma and the haematological and immunity traits were also analysed. Overall, we observed low phenotypic correlations

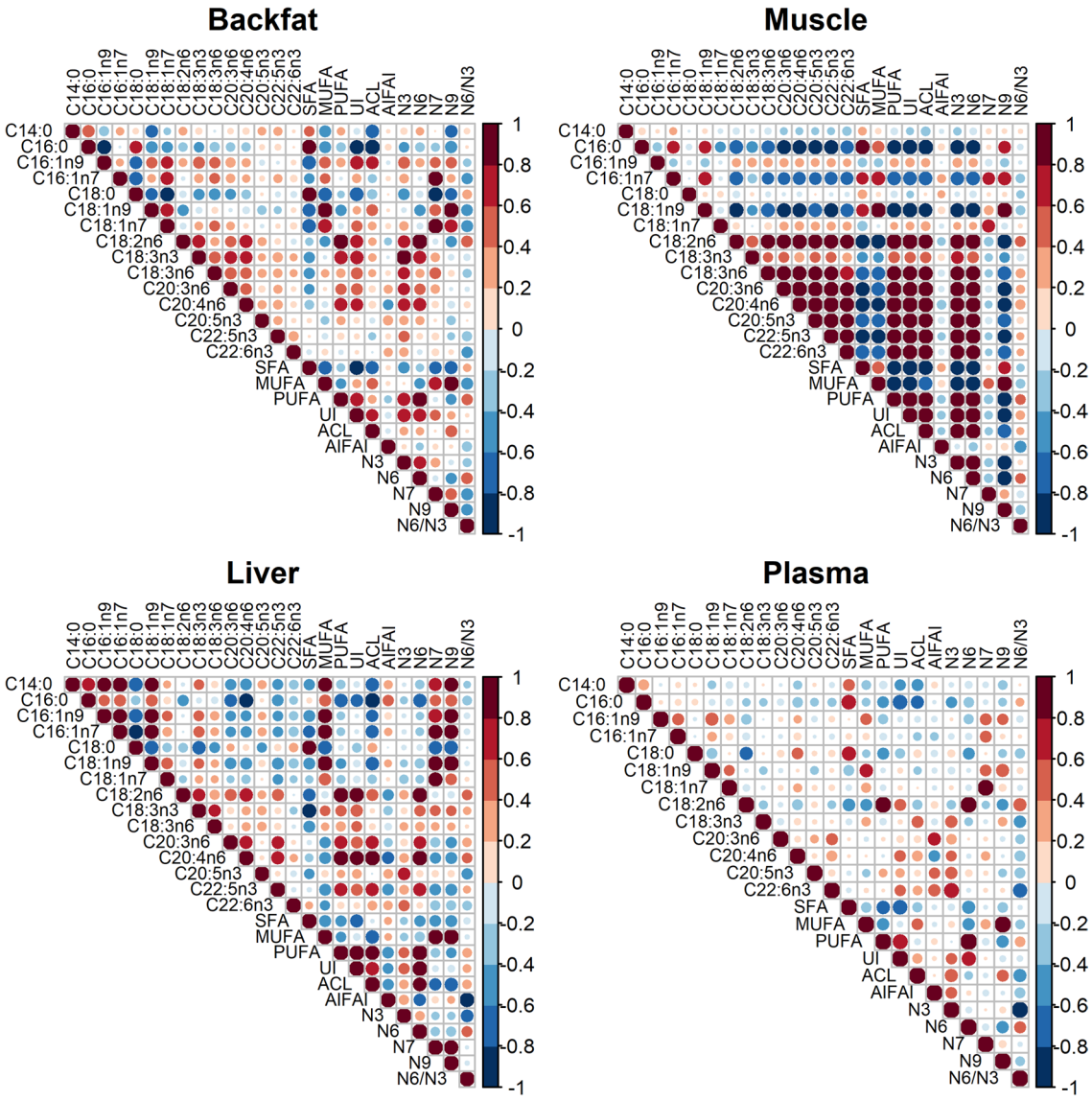

Fig. 1. Heatmap depicting phenotypic correlation coefficients estimated by pairwise combination among the residuals of the lipid components and indices in each tissue (liver ($n = 369$), backfat ($n = 368$), muscle ($n = 345$) and plasma ($n = 349$)). Circle size and colour intensity mark the level of association.

(Supplementary Table S2); only 150 out of 634 significant correlations passed the threshold ($r_p > |0.2|$). Backfat tissue showed the highest number of relevant associations with health-related traits, followed by liver, muscle and plasma. The top correlation was found between IgM levels in plasma and the N6/N3 FA ratio in backfat ($r_p = 0.44$). A group of negative associations was formed between the plasma concentration of immunoglobulins (IgA, IgM and IgG) and the palmitoleic, cis-vaccenic, γ-linolenic, and the omega 3 α-linolenic, n3-DPA and DHA fatty acids in backfat. This pattern of correlations with Ig measurements was also observed in liver for cis-vaccenic, α- and γ-linolenic, with the addition of cis7-hexadecenoic acid. In muscle, we observed that six polyunsaturated fatty acids (PUFAs; C18:3n6, C20:3n6, C20:4n6, C20:5n3, C22:5n3 and C22:6n3) had similar positive associations with phagocytic capacity (PHAGO_FITC) and granulocytes phagocytic capacity (GRAN_PHAGO_FITC) traits.

Focusing on carcass and meat quality traits, they were highly associated to the FA profile of backfat tissue at the phenotypic level (Supplementary Table S2). Two opposed patterns of associations with FA were observed, with the lean meat and loin depth measurements correlating with the different FAs inversely to the fat deposition traits (Fig. 2). Lean meat traits were positively correlated to cis7-hexadecenoic, palmitoleic, cis-vaccenic, linoleic, α-linolenic, γ-linolenic, dihomo-γ-linolenic and arachidonic acids abundances, whereas fat measurements were positively associated with the saturated palmitic and stearic fatty acids. With the exception of monounsaturated N7 fatty acids, carcass weight showed a correlation pattern similar to fatness traits. While liver tissue had few but some significant correlations, with cis-vaccenic acid maintaining the previous correlation pattern, neither muscle

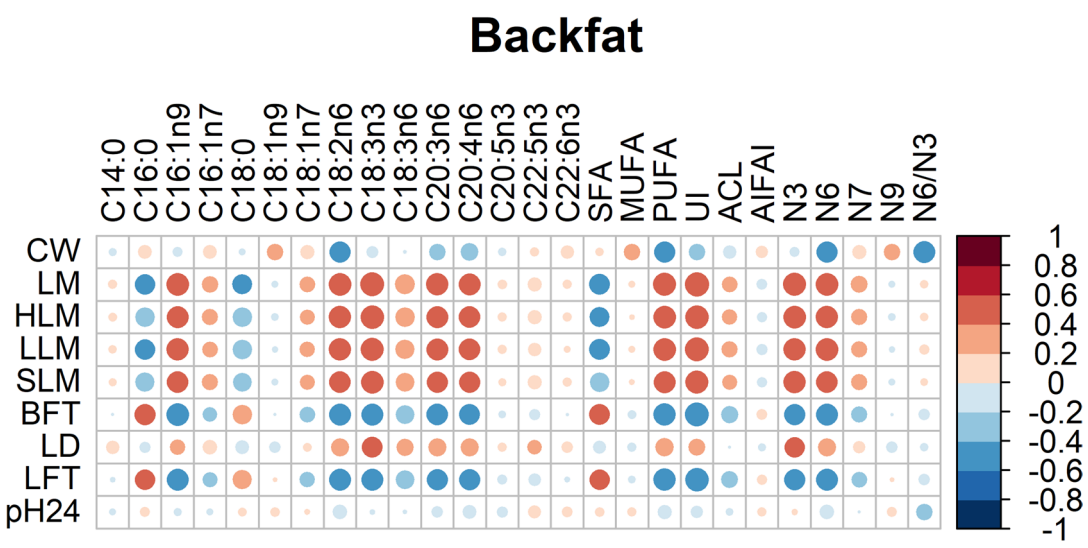

Fig. 2. Heatmap depicting phenotypic correlations between the residuals of the lipid profile in backfat (columns) and carcass and meat quality traits (rows) in pigs ($n = 368$). Circle size and colour intensity mark the level of association. Abbreviations: CW = carcass weight; LM = lean meat percentage; HLM = ham lean meat percentage; LLM = loin lean meat percentage; SLM = shoulder lean meat percentage; BFT = backfat thickness; LD = loin depth; HFT = ham fat thickness; pH24 = pH in semimembranosus at 24 h post-mortem.

nor plasma FA profiles showed any significant association to carcass and meat quality traits (Supplementary Table S2).

Genetic determinism of fatty acid traits

The estimated heritabilities ($\mathbf{h^2}$) for the FA compositional traits of plasma and the three analysed tissues are shown in Fig. 3. Heritability estimates ranged from 0.06 to 0.90, showing considerable variation between FA and, especially, across biological compartments. High heritability values (ranging from 0.42 to 0.90) were obtained for most fatty acids in backfat, with the exception of EPA and n3-DPA. In liver, long polyunsaturated fatty acids showed medium to high heritability ranges ($h^2 = 0.68–0.94$), especially for γ-linolenic. Conversely, low to medium h^2 estimates were found for the FA composition in both muscle and plasma.

Genetic correlations of the fatty acid profiles

The within-tissue/plasma FA correlation pattern at the genetic level (Fig. 4) was found to be closely similar to those at phenotypic level. In muscle, different PUFAs correlated positively with each other while were negatively associated with palmitic, palmitoleic, and oleic acids. Meanwhile liver displayed consistent opposing genetic correlations of PUFAs with SFAs and MUFAs, with the exception of stearic acid. Muscle and liver tissues showed a greater number of highly-probable correlations across the different FA compared to backfat and plasma.

Higher and more significant correlations of the lipid profiles across plasma and tissues were observed at genetic (Supplementary Table S3) than at phenotypic level. Muscle presented the largest number of highly probable genetic correlations with the lipid profiles of the other sample types, especially with liver and plasma. The PUFAs abundance in muscle showed positive correlations with myristic, cis7-hexadecaenoic and oleic fatty acids, and negative correlations with arachidonic acid and n3-DPA abundances in liver. The negative association of muscle PUFAs with arachidonic content was also observed in the plasma profile, jointly with negative correlations with stearic, cis-vaccenic and DHA fatty acids. In contrast, when comparing the lipid profiles of muscle and adipose tissue, the relative abundance of DHA in backfat showed positive correlations with PUFA, and negative correlations with palmitic, palmitoleic and oleic fatty acids. In adipose tissue, the relative abundance of linoleic and α-linolenic acids showed similar correlations with liver and plasma FA profiles, positive with MUFA and SFA (with the exception of stearic) and negative with arachidonic, EPA and DHA.

Estimated genetic correlations ($\mathbf{r_g}$) between FAs profile of backfat, liver, muscle and plasma and the health-related traits can be shown in Supplementary Table S4. In general, the estimated posterior correlations at the genetic level were significantly stronger than phenotypic correlations but had larger standard errors due to the limited population size. When setting a probability threshold, the genetic study revealed a total of 1,144 correlations with a probability higher than 0.7 of being higher than 0.2 or lower than −0.2. Results are summarized in Fig. 5.

The backfat reported the major number of relevant genetic associations with health-related traits, with a total of 326 highly probable correlations. From them, the relative abundance of naïve T cells and cytotoxic T (CTL) cells were found to be the traits most correlated with the FA compositional phenotypes of backfat, showing opposite correlation profiles. On the one hand, naïve T cells reported positive correlations with palmitic, stearic, EPA and DHA acids, and negative correlations with palmitoleic, oleic, cis-vaccenic, linoleic and to a lesser degree with α-linolenic acids, being those correlations reflected in the corresponding indices. On the other hand,

Fig. 3. Violin plot for the distribution of heritability estimates for the abundance of the studied fatty acids per tissue (liver ($n = 369$), backfat ($n = 368$), muscle ($n = 345$) and plasma ($n = 349$)).

CTL cells positively correlated to cis7-hexadecenoic, palmitoleic, cis-vaccenic linoleic, α-linolenic, γ-linolenic, arachidonic acid, PUFA, UI, ACL, and the unsaturated N3, N6 and N7 FA indices, and was negatively correlated to palmitic, stearic, the SFA count and the anti-inflammatory fatty acid index (AIFAI). Another group of strong correlations was found for EPA acid abundance, which was positively correlated to MCHC and platelets count, and negatively to HB, erythrocytes count, and cortisol concentration in hair (CORThair). Focusing on the acute stress markers, cortisol levels in plasma (CORTplasma) presented the strongest genetic correlation with the DHA acid ($r_g = -0.92$, $P = 0.74$) and also high negative correlations with γ-linolenic, arachidonic and n3-DPA acids. Lastly, palmitoleic, cis-vaccenic, dihomo-γ-linolenic and γ-linolenic acids shared similar positive correlations to the quantity of monocytes, neutrophiles and total leukocytes in the white blood cells counts.

The next tissue whose FA profile was most associated with immunity traits was liver, with a total of 306 genetic correlations with $P > 0.7$. In this tissue, CRP was revealed to be the trait with the greatest number of highly probable correlations, being positively associated to myristic, palmitic, palmitoleic, oleic and α-linolenic acids, and the different monounsaturated indices, and negatively to γ-linolenic, arachidonic, EPA, n3-DPA and DHA acids, UI, ACL and the polyunsaturated indices. Eleven of these FA were also correlated with haptoglobin levels in serum. Other immunity traits highly associated with liver FA profile were the percentages of T helper and naïve T cells, which shared positive correlations with EPA, n3-DPA, ACL and the unsaturated N3 FA index, and negative ones with palmitoleic acid and the unsaturated N7 index. The relative abundance of memory T-helper cells showed strong positive correlations with linoleic and n3-DPA acids, PUFA and unsaturated N6 index and negative correlations with cis-vaccenic and EPA acids, AIFAI and the N7 fatty acid index.

The FA composition of muscle showed 265 highly probable associations with the health-related traits. Two main groups of similarly correlated traits were formed. Nitric oxide (NO), the percentage and function of several phagocytic cells, along with the haematologic traits MCV, MCH, and MCHC, were found to be positively correlated with different PUFAs, ACL, and unsaturation indices PUFA, UI, N3 and N6, while showing negative correlations with myristic, palmitic, oleic and cis-vaccenic acids, SFA, MUFA, N7 and N9 indices. CORTplasma and IgM concentrations also showed a similar pattern of correlations with several of aforementioned FA traits. Positive genetic correlations of N7 abundances with HP, LEU, NEU and CTL cells, as well as negative correlations

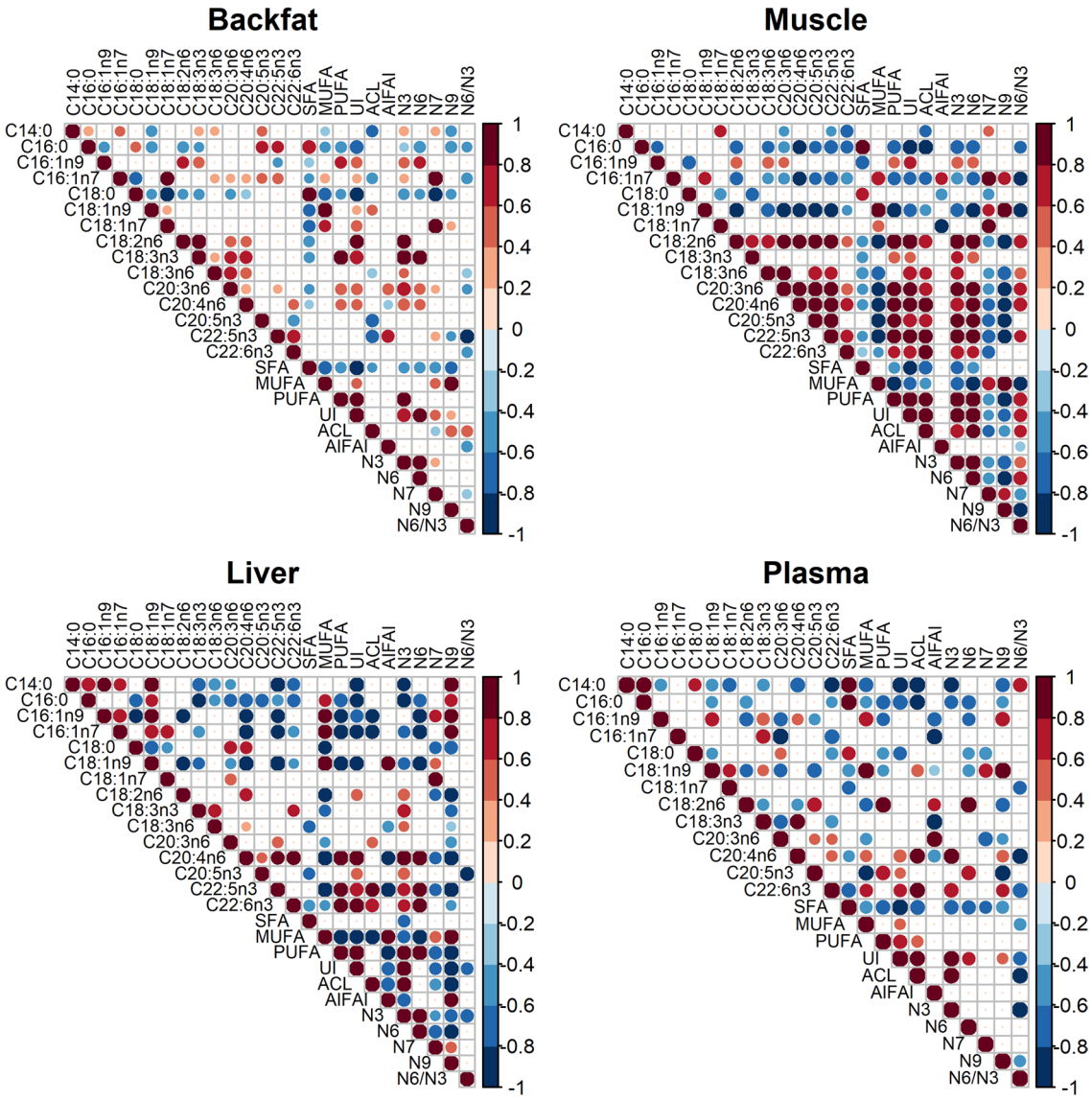

Fig. 4. Heatmap depicting genetic correlation coefficients with a probability higher than 0.7 of being higher than 0.2 (for the positive) or lower than −0.2 (for the negative) estimated by pairwise combination among the lipid components and indices in each tissue (liver ($n = 369$), backfat ($n = 368$), muscle ($n = 345$) and plasma ($n = 349$)). Circle size and colour intensity mark the level of association.

with γδ T cells, NO, memory T cells, T helper cells, and naïve T cells, were detected with high probability not only in muscle but also in liver, plasma, and/or backfat.

Lastly, plasma FA profile showed the fewest number of highly probable genetic associations with immunity traits, with 247 correlations having $P > 0.7$. Despite that, the linoleic acid abundance in plasma showed strong genetic correlations with the percentage of T cells γδ T cells and naïve T cells, while the opposite association (i.e. negative correlation) was observed with the percentage of B cells. Also, strong but negative associations were obtained between haptoglobin and the cis7-hexadecenoic, palmitoleic, oleic, cis-vaccenic, α-linolenic, N7, N9, and the MUFA indices, and positive with myristic, dihomo-γ-linolenic, EPA, DHA, the anti-inflammatory index, the N3 and SFA indices. CORTplasma showed negative correlations with the plasma abundance of myristic, palmitoleic and oleic acids, and positives with linoleic and DHA contents, inversely to the associations observed with muscle FA profile.

Estimated genetic correlations between the FA profiles of the different sample types and carcass quality traits are summarized in Fig. 6. Backfat was the most correlated tissue, with a total of 113 associations with a probability higher than 0.7. Genetic correlations observed for this tissue also followed the same patterns as those found in the phenotypic correlation analysis. Lean meat traits were positively correlated with unsaturated FA and negatively correlated with saturated lipids, while fatness traits showed the opposite pattern. The next most correlated tissue was liver, with a total of 86 high probability associations. As reported in phenotypic correlations and similarly to backfat, an opposite pattern of correlations with liver FAs was observed between fatness and

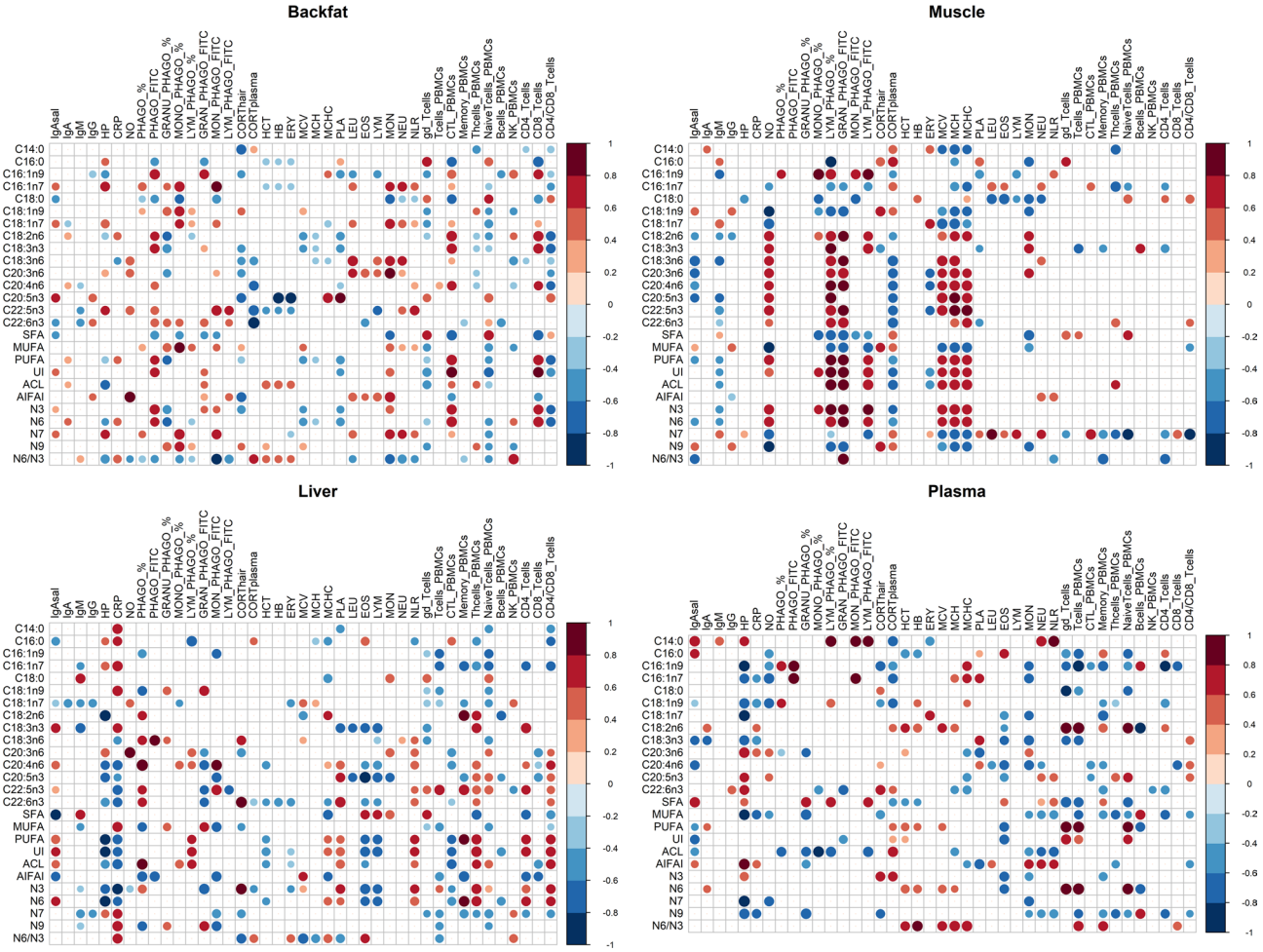

Fig. 5. Heatmap of genetic correlation estimates with a probability higher than 0.7 of being higher than 0.2 (for the positive) or lower than −0.2 (for the negative) between the lipid profiles in each tissue (liver ($n = 369$), backfat ($n = 368$), muscle ($n = 345$) and plasma ($n = 349$)) and the 41 health-related traits. Circle size and colour intensity mark the level of association. Abbreviations: Ig = Immunoglobulin; HP = Haptoglobin; CRP = C-reactive protein; NO = Nitric oxide; CTL = Cytotoxic T cell; NK = Natural killer T cell; PBMC = Peripheral Blood Mononuclear Cells; gd_Tcells = Gamma delta T cells; ERY = Erythrocytes; PLA = Platelets; LEU = Leucocytes; MON = Monocytes; LYM = Lymphocytes; EOS = Eosinophiles; NEU = Neutrophiles; HB = Haemoglobin; HTC = Haematocrit; MCH = Mean Corpuscular Haemoglobin; MCV = Mean Corpuscular Volume; CORThair = Cortisol in hair; CORTplasma = Cortisol in plasma; PHAGO_FITC = phagocytic activity assessed by fluorescein isothiocyanate; PHAGO_% = percentage of phagocytic cells.

lean meat traits. Lean meat traits showed positive correlations with myristic, palmitic and cis-vaccenic acids, and negative ones with arachidonic and EPA acids. Moreover, several FA in liver profile were found to be strongly correlated to the pH at 24 h post-slaughter, which was negatively associated with palmitic, γ-linolenic, the four monounsaturated acids, MUFA, N7 and N9 indices, and positively with stearic and n3-DPA, DHA and the average chain length index. The FA profile of plasma presented 48 correlations with carcass and production traits. Lean meat traits presented genetic associations with the abundance of palmitic and arachidonic acids in plasma, similarly to that observed in liver, but pH measurements showed the opposed correlations than in liver, being positively associated to cis7-hexadecenoic, linoleic, MUFA and N9 content in plasma. Lastly, muscle was the tissue with the fewest number of highly probable genetic correlations. Despite that, a number of genetic correlations with carcass weight were observed for the muscle abundance of stearic and cis-vaccenic (positive correlations), and of cis7-hexadecenoic, linoleic, α-linolenic, γ-linolenic and N6/N3 ratio (negative correlations).

Discussion

In the porcine industry, the selection of specific fatty acid profiles has been addressed to improve the organoleptic and nutritional properties of meat products, while the study of these lipids as bioactive molecules and immunomodulators has received less attention. In this study, we investigated the phenotypic and genetic associations of the FA profiles across diferent anatomic compartments (backfat, liver, muscle and plasma) and focused on their relationship with health- and production- related traits in a healthy Duroc population.

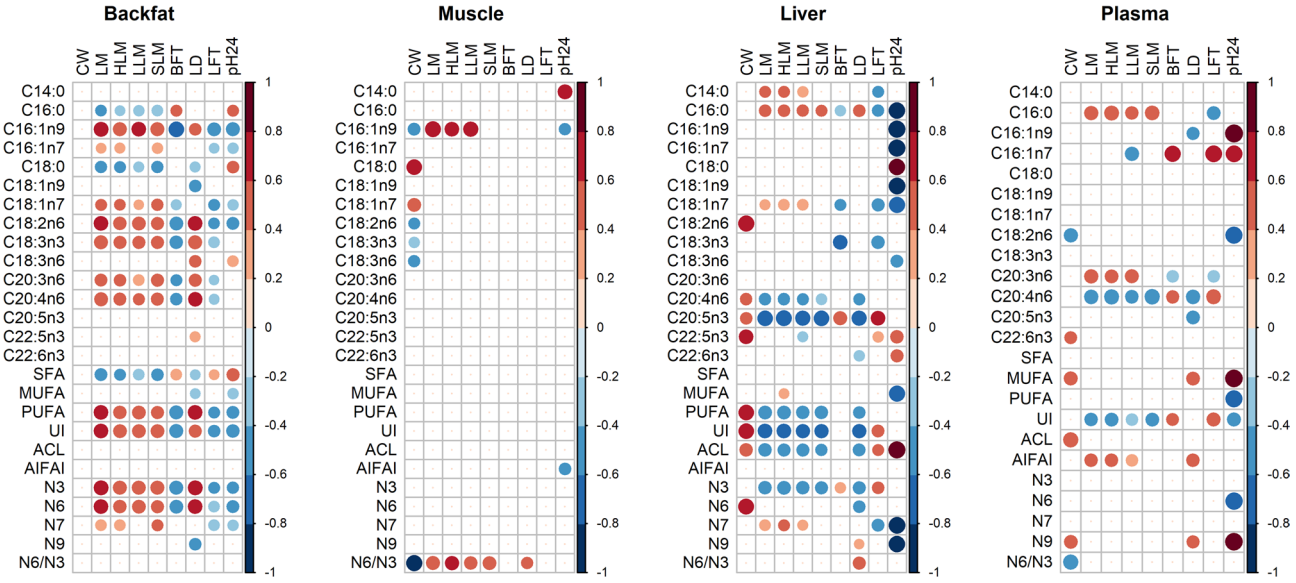

Fig. 6. Heatmap of genetic correlation estimates with a probability higher than 0.7 of being higher than 0.2 (for the positive) or lower than −0.2 (for the negative) between the lipid profiles in each tissue (liver ($n = 369$), backfat ($n = 368$), muscle ($n = 345$) and plasma ($n = 349$)) and the nine production and meat quality traits. Circle size and colour intensity mark the level of association. Abbreviations: CW = carcass weight; LM = lean meat percentage; HLM = ham lean meat percentage; LLM = loin lean meat percentage; SLM = shoulder lean meat percentage; BFT = backfat thickness; LD = loin depth; HFT = ham fat thickness; pH24 = pH in semimembranosus at 24 h post-mortem.

Significant differences in the FA profile of each tissue and plasma samples were observed. Liver FA profile was mainly composed by SFAs while MUFAs were more predominant in muscle and backfat, and PUFAs were found in higher concentrations in plasma. The distribution of FAs across different sample types is influenced by various factors, both environmental and genetic, and is primarily shaped by the biological function of each tissue[36–39]. Previous studies in pigs have identified genomic regions and candidate genes affecting the percentages of different FAs across tissues[35,40]. These findings are in line with genetic regulation at the transcriptional level of key enzymes involved in lipid metabolism[41,42] and may influence the relationships between the different compounds that make up these lipid profiles both within and across tissues. Indeed, previous studies using the same animal material identified a QTL on Sus Scrofa chromosome 14 associated with the abundance of several backfat FA, as well as with SFA and MUFA indices. Within this region, the candidate genes *SCD* and *ELOVL3*, involved in desaturase activity and stearic acid elongation, respectively, were located[35]. The presence and function of these genes may be partially responsible of the negative correlations observed between SFA and MUFA in backfat. Furthermore, the opposite relationship of PUFA with SFA and MUFA contents in backfat and muscle observed in our study has also been previously described in pigs: pigs with high contents of SFA showed an increase of the lipogenic profile and higher fat deposition than pigs with higher lean meat content and PUFAs[43–45].

The estimation of genetic parameters revealed wide variability in the genetic determinism of the FA composition across biological compartments. A particularly high heritability was estimated for most FA abundance in backfat, whereas medium to low heritabilities were obtained in muscle, liver and plasma. Previous findings also reported medium to high heritability estimates for backfat in other Duroc populations[38,46]. Another noteworthy heritability result was found for liver FA profile, where we obtained medium to high heritability estimates for the different long chain omega 3 and omega 6 unsaturated fatty acids. Liver is involved in the metabolism of a wide variety of lipids, including long-chain unsaturated fatty acids, which play a role in the modulation of several immunity mechanisms[47,48]. The ability to genetically select for a higher profile of specific PUFAs, such as arachidonic or EPA, could potentially lead to more efficient immune system modulation. In muscle FA profile, the studied Duroc population had generally lower heritability estimates than those from other Duroc populations[49,50], which can be consequence of the intense selection process for organoleptic quality of meat that has been carried out in this population. The overall lower and highly variable heritability estimates obtained for plasma samples could be due to the highly dynamic nature of this biological matrix.

The correlation analysis performed between the lipid profiles of plasma and the three tissues with immunity phenotypes allowed shedding light on the putative influence of fatty acid composition on immune response, and vice versa. At the phenotypic level, the estimated correlations showed low to moderate values, which is in concordance with the fact that both immunity and FA composition traits are highly multifactorial complex traits. Even so, significant correlations between FA content and immunity traits were observed. The positive association of various unsaturated FA in muscle, especially long-chain polyunsaturated fatty acids, with the phagocytic capacity of granulocytes supports the impact of FA composition on the phagocytic activity of several immune cells. At the genetic level, this pattern of correlations with muscle PUFA content was maintained and

was additionally observed for the proportion of phagocytic lymphocytes and nitric oxide levels. Phagocytic cells require certain long-chain fatty acids for their proper activation and function, as well as for their role as modulators in cytokine secretion[51]. Previous studies showed that the enrichment of macrophages with SFAs such as myristic or palmitic FA was reflected in a reduction of their activity of more than 20%[52]. In agreement with this, we observed a strong negative correlation between the relative abundance of palmitic acid and the percentage of phagocytic lymphocytes. On the other hand, increased values of PUFAs such as α-linolenic, EPA and DHA have been reported to improve the phagocytic capacity of neutrophils and monocytes[53] as well as macrophages[51,54], showing a greater capacity to engulf pathogens[55], zymosan particles and apoptotic cells[56].

In this same tissue, haematological parameters related to red blood cells showed a similar correlation pattern with muscle FA profile than that of the phagocytic phenotypes. Haematopoiesis is a complex and constant process subjected to a wide range of regulatory and energetic pathways that promote the proliferation and differentiation of haematopoietic stem cells to the required cell lines[57]. Lipid availability and metabolism play a role during this process. Polyunsaturated FA influence several red blood cells characteristics, such as MCH and MCV, by enhancing membrane fluidity and deformability[58]. In a previous study in humans, it was reported that higher levels of EPA and DHA in erythrocyte membranes correlated to and improved cellular integrity and function[58]. In addition, a specific lineage of phagocytic cells has been found to specialise in erythrophagocytosis of senescent red blood cells and redistribution of iron for haemoglobin synthesis in erythroid precursors[59]. Our results suggest that animals with a high content of specific long-chain PUFAs in red blood cells membranes may exhibit higher red blood cell functionality phenotypes, along with increased efficiency in erythrophagocytosis and recycling of erythrocytes, which may be reflected in a higher content of these lipids in muscle at the final stages of production.

The cortisol levels in plasma were also found to be highly genetically associated to the lipid profile of muscle, but they exhibited an inverse correlation pattern compared to those of red blood cells and phagocytosis parameters. Moreover, strong negative genetic correlations were also observed between the unsaturated long chain fatty acids content in the adipose tissue and the cortisol in plasma. The concentration levels of this given hormone have an impact on the metabolism of the pig. It has been well established that elevated cortisol levels promote lipogenesis and lead to an increase in fat deposition throughout the body[60,61]. Jia et al. (2022) reported that a higher concentration of hydrocortisone, a form of cortisol, lead to a decrease in the levels of the omega-3 PUFAs, especially EPA and DHA fatty acids[62].

A different set of immunity traits that exhibited a high level of genetic correlations with FA profiles across the different sample types were the proportion of several peripheral blood mononuclear cells populations. Notably, naïve T cells and CTL cells showed an opposite correlation pattern with backfat FA composition. Additionally, naïve T cells reported a similar pattern in liver, maintaining the same directionality reported in backfat. Previous studies in this pig population have shown strong phenotypic and genetic correlations between naïve T cells and γδ T cells, suggesting that the majority of naïve T cells corresponds to this specific lymphocyte population[63]. Additionally, naïve T cells showed a negative genetic correlation with CTL cells[63]. While the main energy source for naïve $CD8^+$ T cell relies on fatty acid oxidation[64], γδ T cells subpopulations depend on mTOR-mediated glycolysis or oxidative phosphorylation, utilising omega-3 PUFAs to modulate interleukin production and immune responses[65]. Although the specific effects of different lipids on cytotoxic T cells are not yet fully understood, arachidonic acid has been shown to regulate cytotoxic T cell function[53]. In addition, activation of cytotoxic T cells is further induced by linoleic acid[66]. Overall, the contrasting FAs patterns observed between these two T cells populations reflect differences in their metabolic signatures and states, and could influence their subsequent activation, proliferation and differentiation[18,64,67]. Consistent with our results, a previous study in the same population found that the percentage of γδ T cells was positively associated with measurements of fat deposition[34], which aligns with the correlations observed between γδ T cells and SFAs in adipose tissue. Lastly, in both backfat and liver tissues, the percentage of T helper cells showed similar genetic correlations with PUFA content than those of the naïve T cells. Previous studies have brought to light the importance of omega-3 unsaturated fatty acids not only in the differentiation but also in the functional regulation of specific T cells[16,24,68]. Lipid molecules such as EPA and DHA can alter the motility and tissue distribution of activated CD4 + T cells, leading to a less inflammatory environment and improved lymphocyte function[69], while increasing the proliferation and differentiation of regulatory and type 2 helper T cells[24].

Among the acute phase proteins, C-reactive protein and haptoglobin showed to be highly correlated to the lipidic profile of liver. These results are on agreement with previous studies[70,71] and support the role of this tissue as producer of these proteins. Both CRP and haptoglobin followed a similar pattern of negative correlations with several PUFAs and positive correlations with SFAs and MUFAs. Variations in liver FA profile have the potential to influence the synthesis of these acute phase proteins. Tamer et al. (2020) observed that feeding mice with a coconut oil based high SFA caused an increase of plasma CRP levels as well as other inflammatory mediators[70]. In humans, while the consumption of diets rich in saturated fats was reflected with an increase of CRP in plasma in few specific male populations[72], a high intake of PUFAs reported to have the inverse effect in both sexes[73]. In the case of haptoglobin, an augment in dietary palmitic acid led to an increase of haptoglobin gene expression[74]. In plasma, however, an opposed correlation pattern of the acute phase proteins with the MUFAs and most PUFAs compared to liver was observed, especially for haptoglobin. Blood is a dynamic tissue that distributes fatty acids to all tissues, thus, an increase in demand for specific lipids would be reflected in a consequent reduction of these metabolites in circulation. A noteworthy finding is the negative correlations of α-linolenic with both acute phase proteins, in concordance with the anti-inflammatory property of this FA. Previous studies with dietary supplementation of α-linolenic acid in humans reported a reduction of the circulatory concentration of CRP[75,76].

The lipid profile of the adipose tissue was found to have the overall strongest phenotypic correlations with the production performance traits, especially those related to lean meat content and fatness. At the genetic level, correlations observed at phenotypic level were maintained and generally increased in intensity. Among the

highly probable correlations, it is worth noting the opposed patterns consistently found between the correlations with lean meat traits and with fatness measurements. As stated before, this found dichotomy between fat and lean meat phenotypes has been widely explored[34,43,77]. Similar associations between adipose fatty acid composition and production phenotypes have been observed in previous studies[8,78]. In contrast, SFAs (C14:0 and C16:0) in liver and plasma were positively associated to lean meat traits and negatively to fatness. It is worth noting that, while production traits were measured at slaughter, plasma fatty acid profiles were obtained at two months of age. Therefore, the levels of these fatty acids in plasma at early age could be considered as a potential indicator of subsequent production performance during growth and fattening periods.

Lastly, liver fatty acid profile was found to be highly correlated to the pH measurements at 24 h postmortem. Liver content of SFAs and MUFAs were negatively correlated to this phenotype, with the exception of stearic acid, which showed positive associations alongside the long chain omega-3 polyunsaturated FA. It is well known the potential effect of energy metabolism and stress in the decline rate and resulting pH of the meat after slaughter[79]. Lipid metabolism is modulated by fatty acid availability; thus, liver fatty acid profile may play a role in this process. Our results show that a higher content of stearic, n3-DPA and DHA acids in liver resulted in a lesser decline of pH over the 24 h postmortem.

Although we delve deeper into the genetic determinism of fatty acids traits and their interactions with health-related traits, our study has potential limitations. First, the available sample size (432 animals) limits the accuracy of the estimated genetic parameters, especially genetic correlations, despite having genealogical information for up to 8 generations. Another limitation stems from the timing differences between the measurements of the diverse sets of phenotypes: plasma FA profile and health-related traits were obtained at 60 days of life, while the FA profiles of backfat, liver and muscle tissues were obtained at slaughter. Nevertheless, plasma FAs levels at 60 days could provide valuable insights into how circulating FAs may influence lymphocyte populations and other immune-related traits, while FA profiles at slaughter offer an indication of the lipid composition the animals have developed throughout their lives, which may have impacted their immunity profile.

In conclusion, our study demonstrates the genetic determinism of fatty acid composition in plasma and three anatomically and physiologically distinct tissues. Furthermore, strong genetic interactions were identified between fatty acid composition and both health and production traits across backfat, liver, muscle and plasma. The fatty acid composition of backfat was the most strongly correlated to both immunity and production traits, while PUFAs from liver and backfat showed the greatest number of associations with various immunity traits. This study contributes to delve into the highly relevant role of different fatty acids and their tissue distribution in shaping immunocompetence and production performance in pigs.

Materials and methods

Ethics statement

This study follows the directives of the Spanish Policy for Animal Protection RD 53/2013, in agreement with European Union Directive 2010/63/EU about the correct practices and protection of animals used in experimentation and were approved by the Ethical Committee of the Institut de Recerca i Tecnologia Agroalimentàries (IRTA). All methods used in this study are reported in accordance with ARRIVE guidelines.

Animal material and previous phenotypic parameters

The study was performed with a population of 432 healthy piglets (217 males and 215 females) belonging to a commercial Duroc pig line. The pigs were selected from 122 litters (two to four animals per litter balancing gender when possible) born from 22 boars and 120 sows. The pedigree of the 432 piglets was traced back six generations, and a genealogy of 1388 animals was considered in the subsequent genetic analyses. Distributed in six consecutive batches (72 ± 1 animals per batch), the piglets were raised on the same farm and fed ad libitum with the same commercial cereal-based diet. The animals showed no symptoms of infection or pathology at the time of sampling.

Every animal was sampled at 60 ± 8 days of age. The external jugular vein was used to draw blood into vacutainer tubes, both with and without anticoagulants (Sangüesa S.A., Spain). Salivette tubes (Sarstedt S.A.U., Germany) were used to collect saliva samples. Pigs were slaughtered at 181–228 days of age (with an average weight of 129 kg) in a commercial abattoir, and samples of backfat (taken between the third and fourth last ribs), liver, and *gluteus medius* muscle were collected and frozen at −80 °C for subsequent analysis of FA profile.

As stated in Ballester et al.[63,80]., classical haematological, immunological, and stress parameters were determined for all animals in this population at 60 days of life, including: the plasma concentration of different immunoglobulins (IgA, IgM and IgG); the serum concentration of C-reactive protein (CRP), nitric oxide and Haptoglobin (HP); the counts of white blood cells leucocytes (LEU), monocytes (MON), eosinophiles (EOS), neutrophiles (NEU), and lymphocytes (LYM); the percentage of phagocytic cells and phagocytosis capacity; haematological red blood cells related traits such as haematocrit (HTC), erythrocytes count (ERY), haemoglobin concentration (HB), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration; and the relative abundance among PBMCs of B lymphocytes, T lymphocytes, and the different cell subsets: memory T-helper cells, naïve T cells, T helper cells, γδ T cells, cytotoxic T cells (CTL) and natural killer cells. Saliva was used to quantify IgA amounts (IgAsal) and hair from the dorsal area of the neck behind the ears was collected to measure cortisol concentration levels (CORThair) by ELISA. Lastly, the levels of cortisol in plasma (CORTplasma) were measured by targeted liquid chromatography tandem mass spectrometry[81].

Nine traits related to carcass and meat quality were obtained for 378 pigs after slaughter as described by Jové-Juncà et al.[34]. Carcass and meat quality traits analysed here included the cold carcass weight (CW); backfat thickness (BFT) measured between the third and fourth last ribs; ham fat thickness (HFT); and loin depth (LD) measured at the same anatomical position as BFT. In addition, the lean meat percentage of the carcass (LM)

and specifically in the ham (HLM), loin (LLM) and shoulder (SLM) was assessed with an ultrasound automatic scanner (AutoFOM, Frontmatec Group, Kolding, Denmark) with a measurement interval of 5 mm. Finally, the pH in muscle was measured at 24 h *post-mortem* (pH24) with the sensION™+ pH1—pH portable meter (Hach, Dusseldorf, Germany).

Fatty acid profiling and statistical description

The FA profiles of liver (n = 369), backfat (n = 368), and *gluteus medius* muscle (n = 345) samples were previously described in Liu et al.[35]. In summary, fatty acid methyl esters were analysed and quantified by gas chromatography in the NUTRICAL-UCM laboratory using a capillary column (HP- Innowax, 30 m x 0.32 mm id and 0.25 µm cross-linked polyethylene glycol) (Agilent Technologies GmbH, Wald-bronn, Germany) and identified by standard comparison (Sigma-Aldrich, Tres Cantos, Madrid, Spain). Swine plasma from 349 samples were analysed at the IRBLleida Lipidomics Core Facility – PLICAT, following the method described in Jové et al.[82]. FA identification was obtained by standard comparison (Larodan Fine Chemicals, Malmö, Sweden).

The concentration of each FA was expressed as percentage of the total FAs. The indices of saturated FAs (SFAs), monounsaturated FAs (MUFAs), polyunsaturated FAs (PUFA), unsaturated omega-3 (N3), omega-6 (N6), omega-7 (N7), omega-9 (N9), and the omega-6/omega-3 ratio (N6/N3) were obtained through the sum of individual FAs. The unsaturated index (UI) was calculated as the sum of the percentage of each unsaturated FA multiplied by the number of double bonds within that FA. Average chain length (ACL) was calculated by the sum of each FA multiplied by the number of carbons and divided by 100. The Anti-inflammatory FA index (AIFAI) was obtained with the following formula: (C20:3n6 + C20:5n3 + C22:6n3)/C20:4n6[83].

Descriptive statistics for these traits describing the FA lipidic profiles of backfat, liver, muscle and plasma were computed and are shown in Supplementary Table S5. Shapiro-Wilk test was used to measure normality of the FA data and, when needed, logarithm transformation was applied to reach normal distribution (p-value > 0.05). Systematic non-genetic putative effects (sex, batch, and backfat thickness between the 3rd and 4th ribs) were tested by using lm() and anova() functions in R software[84] and, when significant, were included in subsequent analyses.

Phenotypic correlations between the residuals (after correcting for fixed effects) of the fatty acid profiles and health-related phenotypes were obtained using Pearson correlation with the cor() function in R software. Following the false discovery rate method for multiple testing described by Benjamini and Hochberg[85], the *p.adjust* function in R was used to adjust the obtained p-values of the correlations. To discard those significant correlations with low impact, we set a relevance threshold at $r_p = |0.2|$. Corrplot package in R software was used to visualize the correlation matrix.

Heritability estimates and genetic correlations

Heritability for the measures of FA traits, as well as their genetic correlations with other phenotypes, were estimated through Bayesian analyses performed by Gibbs sampling under bivariate animal models. The program *gibbs2f90* in BLUPF90 family software[86] was used in all analyses to obtain the marginal posterior distributions of the variance components plus the corresponding heritability and genetic correlation.

Genetic correlations between the different lipid species and health-related traits were estimated in a two-traits animal model described as follows:

$$\begin{bmatrix} \boldsymbol{Y}_{t1} \\ \boldsymbol{Y}_{t2} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X}_{t1} & 0 \\ 0 & \boldsymbol{X}_{t2} \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta}_{t1} \\ \boldsymbol{\beta}_{t2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z}_{t1} & 0 \\ 0 & \boldsymbol{Z}_{t2} \end{bmatrix} \begin{bmatrix} \boldsymbol{u}_{t1} \\ \boldsymbol{u}_{t2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e}_{t1} \\ \boldsymbol{e}_{t2} \end{bmatrix}$$

where $\boldsymbol{Y}_{t1}$ and $\boldsymbol{Y}_{t2}$ are the vectors of phenotypic observations for trait 1 and trait 2, respectively; $\boldsymbol{\beta}_{t1}$ and $\boldsymbol{\beta}_{t2}$ are the vectors of systematic (fixed) effects on each trait (sex and batch for all traits, backfat thickness for the lipid profile in backfat, muscle and liver, and date for phagocytosis phenotypes) and $\boldsymbol{X}_{t1}$ and $\boldsymbol{X}_{t2}$ the correspondent incidence matrices; $\boldsymbol{u}_{t1}$ and $\boldsymbol{u}_{t2}$ are the vectors of animal genetic additive effects on trait 1 or trait 2 (random effects), and $\boldsymbol{Z}_{t1}$ and $\boldsymbol{Z}_{t2}$ the corresponding incidence matrices; finally $\boldsymbol{e}_{t1}$ and $\boldsymbol{e}_{t2}$ are the vectors of residual errors for each trait. The (co)variance matrix of random genetic effects was defined as:

$$Var\begin{bmatrix} \boldsymbol{u}_{t1} \\ \boldsymbol{u}_{t2} \end{bmatrix} = \begin{bmatrix} \boldsymbol{A}\sigma^2_{u1} & \boldsymbol{A}\sigma_{u1,u2} \\ \boldsymbol{A}\sigma_{u1,u2} & \boldsymbol{A}\sigma^2_{u1} \end{bmatrix} = \boldsymbol{A} \otimes \begin{bmatrix} \sigma^2_{u1} & \sigma_{u1,u2} \\ \sigma_{u1,u2} & \sigma^2_{u1} \end{bmatrix}$$

where σ^2_{u1} and σ^2_{u2} are the additive genetic variance of traits 1 and 2, respectively, $\sigma_{u1,u2}$ is the genetic covariance between the traits, and A is the numerator relationship matrix as defined above. Posterior heritabilities ($\widehat{h}^2 = \widehat{\sigma}^2_u / \left(\widehat{\sigma}^2_u + \widehat{\sigma}^2_e\right)$) of each trait plus genetic correlation between the two traits ($\widehat{r}_g = \widehat{\sigma}_{u1,u2} / \left(\widehat{\sigma}_{u1} \cdot \widehat{\sigma}_{u2}\right)$) were obtained in each analysis.

Chains of 100,000 samples were run in each analysis, with a burn-in of 10,000 rounds and sampling every 10 iterations to minimize autocorrelation. Posterior mean and SD plus the highest posterior density regions at 95% (HPD95) of genetic parameters (heritability and genetic correlations with immunity traits) were obtained for all FAs traits. The probability of the estimated genetic correlation being > 0.2 for positive estimates or, alternatively, being <−0.2 for negative estimates was calculated using the R software. Correlations were considered to be relevant if the estimated probability was $P > 0.70$. Corrplot package in R software was used to visualize the correlation matrix.

Data availability

All data generated during this study is included in this publication and its supplementary material. Additional datasets are available upon reasonable request to the corresponding authors.

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Author contributions
M.B. and R.Q. designed the study. M.B., J.M.F. supervised the generation of the animal material. M.B., O.G-R., and R.Q. performed the sampling. M.B. and O.G-R. carried out the laboratory analyses. C.H-B., J.L. T.J-J., M.B., and R.Q. analysed the data. C.H-B., T.J-J., M.P-O., M.B. and R.Q. participated in interpreting and discussing the results. C.H-B., M.B. and R.Q. wrote the manuscript. All authors reviewed and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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