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EDITED BY
James Levi Klotz,
United States Department of Agriculture,
United States

REVIEWED BY
Nicole C. Burdick Sanchez,
Agricultural Research Service (USDA),
United States
Amanda K. Lindholm-Perry,
Agricultural Research Service (USDA),
United States

*CORRESPONDENCE
Ibukun M. Ogunade
ibukun.ogunade@mail.wvu.edu

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Hepatic mRNA expression of innate and adaptive immune genes in beef steers with divergent residual body weight gain

Deborah Ologunagba[1], Modoluwamu Idowu[1], Godstime Taiwo[1], Taylor Sidney[1], Emily Treon[1], Francisca Eichie[1], Frederick Bebe[1,2] and Ibukun M. Ogunade[1]*

[1]Division of Animal and Nutritional Science, West Virginia University, Morgantown, WV, United States, [2]College of Agriculture, Health and Natural Resources, Kentucky State University, Frankfort, KY, United States

Immune function plays a pivotal role in dictating the overall health and productivity of cattle. In a proficient immune system, the liver assumes an integral function in detoxification and metabolic processes and contributes substantially to overall production and immunity. In this study, we evaluated the hepatic mRNA expression of genes involved in innate and adaptive immunity in crossbred beef steers with positive or negative residual body weight gain (RADG). Positive-RADG beef steers (n = 8; RADG = 0.73 kg/d) and negative-RADG beef steers (n = 8; RADG = -0.69 kg/d) were identified from a group of 108 growing crossbred beef steers (average BW = 556 ± 38 kg) after a 56-d performance testing period. At the end of the 56-d period, liver tissue samples were collected from the beef steers for RNA extraction and cDNA synthesis. The mRNA expression of 84 genes involved in innate and adaptive immunity were analyzed using pathway-focused PCR-based arrays. The mRNA expression of genes with false discovery rate-adjusted *P*-values (FDR) ≤ 0.05 and absolute fold change (FC) ≥ 1.2 were determined to be differentially expressed. Out of the 84 genes analyzed, four genes (*IL-2, MYD88, CD-80, NFkB-1*) were differentially expressed and were all upregulated in positive compared with negative-RADG beef steers. IL-2 is a cytokine that plays a critical role in the immune response by activating and proliferating T-cells, which are important for fighting infections. MYD88 is an adaptor protein that is essential for signaling by toll-like receptors, which are involved in pathogen recognition. CD80 is a protein that is expressed on the surface of antigen-presenting cells and plays a critical role in the initiation of an immune response. The activation of NF-κB leads to the production of cytokines and chemokines that help to recruit immune cells to the site of infection. The upregulation of the aforementioned genes in positive-RADG beef steers suggests that they had a better ability than negative-RADG beef steers to quickly recognize pathogens and initiate appropriate responses to effectively fight off infections without causing inflammatory reactions, potentially contributing to their better feed efficiency.

KEYWORDS

feed efficiency, immunity, gene expression, liver, beef cattle

Introduction

In beef production, the cost of feeding is a crucial factor that significantly impacts the overall cost of production. Studies have demonstrated that feed cost accounts for 60 to 70% of the total expenses in animal production (Becker, 2008; Greenwood, 2021). Given this, improving feed efficiency holds the potential to mitigate costs and enhance the economic viability of farms. Moreover, improved feed efficiency can lead to reduced environmental impacts by reducing nutrient wastes and mitigating greenhouse gas emissions (Llonch et al., 2017). There is a growing need to understand the biological mechanisms associated with feed efficiency in beef production systems, considering the complex sustainability factors such as the overall impact of feed cost and environmental footprints. Residual feed intake (RFI) and residual body weight gain (RADG) have been explored for several years as measures of feed efficiency in beef cattle (Crews, 2005; Berry and Crowley, 2012). Residual body weight gain is the difference between the actual daily gain and predicted gain based on body weight and dry matter intake of beef cattle (Northcutt and Bowerman, 2010). Positive RADG values signify more desirable feed efficient animals, while negative RADG values indicate inefficient animals (Crowley et al., 2011).

Several studies have sought to understand how selection for divergent RFI or RADG affects important traits such as metabolism, fertility, rumen microbiome, and carcass characteristics (Cantalapiedra-Hijar et al., 2018; Taiwo et al., 2022; Idowu et al., 2023). In our recent study, Taiwo et al. (2023) investigated expression of immunity-associated genes in the liver and whole blood of crossbred beef cattle with divergent RFI. The results revealed differences in the expression of genes associated with several pathways including pattern recognition receptor activity and immune cell differentiation; however, little is known about how selection based on RADG affects immune gene expression in beef cattle.

The liver functions as a frontline immune organ strategically positioned to detect and clear pathogens entering the body through the gut, underscoring its significant role in the immune response (Loor et al., 2005; Yan et al., 2014). Notably, variations in the expression of immune-related genes in this organ can profoundly affect metabolic function, nutrient availability, and feed efficiency in animals (Vigors et al., 2019; Cheng et al., 2021). Thus, in this study, we hypothesized that the expression of some immunity genes would vary in beef steers with divergent positive or negative RADG. Our objective was to determine the differences in mRNA expression of certain innate and adaptive immune genes in the liver of beef steers with divergent negative or positive RADG phenotypes.

Materials and methods

Animals, feeding, and experimental design

The research procedures described in this study received approval from the Institutional Animal Care and Use Committees of West Virginia (protocol number 2204052569). A total of 108 growing crossbred (Angus × Hereford) beef steers (average body weight (BW) = 556 ± 38 kg; 529 ± 22 d of age), were fed a high-forage total mixed ration (TMR) consisting primarily of corn silage, ground hay, and a ration-balancing supplement (Table 1) for a total of 56 days after a 15-d adaptation period to the feeding facilities and diet. The steers were housed in five dry lot pens (20-22 steers per pen). Two GrowSafe 8000 intake nodes (GrowSafe Systems Ltd., Airdrie, Alberta, Canada) were installed in each pen to monitor individual feed intake. Daily BW measurements were obtained using In-Pen Weighing Positions (IPW, Vytelle LLC). At the end of the 56-d period, the beginning BW, mid-test metabolic BW, and average daily gain (ADG) were calculated by regressing the daily BW for each animal using a simple linear regression. The ADG of each steer was regressed against their daily dry matter intake (DMI) and mid-test metabolic BW (MMTW = mid-test $BW^{0.75}$), and the RADG was calculated as the residual or the difference between the predicted value of the regression and the actual measured value using the following regression equation: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$, where Y represents the ADG (kg/d), β_0 is the regression intercept, β_1 and β_2 are the partial regression coefficients, X1 is the MMTW (kg), X_2 is the observed DMI (kg/d) (Koch et al., 1963; Berry and Crowley, 2012). Upon completion of the feeding trial, the beef steers were ranked based on their RADG coefficients and the most efficient (positive-RADG = +0.76 kg/d, n = 8) and least efficient (negative-RADG = -0.65 kg/d, n = 8) were identified for further analysis.

Liver biopsy, RNA extraction and gene expression

Liver tissues were obtained from the 8 positive-RADG and 8 negative-RADG beef steers using a needle biopsy under local anesthesia. An incision was made in the skin and liver tissue was harvested from the 10th intercostal space through a 14-gauge biopsy needle (Tru-Core-II Automatic Biopsy Instrument: Angiotech, Lausanne, Switzerland). Approximately 1 g of liver tissue sample was obtained from each of the 16 steers by puncture and was immediately transferred into RNA-Protect tubes (cat. No: 76104; Qiagen) and stored at −80°C for further analysis. A sub-sample of the liver tissue (5 mg each) was used for total RNA extraction using RNeasy Micro kit (cat. no. 74004; Qiagen) following the manufacturer's instructions. Samples with >100 ng/μL total RNA were used. RNA concentration was measured using a NanoDrop 2000 spectrophotometer with an A260:A280 ratio from 1.8 to 2.0 (Thermo Fisher Scientific, Waltham, MA, USA). All samples had RNA integrity numbers > 8.0 analyzed using Agilent 2100 Bioanalyzer (Agilent Technologies). Complementary DNA (cDNA) synthesis was then carried out using the extracted, purified RNA. To obtain transcript abundance, cDNA was synthesized via reverse transcription (RT) using the RT^2 first strand kit (cat. no. 330401; Qiagen). RT^2 Profiler cow innate and adaptive immune responses Polymerase chain reaction (PCR) Array (PABT-052ZA; Qiagen) was used for mRNA expression analysis of 84 genes related to innate and adaptive immunity. Each array was a 96-well plate containing 84 adaptive and innate immune-related genes together with five housekeeping genes (β-actin, hypoxanthine phosphoribosyl transferase 1, glyceraldehyde-3-phosphate dehydrogenase, tyrosine 3-monooxygenase, and TATA box-binding protein), three RT, three positive PCR controls, and one genomic DNA control

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TABLE 1 Composition of the total mixed ration.

Ingredients (%DM)	% of dietary DM
Corn silage	41.2
Sorghum haylage	29.4
Mixed grass hay[a]	10.3
Concentrate supplement[b]	19.1
Nutrient analysis	
DM %	52.0
Crude Protein %	14.1
NDF %	36.5
NFC %	38.0
Fat %	4.45
Calcium %	0.53
Phosphorus %	0.46
Potassium %	1.50

[a]Contains a mixture of orchard grass, fescue grass, timothy grass, and red clover.
[b]Traditions 50% beef supplement (Southern States Cooperative, Richmond, VA) contained processed grain by-products, plant protein products, ground limestone, urea, salt, cane molasses, potassium sulfate, magnesium sulfate, sodium selenite, vitamin A supplement, calcium carbonate, vegetable oil, manganous oxide, vitamin D3 supplement, vitamin E supplement, zinc oxide, lecithin, phosphoric acid, basic copper chloride, magnesium chloride, propylene glycol, natural and artificial flavors, ferrous sulfate, calcium iodate, and cobalt carbonate; Guaranteed analysis: 50% CP; 5% Ca; 0.55% P; 2% Na; 3.9% salt; 1% K, and 66,000 IU/kg vitamin A.
DM, dry matter; CP, crude protein; NDF, neutral detergent fiber; NFC, non-fiber carbohydrates.

(Supplementary Table S2). Real-time PCR was performed using the Quant Studio 5 real-time PCR system (Applied Biosystems, Foster City, CA). The PCR cycle conditions were as follows: 40 denaturation cycles of 95°C for 10 min, 95°C for 15 s, and 60°C for 1 min.

Data and statistical analysis

Variables such as initial and final BW, ADG, DM intake, and RADG values were analyzed using the GLIMMIX procedure of SAS version 9.4 (SAS Institute Inc., Cary, NC), with RADG status included as a fixed effect. Significant effects were declared at $P \leq 0.05$. Values of initial body weight were included as a covariate for the final body weight. We used the Gene Globe data analysis center (https://geneglobe.qiagen.com) to analyze the mRNA expression data. The comparative cycle threshold (Ct) method was used for the relative quantification of the gene expression (Pfaffl, 2001). To determine the differences in mRNA expression between the positive- and negative-RADG beef steers, the delta-delta Ct ($2^{-\Delta\Delta Ct}$) method was employed. The raw data were normalized using the geometric mean of the five housekeeping genes (Pfaffl, 2001). The stability of the housekeeping genes was confirmed using ΔCt and NormFinder (Andersen et al., 2004). The PCR arrays employed in this study have an average amplification efficiency of 99%, with a 95% confidence interval ranging from 90 to 110%, enabling accurate simultaneous analysis of multiple genes using the $2^{-\Delta\Delta Ct}$ method. Differentially expressed genes were identified using absolute fold change (FC) ≥ 1.2 and false discovery rate-adjusted *P*-values of 0.05.

Results and discussion

The results showing the growth performance of the beef steers with divergent RADG phenotypes are presented in Table 2. The average RADG values of positive- and negative-RADG beef steers were 0.73 and -0.69 kg/d, respectively ($P = 0.01$). Dry matter intake and initial BW of the two groups were similar ($P > 0.05$). Compared to negative-RADG, final BW and ADG were greater ($P \leq 0.05$) in positive- RADG than negative-RADG beef steers.

The mRNA expression analysis of the 84 innate and adaptive immune genes is shown in Supplementary Table S3. Among the 84 genes analyzed, the mRNA expression of 4 genes encoding interleukin 2 (IL-2), nuclear factor NF-kappa-B (NF-κB-1), myeloid differentiation primary response 88 (MYD88), and the cluster of differentiation 80 (CD80) were differentially expressed and were all upregulated in beef steers with positive RADG (FC ≥ 1.2, $P \leq 0.05$; Table 3). The upregulation of IL-2, MYD88, and NFκB-1 in positive-RADG beef steers suggests a robust immune interaction between the innate and adaptive cells of these animals. Myeloid differentiation primary response 88 (MYD88) plays a crucial role in innate immune signaling, mediating the innate immune response and cytokine production to combat pathogens and stimulate adaptive immunity (Arnold-Schrauf et al., 2014; Li et al., 2020). Upon lipopolysaccharide recognition, MYD88 plays a critical adapter protein role in the TLR4 signaling pathway, which in turn activates downstream signaling molecules that express genes involved in the inflammatory response during bacterial infection (Fitzgerald et al., 2004). Interleukin 2 contributes to immune balance and long-lasting cell-mediated immunity (Liao et al., 2011; Wrenshall et al., 2014). Nuclear factor kappa B is vital for the development, activation, and survival of adaptive immune cells (Lee and Kleiboeker, 2005; Tergaonkar, 2006). It also plays a pivotal role in the innate immune response to pathogens through pattern recognition receptor signaling (Lee and Kim, 2007). Prolonged inhibition of NF-κB-1 can result in inappropriate immune cell development or delayed cell growth (Hinz et al., 1999; Graham et al., 2010).

The increased expression of CD80-1 in the positive-RADG beef steers indicates effective adaptive immune responses. CD80, primarily expressed on antigen-presenting cells like macrophages and dendritic cells, interacts with its receptor CD28 on T cells, providing co-stimulatory signals necessary for sustained T cell activation and

TABLE 2 Growth performance of beef steers with divergent residual body weight gain phenotype.

Item	Positive RADG	Negative RADG	SEM	*P*-value
RADG (kg/d)	0.73	-0.69	0.10	0.01
Initial weight (kg)	494	496	8.90	0.65
Final weight (kg)	564	555	1.93	0.01
ADG (kg/d)	1.25	1.05	0.06	0.04
DMI (kg/d)	13.2	13.3	0.49	0.96

SEM, standard error of the mean; ADG, average daily gain; DMI, dry matter intake.

TABLE 3 Upregulated immune genes in positive RADG beef steers.

Gene symbol	Gene name	FC	FDR
IL-2	Interleukin 2	12.4	0.05
MYD88	Myeloid differentiation primary response 88	1.31	0.01
CD-80	The cluster of differentiation 80 (CD80	1.36	0.02
NFkB-1.	Nuclear factor NF-kappa	1.25	0.03

Fold change (FC; relative to negative RADG steers). Only genes with absolute FC ≥ 1.2 and false discovery rate-adjusted *P*-values ≤ 0.05 are shown. The results of all the 84 genes are presented in Supplementary Table S3.

proliferation (Lenschow et al., 1996; Sharpe and Freeman, 2002). Moreover, CD80 plays a role in regulating the balance between immune activation and tolerance (Martínez-Méndez et al., 2021). The upregulation of CD80 in beef steers with positive RADG suggest a competent immunological memory, enabling rapid response upon re-exposure to previously encountered pathogens.

Conclusion

The results of this study revealed the upregulation of key immune-related genes like IL-2, CD-80, MYD88, and NFκB-1 in the liver of beef steers with positive RADG, suggesting a robust interaction between innate and adaptive immune cells, potentially contributing to their improved feed efficiency. Future research should focus on assessing the immunocompetence of beef steers classified as positive or negative RADG when exposed to pathogen challenges. Such investigations are crucial in unveiling the intricate links between immunocompetence and feed efficiency, thereby enabling targeted interventions to improve livestock health and growth performance.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was approved by The Institutional Animal Care and Use Committees of West Virginia. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

DO: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. MI: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. GT: Data curation, Investigation, Methodology, Visualization, Writing – review & editing. TS: Data curation, Investigation, Methodology, Visualization, Writing – review & editing. ET: Investigation, Methodology, Visualization, Writing – review & editing. FE: Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. FB: Formal analysis, Investigation, Resources, Writing – review & editing. IO: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fanim.2024.1349499/full#supplementary-material

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