Analysis of high-risk stocker cattle transcriptome associates clinical BRD with consistent inflammation-related pathways

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Introduction

Although bovine respiratory disease (BRD) is frequent and costly in beef cattle operations, diagnosis of the disease complex is inaccurate. Metaphylactic use of antimicrobials effectively reduces the risk of BRD, but antimicrobial administration may induce resistance. Therefore, this project was designed to identify differences in levels of transcribed gene expression driven by clinical BRD, both with and without administration of metaphylaxis at-arrival in high-risk stocker cattle. Using RNA sequencing, we aimed to identify predictive gene expression pathways at-arrival in cattle that developed BRD or not, characterize host genomic patterns in response to clinical BRD, and describe differences in gene expression of clinically diseased cattle based on treatment success and time of treatment within the study.

Materials and methods

Upon arrival in a 70-day study, 84 commercial heifers (mean weight = 239 kg, s.d. = 16 kg) sourced from regional auction markets were randomly enrolled into 2 treatment groups: metaphylaxis with tulathromycin according to label instructions (META, n = 42) or negative control (CONT, n = 42). Scheduled jugular blood samples were collected on days 0, 7, 14 and 21, and additional jugular blood samples were collected at time of treatment from cattle diagnosed with BRD. From cattle that remained healthy throughout the study, RNA was sequenced for 7 META and 7 CONT heifers at each scheduled timepoint (sample n = 56). From cattle that required clinical antimicrobial therapy, RNA was sequenced from 16 individuals just prior to their antimicrobial treatment (sample n = 32). Sequencing, completed via NovaSeq 6000 (150bp PE; ~40M reads/sample), was assembled via HISAT2/StringTie2 assembly and inputted into edgeR testing to identify differentially expressed genes (DEGs) in multiple analyses via likelihood ratio testing: 1) predictive analysis, comparing at-arrival samples of healthy vs. treated cattle; 2) BRD characterization analyses, comparing at-arrival vs. first treatment samples for cattle with BRD, healthy vs. treated cattle in week one, and healthy vs. treated cattle in week 2; 3) differentiation of treatment success analysis, comparing transcriptomes at first treatments vs. subsequent treatments in cattle treated multiple times; 4) differentiation of early and late treatment analysis, comparing cattle treated in study week 1 vs. cattle treated in study week 2. Significant DEGs (FDR < 0.05) were analyzed for functional enrichment via KOBAS-i (FDR < 0.05).

Results

When comparing at-arrival samples of healthy cattle vs. cattle treated once or 2 or more times, we identified only 1 and 4 DEGs, respectively. In the comparison of at-arrival vs. first BRD treatment samples, 3,882 DEGs were identified. When comparing healthy cattle vs. cattle treated in the first or second weeks of the study, 1,715 and 767 DEGs were identified, respectively. Forty-four DEGs were identified in the comparison of first vs. subsequent treatments. Finally, in the comparison of treatments in the first versus second week, we identified 1,518 DEGs. Common functional enrichment findings in each of the analyses, other than the predictive analysis, included increased neutrophil degranulation, decreased biosynthesis of specialized proresolving mediators (SPMs), and decreased regulation of the immune system in BRD cattle.

Significance

Presence of clinical BRD and time of treatment had the largest influences on host gene expression. In contrast to our past work, gene expression at arrival minimally corresponded to later development of BRD; this may have been related to relatively low prevalence and/or clinical scores of BRD in this population. However, the consistent inflammatory response identified in cattle treated for BRD, regardless of metaphylactic administration or treatment success, demonstrates a uniform immunological pattern that may be leveraged for clinical disease detection.

