Transcriptome assessment of healthy high-risk stocker cattle defines mechanisms of inflammatory regulation induced by tulathromycin metaphylaxis

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Introduction

Tulathromycin is commonly used as metaphylaxis to reduce bovine respiratory disease (BRD) risk. Current secondary pharmacodynamics characteristics of tulathromycin on the host are poorly understood. RNA Sequencing (RNA-Seq) techniques were used to measure gene expression in healthy cattle administered tulathromycin to elucidate the genomic mechanisms over time.

Materials and methods

Eighty-four commercial heifers (average: 239 kg; s.d. = 16 kg) were randomly enrolled into 2 treatment groups for 70 days: cattle received a one-time subcutaneous injection of tulathromycin on day 0 at label dosing (META, n = 42) or negative control (NOMETA, n = 42). Jugular blood samples from all cattle were collected into Tempus RNA blood tubes at days 0, 7, 14 and 21. Samples for RNA-Seq were randomly selected from 7 META and 7 NOMETA cattle never having been diagnosed with BRD throughout the study. Isolated mRNA from samples were sequenced (NovaSeq 6000, 150bp PE; ~ 40 M reads/sample) and bioinformatically processed via a bovine genome reference-guided HISAT2/StringTie2 pipeline. Differentially expressed genes (DEGs) were identified with the R packages edgeR and glmmSeq (FDR < 0.05). Functional enrichment analysis of DEGs was performed with KOBAS-i API (FDR < 0.05). Protein-protein interactions of DEG products were characterized with String-DB (Interaction Score = 0.150).

Results

One and 4 DEGs were identified at d 14 and d 21, respectively. At d 21, DEGs enriched for regulation of G protein-coupled receptor signaling (increased in META) and interferon alpha and beta signaling (decreased in META). Predicted protein interactions indicated G-couple protein activity with pro-inflammatory cytokine suppression in META at d 21.

Significance

Our study highlights a potential secondary mechanism of action for tulathromycin in high-risk stocker cattle which down-regulates the expression of pro-inflammatory cytokines. Future investigations should focus on uncovering tulathromycin's secondary pharmacokinetics with respect to anti-inflammatory effect and genomic mechanisms in cattle which eventually develop BRD.

