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RNA-Seq analysis of ileocecal valve and peripheral blood from Holstein cattle infected with *Mycobacterium avium* subsp. *paratuberculosis* revealed dysregulation of the CXCL8/IL8 signaling pathway

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Paratuberculosis is chronic granulomatous enteritis of ruminants caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP). Whole RNA-sequencing (RNA-Seq) is a promising source of novel biomarkers for early MAP infection and disease progression in cattle. Since the blood transcriptome is widely used as a source of biomarkers, we analyzed whether it recapitulates, at least in part, the transcriptome of the ileocecal valve (ICV), the primary site of MAP colonization. Total RNA was prepared from peripheral blood (PB) and ICV samples, and RNA-Seq was used to compare gene expression between animals with focal or diffuse histopathological lesions in gut tissues versus control animals with no detectable signs of infection. Our results demonstrated both shared, and PB and ICV-specific gene expression in response to a natural MAP infection. As expected, the number of differentially expressed (DE) genes was larger in the ICV than in the PB samples. Among the DE genes in the PB and ICV samples, there were some common genes irrespective of the type of lesion including the *C-X-C motif chemokine ligand 8* (*CXCL8/IL8*), *apolipoprotein L* (*APOLD1*), and the *interferon inducible protein 27* (*IFI27*). The biological processes (BP) enriched in the PB gene expression profiles from the cows with diffuse lesions included the killing of cells of other organism, defense response, immune response and the regulation of neutrophil chemotaxis. Two of these BP, the defense and immune response, were also enriched in the ICV from the cows with diffuse lesions. Metabolic analysis of the DE genes revealed that the N-glycan biosynthesis, bile secretion, one-carbon pool by folate and purine metabolism were significantly enriched in the ICV from the cows with focal lesions. In the ICV from cows with diffuse lesions; the valine, leucine and isoleucine degradation route, purine metabolism, vitamin digestion and absorption and the cholesterol routes were enriched. Some of the identified DE genes, BP and metabolic pathways will be studied further to develop novel diagnostic tools, vaccines and immunotherapeutics.

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