PURINA PRO PLAN VETERINARY DIETS

Veterinary Medicine and Multi-Omics Research for Future Nutrition Targets: Metabolomics and Transcriptomics of the Common Degenerative Mitral Valve Disease in Dogs (Li et al., 2015)[1].

Introduction

Canine **degenerative mitral valve disease (DMVD)** is the most common form of heart disease that affects approximately 9% of all dogs with a cumulative incidence greater than 40% in advanced ages. The disease is characterized by a slowly progressive mitral valve degeneration and different histopathological changes in the **extracellular matrix (ECM)**, such as proteoglycan deposition and disruption of collagen filaments. However, **molecular changes contributing to DMVD** remain unclear.

The aim of the study was to characterize **molecular and metabolic pathways** that might play a role in the pathogenesis and progression of DMVD, by applying metabolomics and transcriptomics techniques.

Study design

For the **metabolomics** experiment, serum samples from 18 dogs affected by DMVD were collected and gender-matched with serum samples of healthy control dogs. Metabolites were identified and total RNA was extracted and sequenced. In order to confirm the results, a quantitative PCR validation assay was performed. During the analysis, the metabolites were ordered by the strength of their influence on the accuracy of prediction for separation between control and DMVD groups.

For the **transcriptomics** study, **mitral valve (MV)** tissue samples were obtained from 3 control dogs with no evidence of heart disease, and from 3 dogs with DMVD. Tissue samples from the free wall of **left ventricle (LV)** were collected from 4 control dogs and 2 dogs with DMVD. RNA from tissue samples was extracted and sequenced and **differentially expressed transcripts (DETs)** between control and DMVD groups were identified. The heart tissue samples were kindly donated with owner's consent, from dogs that died for reasons unrelated to this study.

Results

Metabolomics analysis of serum showed lower levels of glucose and higher levels of lactate in dogs with DMVD compared with controls. Succinyl- and hexanoyl-carnitine, which facilitate entry of activated acyl-CoA into the mitochondria, were higher in dogs with DMVD compared to healthy controls. In DMVD samples, markers of oxidative status such as oxidiced glutathione (GSSG) were higher compared with controls.

Analysis of serum metabolites showed 3 metabolites with higher influence in the separation between DMVD and control samples: γ-glutamylmethionine, GSSG, and dimethylarginine.

Global transcriptomic analysis in both tissues showed significantly over-represented gene ontology (GO) terms including response to chemical stimulus, response to lipid and response to stress.

Changes in gene expression related to energy metabolism were observed in dogs with DMVD. For instance, expression of fatty acid binding protein was lower, while fatty acid transporter protein was higher compared to controls.

DMVD dogs showed decreased gene expression of acyl CoA synthase and phytanoyl-CoA, important for activating and utilization **long chain fatty acids (LCFAs)** as an alternative source of energy.

Clinical outcomes

This study identified numerous metabolomics and transcriptomics changes that reflect altered energy metabolism, oxidative status, inflammatory mediators, and changes in ECM metabolism in dogs with DMVD.

Both **lipid and glucose metabolism** were altered in dogs with DMVD in the current study. Gene expression changes suggested that long chain fatty acids β-oxidation, branched-chain fatty acid α-oxidation, and ketolysis were compromised, while glucose uptake and glycolysis increased.

The current study showed that the expression of several genes involved in transport of LCFA to the cytoplasm were altered in cardiac tissue from dogs with DMVD. In contrast, expression of genes involved in glucose uptake and anaerobic glycolysis were increased.

Upregulation of several **pro-inflammatory cytokines** and their receptors were observed in DMVD dogs, demonstrating increased expression of the innate/adaptive inflammatory defence system.

Conclusions

Dogs with DMVD presented altered energy metabolism in cardiac tissues as well as an increase in markers of oxidative stress. Many of the observed disturbances may benefit from nutritional or medical management, but additional research is needed to more fully understand these alterations and their possible treatment.

[1]**Li Q, Freeman LM**, *et al. Veterinary Medicine and Multi-Omics Research for Future Nutrition Targets: Metabolomics and Transcriptomics of the Common Degenerative Mitral Valve Disease in Dogs. OMICS A Journal of Integrative Biology. 2015; 19:8.*