MicroRNA profiling of Canine Cervical Spondylomyelopathy.

Principal Investigator(s):

Principal Investigator:
Ronaldo C. da Costa
The Ohio State University
College of Veterinary Medicine
Dept. Veterinary Clinical Sciences
601 Vernon L. Tharp Street
Columbus, OH 43210
dacosta.6@osu.edu
614-292-3551

Project Duration: 2 years

Lay Abstract:

Cervical spondylomyelopathy (CSM) is a common cause of chronic cervical spinal cord dysfunction in large breed dogs most notably Great Danes and Dobermans. CSM causes pain, weakness and incoordination in the affected dogs. A lot of work has been done to document the etiology of this disease. However the disease process is still unclear. We can identify two separate causes of compression; the osseous compression is mainly seen in the Great Danes and other giant breeds whereas the disc-associated form is more common in the Dobermans and other large dogs. Medical and surgical treatment options exist; however, efficacy is variable across the therapeutic options.

Previous studies from our group have shown that canine CSM is a genetic disease; however, the exact mechanisms through which various genetic factors influence multiple aspects of CSM have yet to be fully defined. MicroRNAs (miRNAs) are small non-protein coding RNAs that regulate the expression of networks of genes. MiRNAs may regulate up to one-third of the human genes and thus play key roles in a wide variety of biological processes. In spite of hundreds of studies in humans and rodent models, there are no studies of microRNA investigating spinal cord diseases in dogs. A better knowledge of miRNA will be able to further our understanding of the disease process. Circulating miRNAs have recently been discovered in body fluids such as serum, plasma, urine, milk, and spinal fluid. Recent studies have explored the potential usefulness of disease-specific miRNAs as non-invasive biomarkers for early disease detection, prognosis, and response to treatment. To our knowledge, no miRNA profiling has been done in dogs or in humans affected by a similar disease termed cervical spondylotic myelopathy. Cerebrospinal fluid (CSF) is an ideal biofluid for analysis due to its close proximity to the spinal cord and a tightly regulated barrier from the rest of the body. In this study, we will characterize the miRNA expression profile of CSF from dogs with CSM

and compare that to clinically healthy dogs. We will also investigate specific miRNA. These findings will be used in the future to correlate with the miRNA present in the spinal cord tissue. In addition to building on our understanding of the disease process, miRNA may also be a useful tool to monitor therapeutic responses aiding not only in our canine model but also translating to the human form of CSM.

STUDY PROPOSAL

A. Scientific Abstract

Cervical spondylomyelopathy (CSM) is the most common cause of cervical cord dysfunction in large breed dogs. CSM causes significant gait abnormalities, leading to severe disability and pain. Two different forms of CSM have been documented, osseous-associated compression (OACSM) mainly seen in Great Danes and other giant breeds and disc-associated (DACSM) where Dobermans and other large dogs are commonly affected. CSM is a multifactorial syndrome complicating our understanding of the etiology. A genetic etiology has been documented in Dobermans and is suspected in many other breeds. Medical and surgical treatments have been described, however, their efficacy is variable. A similar condition to canine CSM is also seen in humans, termed cervical spondylotic myelopathy (hCSM).

There is a pressing need for further understanding of the etiology and pathogenesis of CSM. We have documented that CSM is a genetic disease. The exact genes and expression of the disease are currently being investigated with Genomic wide association sequences. MicroRNAs (miRNAs) are small non-protein coding RNAs that regulate gene expression and play key roles in a wide variety of biological processes. These have been used to investigate many neurodegenerative diseases as well as central nervous system malignancies. To our knowledge, no miRNA profiling has been done for CSM in either humans or the canine counterpart; as a matter of fact there are no studies that investigated miRNA expression in any canine spinal cord disease. In this study, we plan to evaluate the cerebrospinal fluid (CSF) of clinically affected dogs and compare the miRNA profile to matched neurologically normal dogs. We will further evaluate miRNA expression directly in spinal cord tissues to correlate the presence of miRNA in the CSF and the spinal cord. Data generated from this project will improve our understanding of the pathogenesis of CSM and identify miRNAs that may serve as clinically useful biomarkers for this disease in both dogs and humans.