Cruciate ligament rupture is a debilitating injury that causes arthritis and affects both dogs and humans. It affects more than one million dogs in the United States every year at an estimated annual impact of 1.3 billion dollars. The reasons why the ligament ruptures and how this injury initiates arthritis in the knee is poorly understood. This limited knowledge prevents comprehensive treatment and the development of novel strategies for the prevention of this disease and/or the arthritis that results from it. For these reasons, genes and proteins that may be linked to this disease or arthritis were investigated. Normal and diseased tissues were initially evaluated to differentially identify genes that may be involved in this disease process. Structural, degradative and inflammatory genes were found to be expressed differentially in these tissues. Proteins from these genes were also investigated and supported the role of these genes in this disease process. The role of mechanical stimulus in ligament health was investigated. Both amount and duration of the stimulus were found to affect these same genes. The role of these genes and proteins was confirmed in live dogs and new methods to identify degradative proteins were evaluated. Further investigation of these genes and molecules in cruciate ligament disease is warranted. This research has implications for both humans and dogs. The identified genes and proteins may assist in the early diagnosis of this disease or may serve as targets for treatment modalities.