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Pathology, protein expression and signaling in myxomatous mitral valve degeneration: Comparison of dogs and humans

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Abstract Myxomatous degenerative mitral valve disease (MMVD) is a common heart disease in dogs. Although several morphological similarities occur between human and canine MMVD differences exist. However, in advanced stages the accumulation of proteoglycans is the main finding in both species.

The extracellular matrix (ECM) in normal canine and human mitral valves is similar. In MMVD of both species proteoglycans is the major alteration, although specific changes in collagen distribution exists.

The valvular expression pattern of matrix metalloproteinases (MMPs) and of their inhibitors (TIMPs) differs, in part, between dogs and humans. The MMPs and TIMPs expression patterns are similar in normal canine and human mitral valves, but they are quite different during degenerative progression.

Valve endothelial cells (VEC) and interstitial cells (VIC) are phenotypically transformed in canine and human MMVD. Inflammation is an unlikely cause of valve degeneration in humans and dogs. There are several lines of evidence suggesting that transforming growth factor β1 (TGF β1) and serotonin signaling may mediate valve degeneration in humans and dogs.

Although human and canine MMVD share structural similarities, there are some differences in ECM changes, enzyme expression and cell transformation, which may reflect a varied pathogenesis of these diseases.

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Abbreviations

CKCS	Cavalier King Charles Spaniel
MMVD	myxomatous mitral valve disease
MMP	matrix metalloproteinase
MVP	mitral valve prolapse
TGF	transforming growth factor
TIMP	tissue inhibitor of metalloproteinase
VEC	valve endothelial cell
VIC	valve interstitial cell

Introduction

Myxomatous mitral valve disease (MMVD) is a common acquired cardiac disease in older small and medium-sized dogs.[1,2] The mitral valve is comprised of two leaflets (anterior or septal and posterior or mural leaflets). Normal valve leaflets are grossly thin and transparent (Fig. 1A).[1] The myxomatous valves are macroscopically characterized by nodular thickening of the valve leaflets (Fig. 1B).[3] The chordae tendineae are elongated.[4–6] Myxomatous mitral valve disease develops mainly in dogs older than seven years of age.[1] Males are more susceptible to develop the disease than females.[7] The etiology of canine MMVD is still unclear. Hemodynamic, endogenous and genetic factors have been discussed.[1,7,8] In dogs, breeds predisposed to connective tissue disorders including intervertebral disc disease, tracheal collapse and cruciate ligament rupture are also affected with MMVD.[9] Such breeds include Dachshund, Cocker spaniel, Poodle, Schnauzer, Chihuahua and Terriers.[1] This disease is considered to be inherited in some breeds including Cavalier King Charles Spaniel (CKCS) and Dachshund.[10–13] Myxomatous mitral valve disease in CKCS occurs at an early age and may be caused by a polygenic inheritance.[12] Clinically, the degeneration of the valves and corresponding chordae tendineae causes an inappropriate coaptation of the leaflets leading to valve regurgitation and finally resulting in left sided congestive heart failure.[1,2,14–17]

In man, a morphologically similar disease (Fig. 1C) has been described.[18] Human MMVD causes prolapse or billowing of mitral valve leaflets into the left atrium during systole. The prevalence of MMVD in the human population is associated with age.[19] Mitral valve prolapse, a risk factor for development of MMVD later in life, is more prevalent in females than males.[20] Patients with mitral valve prolapse tend to have low body mass index, but the reason for this phenomenon is uncertain.[21] The etiology of human MMVD is unknown. The risk factor of mitral valve prolapse may be inherited as an autosomal dominant or a polygenic abnormality.[22,23] It often displays familial transmission.[24] Connective tissue disorders

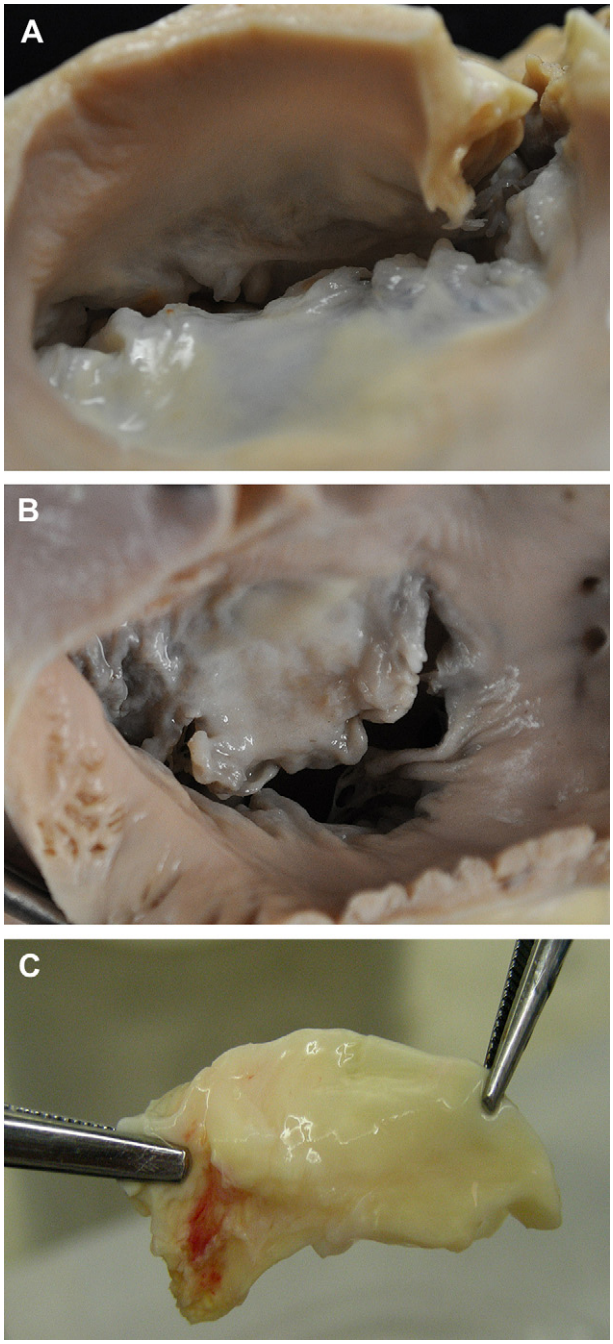

Figure 1 Gross findings in mitral valves (A) Normal mitral valve from a 3-year-old dog. The leaflets are thin and regular and the chordae tendineae are uniform. (B) Marked chronic valve disease from 8-year-old dog: The leaflets of the mitral valve are thickened, white in colour and deformed with the free edges rolled upward. There is evidence of chordal rupture (C) Human surgically removed diseased valve from 59-year-old male. The valve is thickened with irregular surface and hemorrhage.