

Role of Transient Receptor Potential Channels in Marfan Syndrome-induced Aortopathy and Cardiomyopathy

Background: Marfan syndrome (MFS) represents a genetic disorder with variable phenotypic expression. The main cardiovascular sequelae of MFS include aortic aneurysm/dissection and cardiomyopathy. While significant advances in the understanding of TGF- β signaling have led to promising therapeutic targets for the treatment of aortopathy, clinical studies have tempered this optimism. In particular, these studies suggest additional signaling pathways that play a significant role in aortic disease progression. Furthermore, even less is known with respect to effectors involved in MFS-induced cardiomyopathy. To date, studies aimed at elucidating molecular mechanisms involved in MFS-induced disease progression have been hampered by the lack of an accelerated disease model. Meanwhile, transient receptor potential (TRP) channels have been implicated as key effectors in other vascular smooth muscle and cardiomyocyte pathologies, yet there is a paucity of investigation focused on their involvement in the aortopathy and cardiomyopathy of MFS. In these studies, we investigate the importance of TRP channels in the pathogenesis of MFS-induced aortopathy and cardiomyopathy by evaluating differential expression in a novel murine model of accelerated MFS etiology.

Methods: B6.129 (Wild-type [WT]) and Fbn1C1039G/+ (MFS) mice were used to create accelerated aortic aneurysms and cardiomyopathy via subcutaneous osmotic mini-pump installation in 3 treatment groups: WT + 0.9% saline (vehicle); MFS + vehicle; MFS + angiotensin II (4.5mg/kg/day) (accelerated group). Gene expression of aortic tissue was attained through quantitative PCR. Cardiac tissue differential expression of TRP channels among treatment groups was attained by harvesting mouse hearts and performing quantitative PCR, RNA sequencing, and western blotting.

Results: The accelerated murine MFS model demonstrates increased mortality from MFS-related maladies (63% at 28 days versus 0% for non-accelerated MFS mice). Aortic root diameters in accelerated MFS mice were significantly enlarged at 10 days after minipump implantation and correlated with a higher degree of elastin fragmentation. Dilated cardiomyopathy was demonstrated within 14 days, with 60% penetrance (based upon <80% ejection fraction and an indexed end-diastolic volume >1.75 (μ l/g of body mass)) and correlated with histopathologic changes. Using the same criteria, at least 40% of the accelerated MFS mice with mild to no aortic insufficiency presented with an intrinsic dilated cardiomyopathy. Importantly, none of the vehicle treated mice met the dilated cardiomyopathy criteria. Differential gene expression of TRP channels in aortic tissue attained through quantitative PCR revealed a 9.9-fold increase in TRPC4 when comparing the accelerated MFS model with WT mice. In cardiac tissue, TRPC6 expression was enhanced in the accelerated model at the DNA (2-fold increase), RNA (1.7-fold increase) and protein (5-fold increase) level.

Conclusions: This new accelerated murine model creates consistent and accelerated MFS-induced aortic aneurysms and primary cardiomyopathies to aid in the expedited investigation of the disease. This study suggests a potential role for TRPC4 in MFS-induced aortic aneurysm formation and TRPC6 in MFS-related cardiomyopathy.