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Towards Multi-Modality Therapy for Marfan Syndrome: Synergistic Effect of Angiotensin and TRPC4 Receptor Blockade on Ascending Aortic Aneurysms

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Background

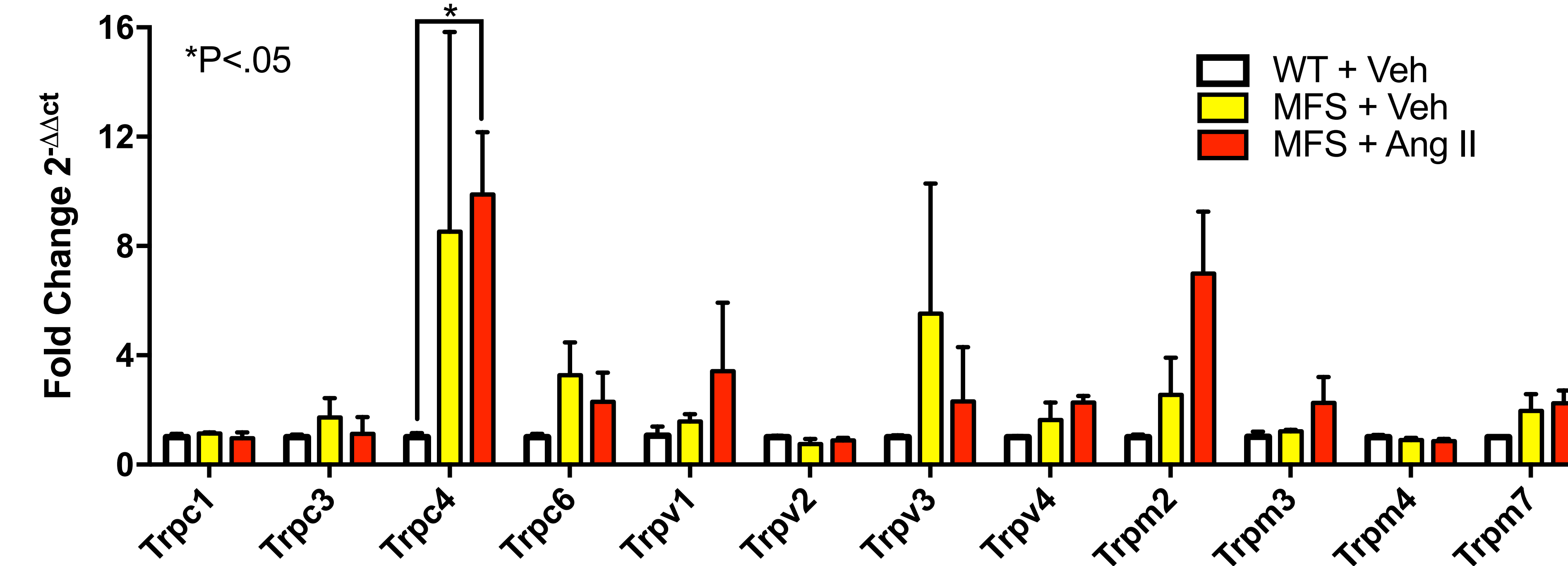
Marfan syndrome (MFS) is a genetic disease that commonly presents with aortopathy. While promising therapies have been studied, complete attenuation of MFS-induced aortic aneurysms in the clinical arena has been elusive. The presence of significant, not-yet described MFS signaling pathways has been suggested as a reason for the less than ideal clinical response to single drug therapy. Transient receptor potential (TRP) channels have emerged as likely regulators of vascular smooth muscle cell (VSMC) activity. In this regard, they are abundantly found in VSMCs and are associated with increased matrix metalloproteinase 9 activity. The current study seeks to explore the role of TRP channels in MFS.

Methods

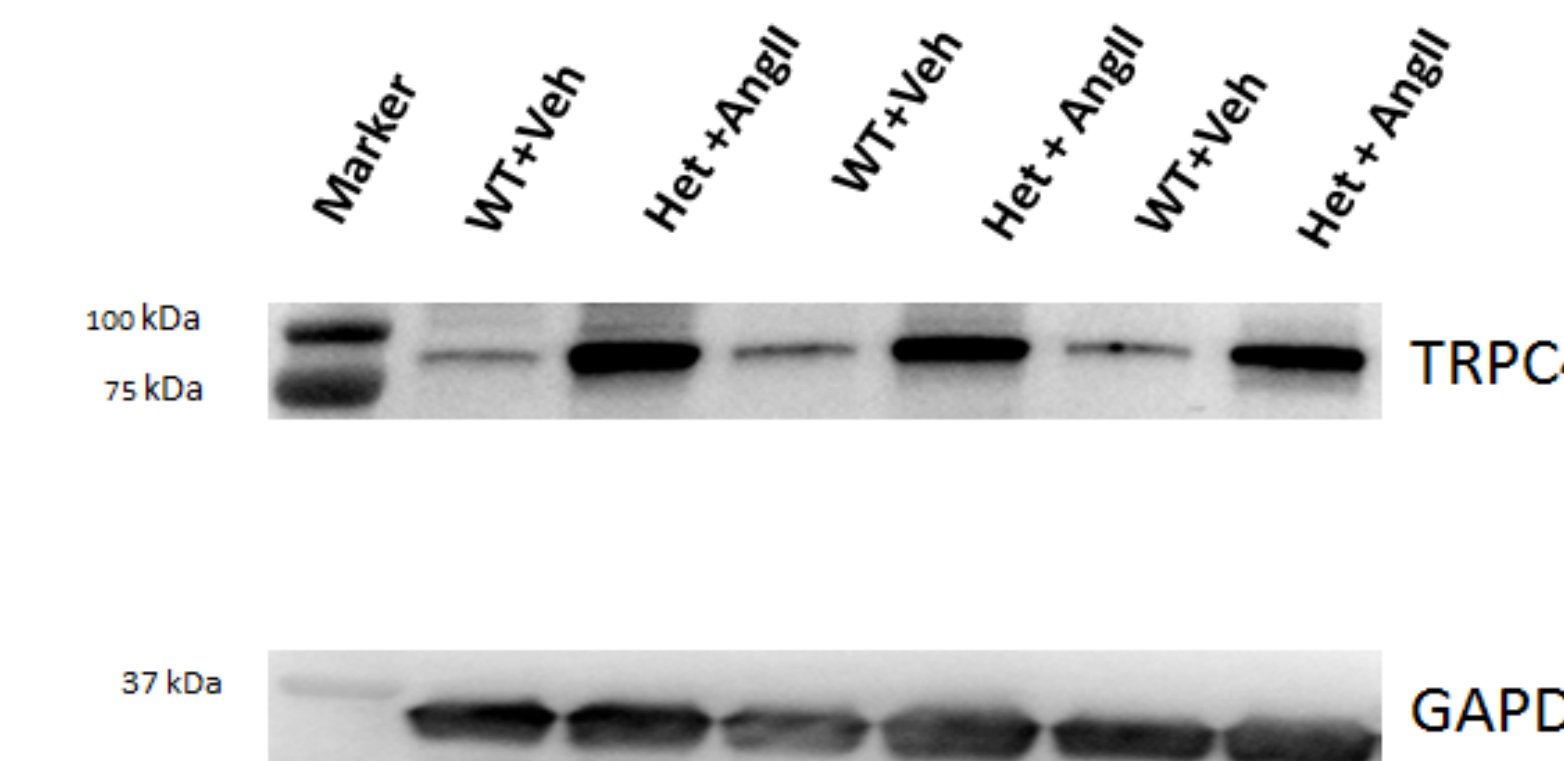
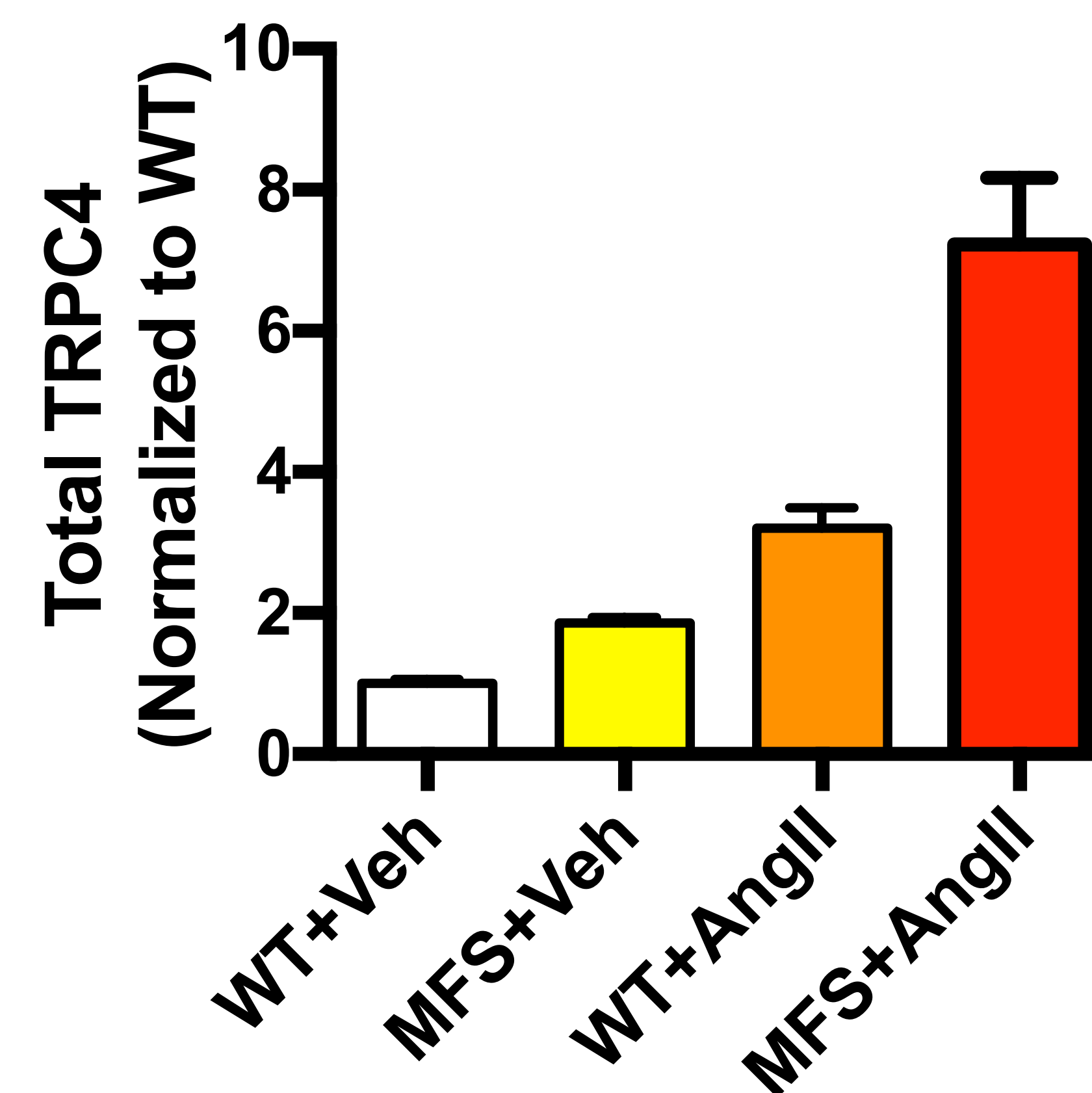
A Fbn1C1039G/+ heterozygous mouse, with a mutation in fibrillin-1, was supplemented with angiotensin II (4.5 mg/kg/day) to accelerate aneurysmal formation. Mice analyzed were wild type (wt) (saline +/- angiotensin II) and heterozygous (saline +/- angiotensin II). Quantitative PCR and western blotting was used to examine differential expression of TRP channels across the various cohorts. The TRPC4 antagonist, ML204 (10mg/kg/day), was given daily during two weeks of angiotensin II infusion. Mice were echoed before and after to assess aortic diameter.

Results

Quantitative PCR of the accelerated model revealed a near 10-fold increase in TRPC4 transcription with respect to wt mice. ML204 and losartan worked synergistically to ameliorate aortic dilation.



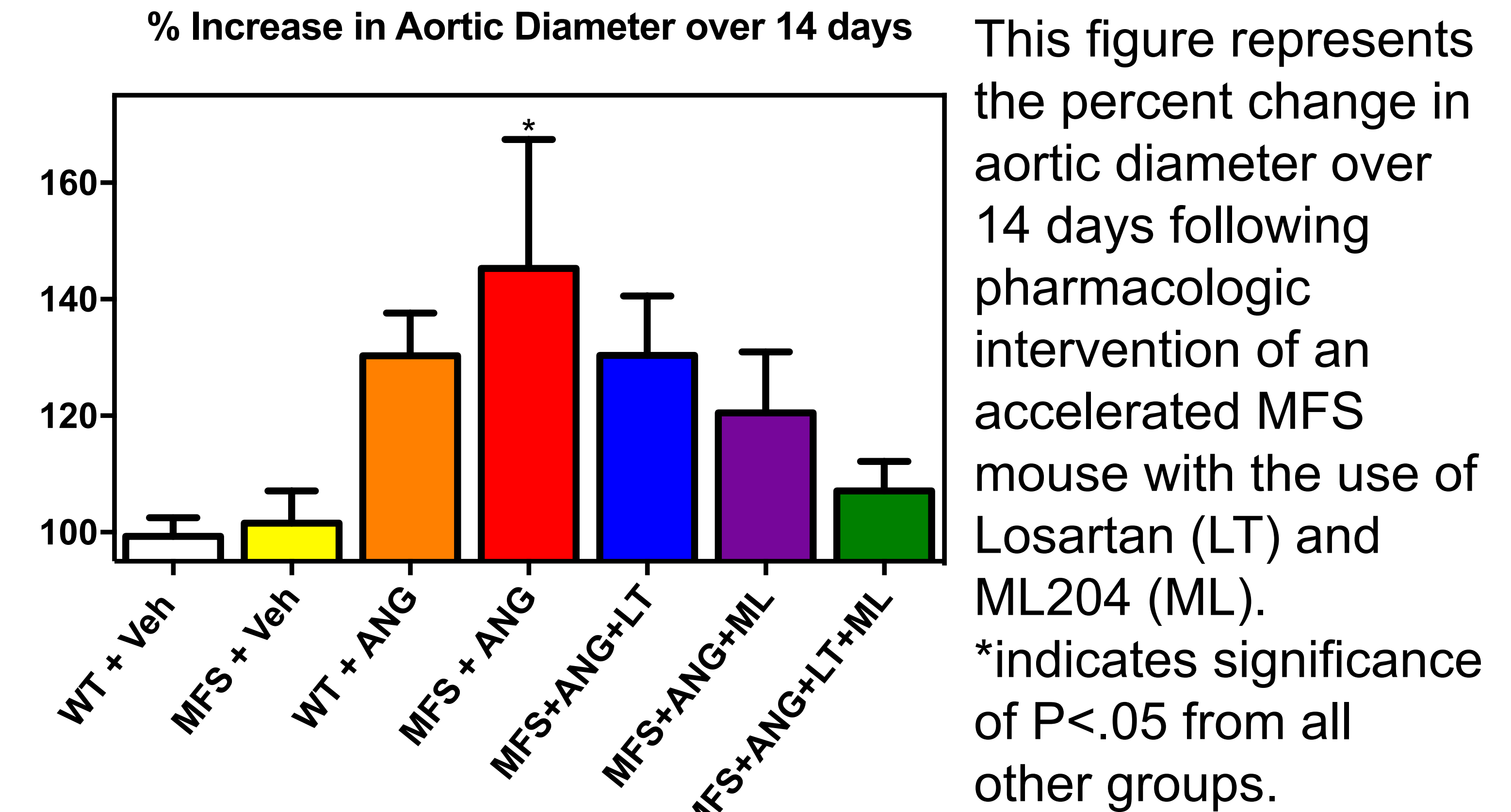
This figure represents relative transcription of transient receptor potential channels with normalization to wt mice in triplicate.



Left: Protein expression of TRPC4 normalized to wt mice from western blots of aortic tissue.

Above: Transillumination of a sample TRPC4 western blot.

Murine Model Aortic Diameter



This figure represents the percent change in aortic diameter over 14 days following pharmacologic intervention of an accelerated MFS mouse with the use of Losartan (LT) and ML204 (ML). *indicates significance of P<.05 from all other groups.

Conclusions

These studies suggest a complementary role for TRPC4 in MFS-induced aortic pathology. Antagonism of this novel target shows promise toward multi-drug therapy for the treatment of aortic aneurysms in MFS.

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