Blockade of Serum and Glucocorticoid Inducible Kinase-1 (SGK-1) can Attenuate Abdominal Aortic Aneurysm (AAA) Growth

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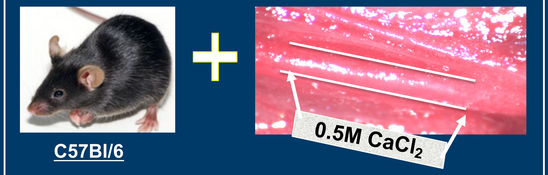
IL-6 and AAA

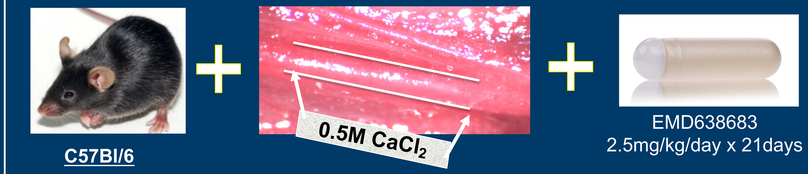
- Interleukin-6 (IL-6) levels elevated in serum and tissue of patients with AAA
- IL-6 signaling pathway promotes MCP-1 expression to accumulate macrophages
- Murine model of IL-6 infusion amplified aortic macrophage infiltration and promoted dilation
- Cyclic stretch of VSMCs can induce IL-6 expression

AAA Induction with $CaCl_2$



SGK-1 Blockade with EMD638683

AAA Induction with SGK-1 Blockade



What tension-induced signaling pathway is activated?

SGK-1

- Mechanosensitive kinase implicated in vein bypass graft remodeling, pulmonary hypertension, and pro-inflammatory cytokine production
- Upregulated in rabbit carotid aneurysm model
- EMD638683 is a commercially available selective inhibitor of SGK-1

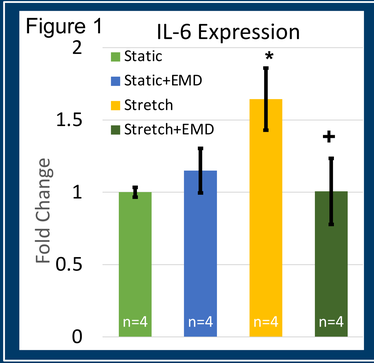


Figure 1. IL-6 expression in aortic VSMCs following 3hrs of cyclic stretch.

By ANOVA,
*p<0.05 vs Static
+p<0.05 vs Stretch

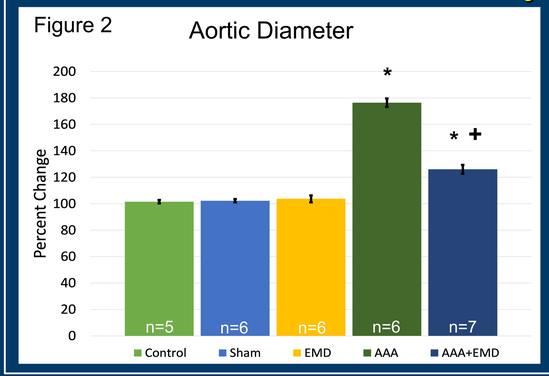
Inhibition of SGK-1 reduced IL-6 expression

Can this be applied to modulate AAA growth?

Hypothesis

Blockade of SGK-1 activity can attenuate AAA growth

SGK-1 Blockade Attenuates Aneurysm Growth with No Effect on Systolic Blood Pressure



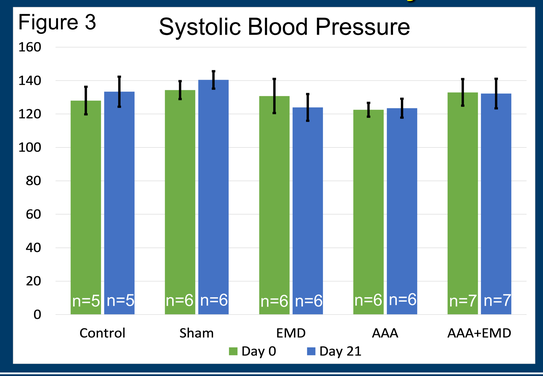
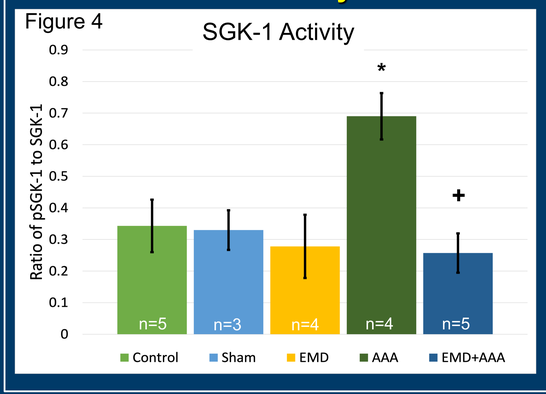


Figure 2. Aortic diameter percent change above baseline at day 21 in C57Bl/6 mice +/- EM638683 infusion, +/- AAA

Figure 3. Systolic blood pressure at day 0 and day 21 in C57Bl/6 mice +/- EM638683 infusion, +/- AAA

By ANOVA,
*p<0.05 vs Control
+p<0.05 vs AAA

SGK-1 Activity Increased in AAA and Promoted Macrophage Accumulation



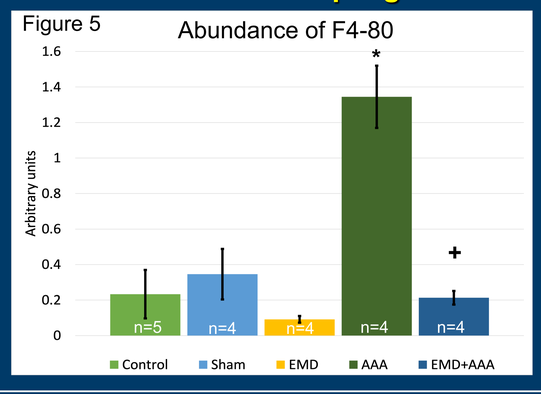


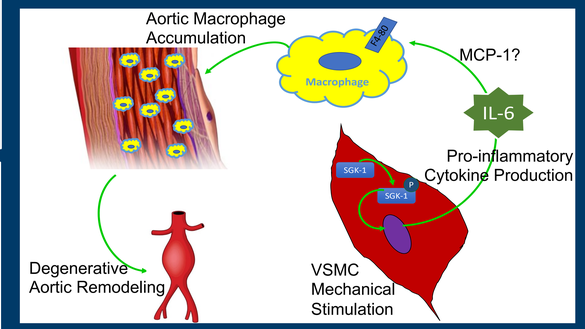
Figure 4. Activity of SGK-1 in abdominal aorta of C57Bl/6 mice +/- EM638683 infusion, +/- AAA

Figure 5. Abundance of F4/80 in abdominal aorta of C57Bl/6 mice +/- EM638683 infusion, +/- AAA

By ANOVA,
*p<0.05 vs Control
+p<0.05 vs AAA

Summary

- SGK-1 activity was increased in AAA and when inhibited by EMD638683, aortic dilation as well as macrophage accumulation were significantly decreased without effecting blood pressure
- These data support SGK-1 signaling as a major contributor to macrophage accumulation and propagation of AAA growth



Conclusion

- Systemic therapy to attenuate SGK-1 activity can modulate aortic macrophage accumulation to reduce aortic degenerative remodeling
- SGK-1 may represent a novel pharmacotherapeutic target to abrogate AAA growth