

from explanted aortas ($p < 0.05$). Explanted aortas from Nox2-Tg had significantly higher levels of secreted pro-inflammatory cytokine, cyclophilin A (Cypa) at both baseline and after 5 days of in vivo AngII treatment compared to WT littermates. Compared to primary WT EC and VSMC, Nox2-Tg primary EC, but not primary VSMC, had increased ROS production which was accompanied by increased Cypa secretion and ERK1/2 activation. Furthermore, conditioned media from Nox2-Tg EC induced a greater ERK1/2 phosphorylation compared to the media of WT controls. In conclusion, we demonstrate for the first time that a specific increase in endothelial ROS through the over-expression of Nox2 is sufficient to induce aortic dissection in response to AngII stimulation. Endothelial secreted Cypa could be the signalling mechanism by which increased endothelial ROS regulates the inflammatory response and the susceptibility to aortic dissection.

D ENDOTHELIUM SPECIFIC INSULIN RESISTANCE LEADS TO ACCELERATED ATHEROSCLEROSIS: A ROLE FOR REACTIVE OXYGEN SPECIES

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Background Global insulin resistance and endothelial dysfunction have been identified as predisposing factors for atherosclerosis. However, it is unclear whether selective insulin resistance in endothelial cells alone, is sufficient to promote atherosclerosis. We addressed this question by crossing Endothelial Specific Mutant Insulin Receptor Over-expressing (ESMIRO) mice with ApoE^{-/-} mice. ESMIRO mice over-express a human insulin receptor with an Ala-Thr1134 mutation in the tyrosine kinase domain (which disrupts insulin signalling) selectively in endothelial cells under the control of the tie-2 promoter/enhancer.

Methods Male ApoE^{-/-}/ESMIRO mice were compared with sex-matched littermate ApoE^{-/-} mice (both on a C57Bl6 background) after feeding a Western-style diet for 12 weeks.

Results ApoE^{-/-}/ESMIRO mice were morphologically indistinguishable from ApoE^{-/-} control littermates and showed normal development with no differences between groups in body mass. Heart rate, systolic blood pressure, glucose tolerance, insulin sensitivity and fasting glucose levels were similar in ApoE^{-/-}/ESMIRO and ApoE^{-/-} mice. ApoE^{-/-}/ESMIRO cultured endothelial cells demonstrated insulin resistance through significantly reduced insulin mediated eNOS activity ($p = 0.003$). Aortic lipid deposition along the whole aorta, assessed by en-face oil red O staining, was similar in ApoE^{-/-}/ESMIRO and ApoE^{-/-} mice ($6.4\% \pm 0.5\%$ vs $5.8\% \pm 0.5\%$; $p = 0.39$). Analysis of lipid deposition along the lesser curvature of the aortic arch revealed a significant increase in ApoE^{-/-}/ESMIRO when compared to controls (9.4 ± 0.89 vs $12.43 \pm 1.19\%$ $p = 0.035$). Atherosclerotic lesion area in cross sections of aortic sinus was also significantly increased in ApoE^{-/-}/ESMIRO mice compared to ApoE^{-/-} controls ($24.8\% \pm 2.4\%$ vs $16.6\% \pm 2.4\%$; $p = 0.02$). Vascular function assessed through relaxation responses of aortic rings in response to the endothelial specific vasodilator acetylcholine revealed that aortic rings from ApoE^{-/-}/ESMIRO mice had blunted relaxation responses to acetylcholine (E_{max} ApoE^{-/-} 102.88 ± 6 , E_{max} ApoE^{-/-}/ESMIRO $65 \pm 41\%$, $p = 0.02$), which was restored by the superoxide dismutase mimetic and antioxidant MnTMPyP (E_{max} ApoE^{-/-}/ESMIRO without MnTMPyP $65 \pm 41\%$, with MnTMPyP $112 \pm 15\%$ $p = 0.048$). Endothelial cells from ApoE^{-/-}/ESMIRO mice had significantly increased basal generation of superoxide (1.87-fold increase compared to ApoE^{-/-} $p < 0.05$) which was blunted by the selective NADPH oxidase inhibitor gp91ds-tat (11% reduction ± 0.02 , $p = 0.03$) and the

non-selective NO synthase inhibitor L-NMMA (6% reduction ± 0.01 , $p = 0.03$).

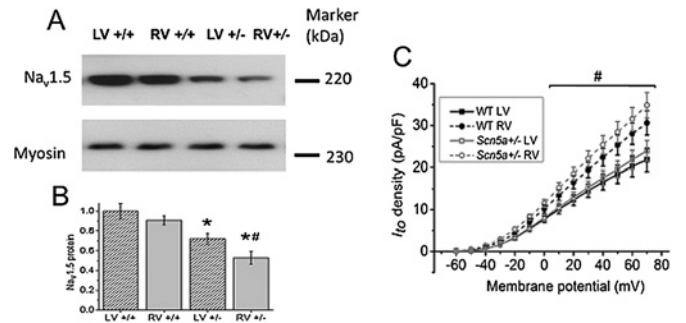
Conclusions Endothelial specific insulin resistance is sufficient to promote atherosclerosis and increase lesion area in ApoE null mice potentially via the increased ROS displayed in this model. This suggests that enhancing endothelial insulin sensitivity may be an appropriate target to prevent atherosclerosis in insulin-resistant conditions.

E RIGHT VENTRICULAR ORIGIN OF ARRHYTHMIAS IN Scn5A^{+/-} MICE IS DUE TO REDUCED NA⁺ AND HIGHER K⁺ CHANNEL EXPRESSION AND FUNCTION

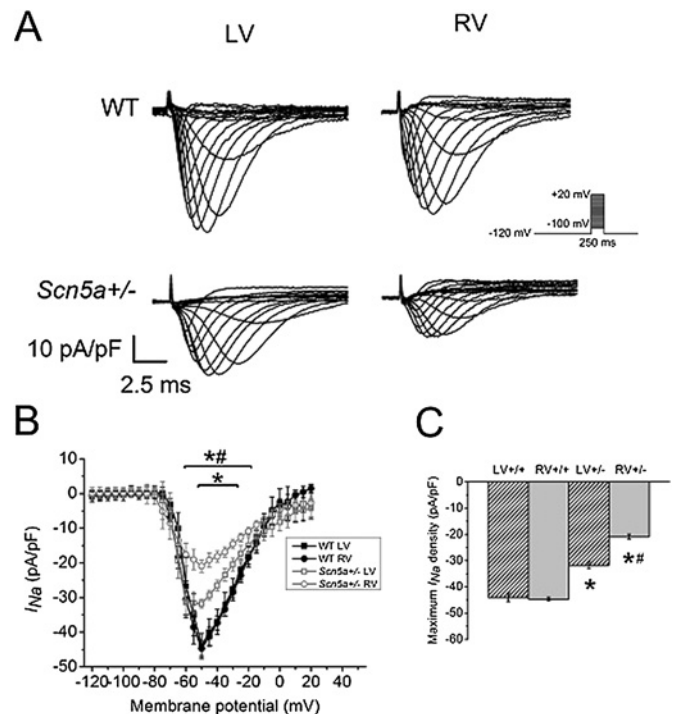
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Introduction Brugada syndrome is associated with ventricular tachycardia originating in the right ventricle (RV); this has been



Abstract E Figure 1



Abstract E Figure 2