cardiomyocytes with the titin truncating variant showed poorer sarcomere organization compared to wildtype (62.0 ± 3.9 vs. 82.9 ± 2.9; p = 0.008; Figure 1C).

CONCLUSION: Titin truncating variants lead to abnormal sarcomere organization in both atrial and ventricular iPSC-derived cardiomyocytes, and this phenotype can be reverted through CRISPR/Cas9 correction of the titin truncating variant to wildtype. These findings further our understanding of the role of titin in the atria and provide insight to the mechanisms by which titin truncating variants may promote arrhythmogenesis.

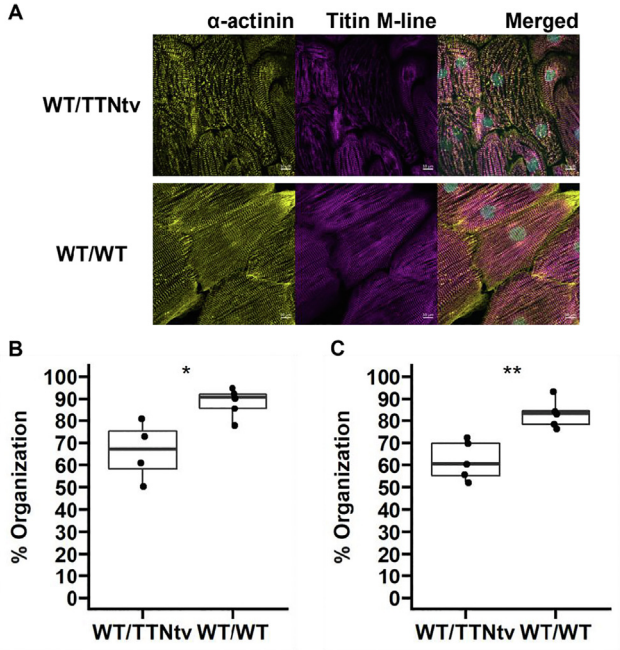

Figure 1. Assessment of sarcomere structures. (A) Confocal microscope images of iPSC-derived atrial cardiomyocytes stained for sarcomere α-actinin, titin, and DNA. Quantification of sarcomere organization in iPSC-derived (B) atrial and (C) ventricular cardiomyocytes (n = 4-5 biological replicates). Abbreviations: TTNtv, titin truncating variant; WT, wildtype.

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P003
CORRELATION OF CELL SENESCENCE WITH THE AGE-ASSOCIATED INCREASE IN VWF EXPRESSION

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BACKGROUND: Von Willebrand factor (VWF) is an endothelial-specific pro-coagulant protein with a major role in thrombosis. It mediates the primary step in thrombogenesis, which is platelet adhesion to the endothelium/sub-endothelium surfaces. Increased VWF level is a significant risk factor for thrombus formation and has been associated with aging. However, the mechanism underlying this age-related increase in VWF remains unknown. We explored the molecular mechanism and functional consequences of age-related upregulation of VWF.

METHODS AND RESULTS: Elisa, western blot and RT-PCR analyses were used to determine circulating plasma levels, cellular protein, and mRNA levels of VWF, in young and aged mice. Immunofluorescent analyses of major organs were performed to establish vascular patterns of VWF and the presence of platelet aggregates. Cultured endothelial cells were used as an in vitro model of aging to explore the mechanism of increased VWF levels. Increased plasma levels of VWF were observed in aged mice. VWF mRNA and protein levels were increased in the endothelium of the brains, lungs and livers, but not kidneys and hearts of aged mice. The distribution of VWF expression in organs was altered from primarily large vessels in young, to include small vessels in the aged mice. Increased platelet aggregates formation in vessels of aged organs was concomitant with increased VWF expression, consistent with increased thrombogenicity. Aspirin treatment significantly reduced platelet aggregates formation in aged mice. Prolonged maintenance of endothelial cells in culture, resulting in cell senescence, correlated with increased VWF at mRNA and protein levels. When cultured endothelial cells were separated into senescent and non-senescent populations VWF levels were consistently higher in the senescent population. Senescence marker β-galactosidase and senescence-associated transcription factor p53 were detected specifically in aged (but not young) brain microvascular endothelial cells that exhibited VWF expression. Aged mice treated with proteolipid vehicles (PLV) encapsulating a DNA-based senolytic targeting senescent cells with elevated p53 transcriptional activity for destruction, exhibited a significant reduction in platelet aggregates formation in the brain vasculatures when compared to control animals.

CONCLUSION: VWF levels and expression patterns were increased in response to aging in an organ-specific manner. This was concomitant with increased platelet aggregate formation, which is a risk factor for age-associated thrombotic disorders. The potential mechanism of age-associated increase in VWF expression may include cell senescence.

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P004
EFFECT OF GLYCOSAMINOGLYCANS ON OPENING ANGLE OF INTACT & CROSSLINKED AORTAS

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BACKGROUND: Ruptures caused by aortic aneurysms and dissections occur when the mechanical stresses in the aortic wall exceed the local aortic strength. In-vivo stresses are strongly mediated by residual stresses (RS), those existing in the absence of