Loss of SPRR3 In *ApoE*$^{-/-}$ Mice Leads to Increased Atheroma Vulnerability and Evidence of Plaque Rupture and Cardiac Infarcts

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Atheroma rupture is the leading cause of myocardial infarction. While studies have examined inflammatory cell-mediated effects on plaque vulnerability, less is known about the role of vascular smooth muscle cells (VSMCs) or specific molecular players in the maintenance of atheroma stability. We reported that loss of small proline-rich repeat protein 3 (SPRR3), enriched in atheroma VSMCs, leads to increased VSMC death and significantly accelerates atherosclerosis progression in *ApoE*$^{-/-}$ mice. Here, we show that loss of SPRR3 promotes features in plaques of brachiocephalic arteries common to unstable lesions, such as increased necrotic core size, reduced cap collagen content, and reduced VSMC content. Moreover, *ApoE*$^{-/-}$ mice lacking SPRR3 develop coronary artery lesions with advanced features, including intraplaque hemorrhage. In addition, *Sprr3*$^{-/-}$*ApoE*$^{-/-}$ mice fed a high-fat diet for 6 months develop spontaneous myocardial infarction. *In vitro*, SPRR3 deficient VSMCs show reduced expression of procollagen type I, an event associated with Akt activation. SPRR3-deficient VSMCs also show increased expression of MMP2 transcripts, and aortic root lesions of *Sprr3*$^{-/-}$*ApoE*$^{-/-}$ mice have increased gelatinase activity consistent with MMP2 activation. Our data demonstrate that SPRR3 loss in *ApoE*$^{-/-}$ mice decreases VSMC survival and collagen I synthesis while increasing MMP2 synthesis and activity, resulting in atheroma instability with evidence of downstream myocardial infarction. Taken together the results present the *Sprr3*$^{-/-}$*ApoE*$^{-/-}$ mouse as an experimental model of plaque rupture. This model will be used for additional experimental studies including *in vivo* genetic modulation of the Akt pathway as well as *in vitro* studies to determine phenotypic outcome, i.e. coronary arterial lesions, myocardial infarction, VSMC survival and collagen synthesis. We hope to establish a mechanistic link between altered Akt signaling and matrix integrity in the context of atheroma rupture, as well as potentially use SPRR3 as a molecular marker which could lead to detection of plaque instability as well as therapeutic intervention methodologies.

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