Abstract: **P715**

**Deletion of fibroblast activation protein decreases experimental atherosclerotic plaque formation and vulnerability**

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**Background:** Fibroblast activation protein (FAP) is a serine protease that is upregulated in sites of tissue remodeling, including arthritis, tumors and atherosclerosis. We have reported that FAP degrades type I collagen in human thin-cap fibroatheromata; its expression is enhanced in advanced human plaques and induced by inflammation. However, the role of endogenous FAP in atherosclerosis remains unknown.

**Purpose:** To investigate the effects of constitutive Fap loss-of-function on atherosclerotic plaque formation and vulnerability.

**Methods and Results:** Male 8-week-old Apoe⁻/⁻ Fap⁺/+ and Apoe⁻/⁻ Fap⁻/- mice were fed a high-cholesterol diet (1.25% chol) for 12 weeks. En face analyses of thoracoabdominal aortae using Oil Red O (ORO) revealed decreased plaques in Apoe⁻/⁻ Fap⁻/- mice (5.7 ± 0.5%; n=21) compared to Apoe⁻/⁻ Fap⁺/+ mice (10.7 ± 0.7%; n=24; p<0.0001). In parallel, ORO analyses of serial aortic root cross sections showed diminished plaques in Fap-deficient mice (18.4 ± 3.4% vs 27.6 ± 2.1%). As a surrogate of plaque vulnerability, fibrous cap thickness was increased in Apoe⁻/⁻ Fap⁻/- mice (65 ± 6 mm vs 35 ± 3 mm; p<0.01), whereas necrotic core size, plaque macrophages (CD68) and T cells (CD3) accumulation, as well as VCAM1 expression did not differ. These changes were independent of plasma triglycerides, total and LDL-cholesterol levels. Plasma of Fap-deficient mice showed decreased FAP activity compared to Fap wildtype controls. Notably, second harmonics generation in cross sections of aortic root plaques showed that the deposition and density of fibrillar collagens was enhanced in Fap-deficient (25.5 ± 4.4%) compared to control plaques (13.8 ± 2.5%; p<0.05). Consistently, Fap deletion led to an accumulation of uncleaved pre-COL3A1, a proteolytic target of FAP.

**Conclusions:** Constitutive Fap deletion decreases experimental atherosclerosis and features of plaque vulnerability. Thus, inhibition of FAP expression or activity may be a promising therapeutic target in atherosclerosis.