**A TRANSGENIC MOUSE MODEL OF ATHEROSCLEROTIC PLAQUE CALCIFICATION**

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*Objective*: To create a model of calcified atherosclerotic plaque.

*Background*: Arterial calcification is associated with cardiovascular mortality independent of other risk factors. This association, however, is complex. Microcalcification is thought to promote inflammation and destabilize atherosclerotic lesions leading to plaque rupture and adverse cardiovascular events, whereas macrocalcification is associated with stable fibroatheromas. Here we designed and implemented a genetic approach to manipulate the level of plaque calcification in a mouse model. We report our initial characterization of these transgenic animals, in which TNAP – an essential enzyme that promotes biomineralization – was overexpressed in monocytes and macrophages and led to plaque calcification.

*Methods*: Expression of TNAP-encoding transgene (Sheen et al, 2015) was activated by the Cre recombinase driven by myeloid-specific (lyzM) gene promoter. Both the reporter (TNAP) and the driver (LyzM-cre) mice were also homozygous for a mutation in the low density lipoprotein receptor (Ldlr^Hlb301). Atherosclerosis was induced in TNAP-overexpressor and control mice by feeding an atherogenic diet for 10 weeks (Paigen’s diet). Plaque area in the aortic root and plaque calcification (% of total plaque area) were measured by Oil Red O (lipids) and Alizarin Red (calcium) staining.

*Results*: In the absence of hypercholesterolemia, no appreciable soft tissue calcification was observed in the adult TNAP mice by full-body necropsy (n=2). During progression of atherosclerosis, plaque calcification was significantly greater in TNAP mice when compared with controls (4.85% of total plaque area in TNAP vs. 0.02% in controls, p<0.001, n=8 per group). Total plaque area in the aortic root region was not affected by calcification in this model (0.40 mm^2 in TNAP; 0.38 mm^2 in controls; p=0.75).

*Conclusions*: Overexpression of TNAP in macrophages can lead to plaque calcification. An animal model was developed, in which the effects of calcification on plaque stability can be studied experimentally.