Role of TNAP in inflammation and calcification of atherosclerotic plaques

Line Kawtharany

ICBMS, MEM2, Villeurbanne

Lynn.kawtharany@etu.univ-lyon1.fr

Atherosclerosis plaque rupture is one of the leading causes of death worldwide. Increasing evidence suggests that unstable plaques are characterized by the presence of inflammatory cells, necrotic debris and microcalcifications. Moreover, recent data suggests that resolution of plaque inflammation is associated with plaque ossification and stabilization. However, this paradigm has not yet been demonstrated experimentally. Previous results from our laboratory showed that tissue-non specific alkaline phosphatase (TNAP), the key enzyme in bone and cartilage mineralization, is stimulated by inflammation in vascular smooth muscle cells (VSMCs), and sufficient to induce calcification in VSMC cultures. The main aim of this PhD thesis was to determine the effects of the TNAP inhibitor SBI-425 on atherosclerosis plaque development in mice deficient in apolipoprotein E. The first task consisted in the thorough characterization of TNAP activation and microcalcification deposition. We observed that TNAP activity perfectly colocalizes with plaque calcification as detected by histology with a fluorescent bisphosphonate dye. We then chose to treat mice with SBI-425 five weeks before the appearance of microcalcifications, and to stop the treatment in mice aged 25 weeks, which mainly have microcalcifications in their plaques, or in mice aged 31 weeks, which have bigger calcified cartilage metaplasia. TNAP inhibition with SBI-425 significantly inhibited the deposition of microcalcifications in early plaques, and decreased plaque inflammation. Interestingly, the microcalcifications that still formed in mice treated with SBI-425 evolved to a faster extent towards calcified cartilage with an upregulation of chondrocyte trans-differentiation markers. This results suggest that TNAP inhibition has beneficial effects on plaque development. This has to be confirmed with the quantification of lipid deposition, metabolic makers and inflammation. Furthermore, the analysis of the effects of microcrystals on VSMCs in vitro will bring new information at the molecular level on their effects on plaque evolution.