This editorial refers to 'Leucocyte cathepsin K affects atherosclerotic lesion composition and bone mineral density in low-density lipoprotein receptor deficient mice' by Guo et al.,4 pp. 278–285, this issue.

Cathepsins, cysteine proteases of lysosomes and endosomes, play major physiological roles in general intracellular protein turnover. When they are directed outside the cell, these enzymes also take part in remodelling the extracellular matrix of bone1 and other tissues. Once in the extracellular matrix, the cathepsins degrade elastin and collagen. Since remodelling of the extracellular matrix of arteries is germane to the stabilization of established atherosclerotic plaques, considerable interest is being focused on cathepsins as possible therapeutic targets for plaque stabilization. Undesirable as they may be, atherosclerotic plaques, once formed, have to be maintained in a stable condition to avoid rupture of their collagenous fibrotic cap and the ensuing occlusion of critical cardiac vessels or arteries of the brain and, hence, coronary artery disease or stroke. Plaques with high collagen levels are more stable than plaques containing lower amounts of this matrix protein. Thus, increasing the collagen content of the plaque supports plaque stability, and modulation of plaque collagen content by manipulating the cathepsins with inhibitors potentially constitutes a means by which the stability of the existing plaques might be controlled therapeutically. Cathepsins B, F, L, K, and S are indeed expressed in plaques, suggesting involvement of these enzymes in degrading plaque collagen and implicating that the cathepsins exert a baleful effect on plaque stability.2 Ironically, the collagen content in atherosclerotic plaques of ApoE−/− mice deficient in cystatin C, a natural inhibitor of the cathepsins, was not reduced, as would be expected after deletion of the cathepsin inhibitor, but increased,3 seemingly a boon for plaque stability. These contradictory findings indicate how the influence of cathepsins on plaque integrity during atherogenesis is more complicated than initially meets the eye.

Guo et al.4 sheds light upon this interesting issue. They studied the mechanisms by which cathepsin K of specific cell types influence the development of atherosclerotic plaques. Cathepsin K, which is the most potent mammalian elastase of the cathepsin family yet known,5,6 shows collagenolytic as well as elastinolytic activity.7 Cathepsin K is known to be expressed by the major cells involved in plaque formation, including endothelial cells,8 smooth muscle cells (SMC),9 and macrophages.10 Guo et al.4 established an atherosclerotic mouse model with leucocytes lacking cathepsin K by transplanting bone marrow from cathepsin K-deficient mice into X-ray irradiated, LDL-receptor-deficient mice. They found that plaque collagen content was dramatically reduced—instead of being increased as expected—when cathepsin K was abolished in macrophages. The authors explain that this finding, at first glance contradictory, is attributable to the absence of the elastinolytic activity of the deleted cathepsin K from bone marrow-derived macrophages. SMC are the primary producers of plaque collagen. They migrate from the media through the elastic lamina into the plaque (see Figure 1). A prerequisite for their migration is fragmentation of the elastic lamina. In the absence of the elastinolytic activity of macrophage cathepsin K, the elastic lamina remains intact and the SMC cannot migrate into the plaque and do not express collagen there. In addition, the authors demonstrated diminished elastic lamina fragmentation in plaques of mice lacking leucocyte cathepsin K, indicating that macrophages secreting cathepsin K are the critical cell type for supporting migration of SMC into the plaque. It would be important to address future experiments towards substantiating this cell type-specific effect in other systems.

Cathepsin K deficiency also affects the macrophages and lipid metabolism in atherosclerotic plaques. Along with the reduction of plaque collagen content, Guo et al. demonstrated a marked increase in the numbers of macrophages in plaques of leucocyte cathepsin K-deficient mice. Lutgens et al.9 have shown that plaque-resident macrophages are also larger due to their transformation into foam cells in whole-body cathepsin K-deficient mice. Therefore, cathepsin K deficiency enhances the formation of foam cells, which destabilize atherosclerotic plaques, but the reason for this is unclear. Furthermore, the uptake of modified lipoproteins is enhanced in cathepsin K-deficient macrophages and involves caveolin-1 and the scavenger receptor CD-36 pathway,11 and the efflux of cholesterol is depressed in cathepsin K-deficient macrophages.12
lipoproteins likewise act to destabilize atherosclerotic plaques. These findings indicate that lowered levels of cathepsin K generally favour both foam cell formation and retention of lipoproteins in the plaque and hence cause plaque destabilization rather than stabilization.

If reduction of cathepsin K does influence atherosclerotic plaque stability, can manipulation of cathepsin K be therapeutically useful? Plaque area in whole-body cathepsin K-deficient mice was reduced by almost half, suggesting that lowering cathepsin K levels, perhaps by using specific inhibitors of cathepsin K, might prove to be useful in the treatment of atherogenesis. Because of the known negative effect of cathepsin K on bone formation, several cathepsin K inhibitors, Relacatib, for example, have been tested for treating osteoporosis, but there are no data for their use in countering atherosclerosis in animals or humans. The findings of Guo et al. suggest that abolishing cathepsin K in macrophages may be detrimental for stabilizing atherosclerotic plaques. Other authors have also shown that the absence of cathepsin K appears to destabilize atherosclerotic plaques by interfering with macrophages and lipid metabolism in the plaque, as discussed above, but this adverse condition might be counteracted by combining cathepsin K reduction with lipid-lowering agents. Nevertheless, the study by Guo et al. clearly gives valuable initial insight into which cells might be suitable targets for therapeutic intervention at the level of cathepsin K. Obviously, additional experiments are still needed to determine whether cathepsin K is really beneficial or detrimental to atherosclerotic plaque stability.

References