Decayed Apoptosis and Tissue Factor Expression After Lipid Lowering

To the Editor:

We have read with interest the article by Aikawa et al.1 The authors found a drastic decrease in tissue factor expression and tissue factor activity in rabbit atherosclerotic plaques after lipid lowering. This was associated with a strong decrease in the number of macrophages in the plaques. Aikawa et al proposed that this could be a consequence of decreased macrophage replication or induction of apoptosis. Interestingly, we found that apoptosis was not increased but decreased after lipid lowering in this model.2 Moreover the proapoptotic protein Bax, which is upregulated in both human3 and experimental atherosclerotic plaques, was strongly decreased after lipid lowering.2 Furthermore, we demonstrated that the changes in cell composition of the plaques could be a consequence of a strong decrease in DNA synthesis of the macrophages.

To our understanding, the way in which the macrophages disappear from the plaques is important with respect to the effects of aggressive lipid lowering on plaque stabilization. Since apoptotic cells show an increased tissue factor activity, induction of apoptosis in atherosclerotic plaques could be responsible for an unwanted increased tissue factor activity in plaques after prolonged lipid lowering, as well as this group’s other key contributions to this area.1,2 We agree fully that diminished replication could contribute to the decreased macrophage number after lipid lowering. Diminished recruitment of monocytes due to attenuated endothelial cell activation or dysfunction might also be important.3 In addition to reduced replication and recruitment, we should also consider altered egress of monocytes/macrophages as a determinant of inflammatory cell number in arterial lesions under different conditions. Neither of our studies evaluated these mechanisms definitively, because our measurements have been limited to selected time windows that do not encompass the entire period of lesion change by lipid lowering. The decrease in markers of apoptosis in the study by Kockx et al was measured at 6 months, the end of the experiment, when macrophage number had already decreased substantially (parallel with our findings).4,5 The comparisons of apoptotic indices were not made with a contemporaneous control group but rather to specimens from rabbits studied 6 months earlier, before the lipid lowering began. We do not know from their data what balance between macrophage replication and death prevailed during the period of decline of this cell population over the 6 months of lipid lowering preceding the “slice in time” provided by the measurements at the final time point in the lipid-lowering group. Although further experimental work will be required to elucidate fully these various possibilities, we agree with the main points raised by Kockx et al in their letter, including the possibility that some extracellular tissue factor in plaques may arise from vesicles shed from cells, including those undergoing apoptosis.

Response

We are aware of the important work published by Kockx et al showing a decrease in indices of apoptosis in cells populating the arterial intima (presumably including macrophages) after prolonged lipid lowering, as well as this group’s other key contributions to this area.2,3 We agree fully that diminished replication could contribute to the decreased macrophage number after lipid lowering. Diminished recruitment of monocytes due to attenuated endothelial cell activation or dysfunction might also be important.3 In addition to reduced replication and recruitment, we should also consider altered egress of monocytes/macrophages as a determinant of inflammatory cell number in arterial lesions under different conditions. Neither of our studies evaluated these mechanisms definitively, because our measurements have been limited to selected time windows that do not encompass the entire period of lesion change by lipid lowering. The decrease in markers of apoptosis in the study by Kockx et al was measured at 6 months, the end of the experiment, when macrophage number had already decreased substantially (parallel with our findings).4,5 The comparisons of apoptotic indices were not made with a contemporaneous control group but rather to specimens from rabbits studied 6 months earlier, before the lipid lowering began. We do not know from their data what balance between macrophage replication and death prevailed during the period of decline of this cell population over the 6 months of lipid lowering preceding the “slice in time” provided by the measurements at the final time point in the lipid-lowering group. Although further experimental work will be required to elucidate fully these various possibilities, we agree with the main points raised by Kockx et al in their letter, including the possibility that some extracellular tissue factor in plaques may arise from vesicles shed from cells, including those undergoing apoptosis.

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Decreased Apoptosis and Tissue Factor Expression After Lipid Lowering
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