**Letter to the Editor**

**Decreased Atherosclerosis in Mice Deficient in Tumor Necrosis Factor-α Receptor-II (p75)**

**To the Editor:**

Tumor Necrosis Factor-α (TNF-α) induces a variety of proatherogenic molecules, and inhibition of TNF-α in apoE-/- mice results in diminished atherosclerosis suggesting the involvement of TNF-α in atherogenesis. TNF-α elicits its effects by activating 2 cell-surface receptors, namely p55 and p75. Earlier, Blessing et al reported that apoE-/- mice lacking p55 fed a chow diet did not show altered lesion progression or plaque composition. Recently, we showed that p75 is required for TNF-α-induced leukocyte–endothelial cell interaction and inflammation in vivo. Because inflammation plays an integral role in atherogenesis, we tested whether the proatherogenic activity of TNF-α was mediated by p75. We determined the role of p75 in atherogenesis using apoE-/- mice lacking p75 receptor. We generated p75-/-apoE-/-, p75-/-apoE-/-, and p75+/+apoE-/- littermates by sister-brother mating of p75+/+apoE-/- parents. Atherosclerotic lesion areas in aortic roots were measured after staining with Oil red O in 16-week-old chow diet-fed female mice. As shown in the Figure, the p75-/-apoE-/- mice had a mean lesion area of 125 000±32 000 mm² (n=10). Lesion area in the hemizygous p75+/+apoE-/- mice was 116 000±48 000 mm² (n=10), which was similar to that in the p75+/+apoE-/- mice, suggesting that one copy of the p75 gene is sufficient to promote its proatherosclerotic effect. The p75+/+apoE-/- mice had a mean lesion area of 72 000±28 000 mm² (n=10), representing a 43% reduction in lesion area compared with the p75+/+apoE-/- mice (P<0.01), and a 37% decrease compared with the p75+/+apoE-/- mice (P<0.05). Body weights, lipid composition, and total plasma cholesterol were similar in the p75+/+apoE-/- and p75+/+apoE-/- genotypes. Our results are not consistent with the earlier observation by Schreyer et al in which the lack of p75 did not alter atherosclerosis development. However, this group used a distinct model, in which C57BL/6 mice were fed a high-fat, high-cholesterol, cholate-containing diet. The apoE-/- model is more robust, yielding larger lesions in a shorter time period. Our results indicate that the proatherogenic effect of TNF-α is primarily mediated via the activation of p75 in apoE-/- mice.

We wished to determine whether p75 activity shifts the homeostasis of cytokine production toward an inflammatory phenotype. We used a Multiplex assay system (LINCOpex kit, Linco Research Inc) to measure 22 cytokines from the plasma of individual chow-fed female p75+/+apoE-/- (n=4) and p75+/+apoE-/- mice (n=4) at 16 weeks of age. As shown in the Table, we identified significant increases in the levels of TNF-α and interleukin (IL)-17 (both are proinflammatory cytokines), and in the levels of the antiinflammatory cytokine IL-10 in the p75+/+apoE-/- mice. The TNF-α level was elevated 2.2-fold, the IL-17 level was elevated 2.0 fold, and the IL-10 level was elevated by 1.8-fold in the p75+/+apoE-/- mice compared with p75+/+apoE-/- mice. Furthermore, we identified a significant 42% decrease in the plasma level of the proinflammatory cytokine IL-1β in the p75+/+apoE-/- mice. The plasma levels of TNF-α, IL-17, IL-1β, and IL-10 were undetectable in the age-matched p75+/+apoE-/- mice, suggesting that the lack of the apoE gene caused an upregulation of TNF-α, IL-17, IL-1β, and IL-10 with p75 having a regulatory role in the process. Because p75+/+apoE-/- mice developed smaller atherosclerotic lesions than p75+/+apoE-/- mice, it is possible that the upregulation of IL-10 accompanied by the downregulation of IL-1β could override the proinflammatory activity of IL-17 in the p75+/+apoE-/- mice.

In conclusion, we have demonstrated that TNF-α receptor p75-deficiency in apoE-/- mice reduced atherosclerotic lesion development in the aortic root. This reduction in the lesion size is associated with altered plasma cytokine production, but without an effect on plasma cholesterol levels.

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Correction

In the letter by Chandrasekharan et al in the March 2007 issue (Arterioscler Thromb Vasc Biol. 2007;27:e16–e17), the order of authorship was listed incorrectly. The correct order should have been:

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The authors regret this error.