ApoE KO Mouse crossed with p75 Neurotrophin Receptor KO Mouse on a C57 Background

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Technology description

The biochemical events that lead to atherosclerosis, the formation of vulnerable plaque, and the rupture of plaques are still being worked out. A lab at Cornell has developed mice that model these processes.

Previous studies at Cornell have identified the neurotrophin p75 receptor as a potent inducer of smooth muscle cell apoptosis. In addition, immunohistochemical analysis demonstrated that p75NTR is expressed in both murine and human atherosclerotic lesions. Finally, there is increased lesion development and decreased apoptosis in the ligated carotid artery of p75NTR knockout mice when compared to wild type mice. Thus, these studies demonstrated that expression of p75NTR regulates lesion development following vascular injury. However, this model of vascular injury is non-physiological because the injury occurs adluminally and the lesions that develop do not represent those that develop in response to elevated cholesterol, a major risk factor for development of atherosclerotic lesions in human.

We therefore decided to assess the role of p75NTR in a murine model of atherogenesis, the Apo E null mutant mouse. In this model, Apo E deficiency results in elevated plasma cholesterol of 400-500 mg/dl, primarily in the form of cholesterol ester particles in beta-VLDL. These mice develop atherosclerotic lesions, a process that is accelerated when they are maintained on a diet high in fat and cholesterol. The lesions have been well characterized and resemble human lesions in that they progress with age from the fatty streak stage to the intermediate stage of fibroproliferative lesions. The lesions are characterized by fibrous and cholesterol clefts, necrotic cores, calcification, the accumulation of macrophages and T-cells, and the formation of a thin to moderate fibrous cap composed to smooth muscle cells and matrix. As in human atherosclerosis, lesions form throughout the vascular tree, but are most prevalent in the aortic root, lesser curvature of the arch, proximal carotid arteries, and at branch points. There is also evidence for apoptosis. To directly assess the role of p75NTR in lesion development in Apo E -/- mice, p75NTR (-/-) mice on a C57Bl/6 background were backcrossed to Apo E (-/-) mice on a C57Bl/6 background.

Loss of p75NTR expression in Apo E (-/-) mice was associated with a significant increase in lesion development in both the whole aorta and in the aortic sinus. In the whole aorta, there was a 60% increase in the area of the aorta covered with lesions in the Apo E p75NTR double knockout mice, when compared to Apo E (-/-) mice with normal p75NTR expression. A similar increase in lesion size

was observed in the aortic sinus of male p75NTR (-/-) Apo E (-/-) mice when compared to male p75NTR (+/+) Apo E (-/-) mice. Thus, similar to what we observed in the carotid artery ligation model of acute vascular injury, the loss of p75NTR expression is associated with an increase in lesion development.

Institution

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