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The effects of oncogenic Ras on the ocular lens

Ras is a small GTP-binding protein in the signal transduction machinery. In most cell types, activation of Ras by growth factors is essential for normal cell proliferation. A mutation in the Ras gene can lead to a constitutive active (or oncogenic) state of Ras regardless of the upstream stimuli present. In fact, about thirty percent of human cancer is associated with a mutation in the Ras gene. When we generated transgenic mice over-expressing oncogenic Ras mutant in the ocular lens, we observed hyperplasia of the lens epithelial cells followed by vascularization in the lens fiber mass. The purpose of this study is to examine the abnormal development of the vascular system in the Ras transgenic lens, and foremost to analyze the molecular mechanisms which induce these abnormalities. Histological analysis was performed in three different transgenic lines to determine the onset of the lens vascularization. We found that the lens capsule, which is the basement membrane of the lens cells, was disrupted in the transgenic mice. Subsequently, the hyaloid vascular cells surrounding the lens began to invade into the transgenic lens at embryonic day 13 to 15. Furthermore, the transgenic mice from the highest expressing lines develop the blood vessel in the lens at the earliest stage and in the most severe state, suggesting that the defect has a direct correlation with the oncogenic Ras activity. Semi-quantitative RT-PCR was used to examine gene expression levels in the wild type and Ras transgenic lenses. Results showed that oncogenic Ras induces upregulation of the genes which are responsible for angiogenesis, such as vascular endothelial growth factor (VEGF), hypoxia-inducible factor1(HIF1), and erythropoietin (EPO). Additionally, the genes involved in basement membrane remodeling, including matrix metalloproteinase 2, 9, and 14 (MMP-2, 9, 14), were also upregulated in the transgenic lens. We conclude that the Ras transgenic mice can be used as an alternative in vivo model for the study of angiogenesis and vascularization during cancer development.