Abstract

The Role of Endothelin 3 in Melanoma Progression and Metastasis

by

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Endothelin receptor b (Ednrb) and its ligand Endothelin 3 (Edn3) have been implicated in melanoma. Several studies have shown an upregulation of EDNRB and EDN3 at both the protein and mRNA levels, as melanoma becomes more aggressive. This study investigated the putative role played by Edn3 over-expression in melanoma progression and angiogenesis in vivo.

We crossed Tg(Grm1)Epv transgenic mice that aberrantly express metabotropic glutamate receptor1 under the Dopachrome tautomerase promoter, leading to spontaneous melanocytic lesions in the ears and tails that do not metastasize, with transgenics that overexpress Edn3 under the Keratin 5 promoter (K5-Edn3) or overexpress Ednrb in melanocytes (Tg(Ednrb)1Lk). In both the Tg(Grm1)Epv/K5-Edn3 and Tg(Grm1)Epv/Tg(Ednrb)1Lk mice, tumors appeared earlier and grew significantly larger and faster when compared to Tg(Grm1)Epv mice. Approximately eighty-one percent of Tg(Grm1)Epv/K5-Edn3 mice and 76% of Tg(Grm1)Epv/Tg(Ednrb)1Lk mice had pigmented lesions in distant organs such as the lung and brain. Real Time PCR analysis showed higher expression levels of genes involved cell-cell and cell-matrix interactions and angiogenesis in lesions of Tg(Grm1)Epv/K5-Edn3 when compared to controls. Considering the faster tumor growth rate of in the Tg(Grm1)Epv/K5-Edn3 mice, differences in the angiogenic response compared to control mice were investigated.

Immunofluorescence analysis with the endothelial cell marker CD31 showed that there were more endothelial cells per tumor area in the Tg(Grm1)Epv/K5-Edn3 mice than the controls. Proteome analysis showed that the Dct-Grm1/K5-Edn3 mice had significant increases in other angiogenic related genes such as Angiogenin, CXCL 16 and Endoglin, when compared to controls, while real time PCR analysis of tail tumors also showed higher expression levels of angiogenic related genes such as Hif-1α. The results of this study showed that the EDNRB/EDN3 axis is sufficient to alter the kinetics of melanocytic tumors’ progression, lead them to a fully malignant state, and increase the tumor angiogenic response.