

Integrin-mediated Epithelial-to-Mesenchymal Transition is Suppressed by Hedgehog Signalling in Basal Cell Carcinoma

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Background & Aims: Basal cell carcinoma (BCC) is the most prevalent cancer in the Western world, and its incidence is rising. The pathogenesis of BCC involves deregulated Sonic Hedgehog signalling, leading to activation of the Gli transcription factors. We have previously shown that the epithelial-specific integrin $\alpha\text{-x}\beta\text{-x}6$ is up-regulated in squamous cell carcinoma, promoting invasion. The aim of this study was to examine the interactions between $\alpha\text{-x}\beta\text{-x}6$ and Gli1 in nodular and morphoeic BCC. **Methods:** Tissue microarrays were generated from paraffin-embedded formalin-fixed BCC cases and immunohistochemistry for a panel of molecular markers was carried out. Gli1 cDNA was introduced into NTert1 and HaCaT skin keratinocytes using retroviral infection, and expression was confirmed by Western blotting. A three-dimensional model of BCC was generated using organotypic gels in an air-liquid interface. EMT was induced by EGF stimulation and EMT marker expression was examined using Western blotting, fluorescence microscopy, flow cytometry and q-RT PCR. **Results and Discussion:** Molecular profiling of BCC showed that $\alpha\text{-x}\beta\text{-x}6$ was significantly upregulated in the more aggressive morphoeic subtype ($p < 0.05$). Gli1 significantly down-regulated $\alpha\text{-x}\beta\text{-x}6$ expression on protein and mRNA levels in vitro ($p < 0.01$). $\alpha\text{-x}\beta\text{-x}6$ -dependent TGF- β activation and invasion were also down-regulated by Gli1. EMT studies showed that Gli1 expression was associated with membranous E-cadherin localisation. This was recapitulated in clinical specimens, where E-cadherin was delocalised to the cytoplasm in morphoeic BCCs, which also displayed loss of nuclear Gli1 expression. These results suggest that morphoeic BCC may represent a form of BCC EMT, and that $\alpha\text{-x}\beta\text{-x}6$ represents a potential target.