Overexpression of interleukin-6 in human basal cell carcinoma cell lines increases anti-apoptotic activity and tumorigenic potency.

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Abstract

Interleukin-6 (IL-6) is a pleiotropic cytokine that is capable of modulating the diverse functions of cells such as acute phase responses and inflammation. Excessive or insufficient production of IL-6 may contribute to certain diseases of the skin. The aim of this study was to investigate the possible role of IL-6 in the tumorigenesis of basal cell carcinoma (BCC). Initially, we transfected IL-6 expression vector, under the control of a CMV promoter, into human BCC cells and successfully obtained IL-6-overexpressing clones (BCC/IL-6-c1 and BCC/IL-6-c2) and a mixture (BCC/IL-6). DNA synthesis assay determined using (3)H-thymidine pulse incorporation revealed that IL-6-expressing BCC cells exhibited a much higher DNA synthesis rate than the neo control or parental BCC cells. We also detected a greater abundance of IL-6-expressing cell colonies formed in soft agar than in the vector control cells. Furthermore, BCC/IL-6 cells, but not vector control cells, were resistant to UV and photodynamic therapy (PDT)-induced apoptosis, as confirmed using DNA fragmentation and morphologic change analyses. Immunoblot analysis showed that Mcl-1, an anti-apoptotic protein, was specifically up-regulated IL-6 transfectants but not in the control cells. Transient transfection of IL-6 transfectants with antisense mcl-1 greatly enhanced their apoptosis frequency by UV treatment. In tumorigenesis assay, IL-6 transfected clones formed tumors in nude mice more rapidly than the control cells. These tumors appeared to be highly vascularized using pathological examination. Supportive of this finding, we found that IL-6 transfected cells expressed elevated levels of two angiogenic factors, cyclooxygenase (Cox)-2 and vascular endothelial growth factor (VEGF). These results suggest that overexpression of IL-6 enhances the tumorigenic activity of BCC cells by both suppressing apoptosis and actively promoting angiogenesis.