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## **Role of the bone morphogenetic protein signalling in skin carcinogenesis. Effect of transgenic overexpression of BMP antagonist Noggin on skin tumour development; molecular mechanisms underlying tumour suppressive role of the BMP signalling in skin.**

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## **Abstract**

### **Role of the Bone Morphogenetic Protein signalling in skin carcinogenesis**

Bone morphogenetic protein (BMP) signalling plays key roles in skin development and also possesses a potent anti-tumour activity in postnatal skin. To study mechanisms of the tumour-suppressive role of BMPs in the skin, a transgenic (TG) mouse model was utilized, in which a transgenic expression of the BMP antagonist Noggin was targeted to the epidermis and hair follicles (HFs) via Keratin 14 promoter. K14-Noggin mice developed spontaneous HF-derived tumours, which resembled human trichofolliculoma. Initiation of the tumours was associated with a marked increase in cell proliferation and an expansion of the hair follicle stem/early progenitor cells. In addition, the TG mice showed hyperplastic changes in the sebaceous glands and the interfollicular epidermis. The epidermal hyperplasia was associated with an increase in the susceptibility to chemically-induced carcinogenesis and earlier malignant transformation of chemically-induced papillomas.

Global gene expression profiling revealed that development of the trichofolliculomas was associated with an increase in the expression of the components of several pro-oncogenic signalling pathways (Wnt, Shh, PDGF, Ras, etc.). Specifically, expression of the Wnt ligands and  $\beta$ -catenin/Lef1 markedly increased at the initiation stage of tumour formation. In contrast, expression of components of the Shh pathway was markedly increased in the fully developed tumours, compared to the tumour placodes. Pharmacological treatment of the TG mice with the Wnt and Shh antagonists resulted in the stage-dependent inhibition of the tumour initiation and progression, respectively.

Further studies revealed that BMP signalling antagonizes the activity of the Wnt and Shh pathways via distinct mechanisms, which include direct regulation of the expression of the tumour suppressor Wnt inhibitory factor 1 (Wif1) and indirect effects on the Shh expression.

Thus, tumour suppressor activity of the BMPs in skin epithelium depends on the local concentrations of Noggin and is mediated, at least in part, via stage-dependent antagonizing of the Wnt and Shh signalling pathways.

**Keywords:** BMP signalling Wnt Shh Noggin Wif1 skin hair follicle cancer

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