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## $\beta$ -catenin overexpression initially inhibits papilloma formation protecting the skin from malignant progression in squamous cell skin carcinogenesis

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$\beta$ -catenin is a protein that is known to have dual functions, in cell adhesion by interacting with membranous E-cadherin, and being a key regulator of proliferation through its crucial role in the Wnt signalling canonical pathway. Genetic mutation of  $\beta$ -catenin or its deregulation via altered signalling in regulatory molecules such as GSK3- $\beta$  and APC are associated with several types of cancer. Therefore to investigate its roles in skin carcinogenesis,  $\beta$ -catenin status was analysed in stage-specific tumours and skin biopsies derived from transgenic mice expressing an RU486-inducible, cre/loxP-mediated ablation of PTEN exon 5 [K14. $\Delta$ 5PTEN<sup>flx</sup>] together with exclusive epidermal expression of activated ras [HK1.ras] and activated fos oncogenes [HK1.fos]. Potential  $\beta$ -catenin roles in this model of skin carcinogenesis were first observed in cooperation of HK1.fos/ $\Delta$ 5PTEN<sup>flx</sup> where loss of PTEN mediated AKT regulation, resulted in high levels of p-AKT that continuously deactivated GSK3- $\beta$ , the main down regulator of  $\beta$ -catenin. These high levels of inactivated GSK3- $\beta$  have triggered compensatory responses of p53 and p21 which resulted in inhibition of AKT oncogenic activity and alongside fos activation resulted in formation of a benign keratoacanthomas. Analysing  $\beta$ -catenin statues confirmed that basal layers  $\beta$ -catenin expression was increased in cells membrane with properly nuclear localization. This was due to GSK3 $\beta$  inactivation which resulted in increasing cytoplasmic  $\beta$ -catenin which caused a possible nuclear localization of  $\beta$ -catenin via Wnt signalling. This in return has triggered p53 and p21 expression in attempt to prevent the increasing nuclear expression of  $\beta$ -catenin as well as keeping its cell adhesion function intact by interacting with membranous E-cadherin, which known to be a suppressor of invasion and metastasis, that in result helped in preventing any possible malignant progression. Another analysis of  $\beta$ -catenin in HK1.ras/ $\Delta$ 5PTEN<sup>flx</sup> model showed an increasing loss of membranous expression of  $\beta$ -catenin in basal layers with more nuclear expression as the papilloma formed accompanied also by high levels of p53 and p21. These findings were compared to the early hyperplasia stage before papilloma formation where  $\beta$ -catenin expression was fairly normal in basal layer with slightly elevated levels of p53 and p21. However, in tri-genic HK1.ras/fos/ $\Delta$ 5PTEN<sup>flx</sup>, which destined to convert to malignancy, it was observed that  $\beta$ -catenin lost its membranous expression with strong nuclear  $\beta$ -catenin expression as well as possible loss of E-cadherin upon converting to malignancy combined with the loss of p53 and p21 due to several oncogenic effects. All of this data suggests that  $\beta$ -catenin overexpression could play a critical role in triggering tumour suppression responses to prevent malignant progression. This finding also makes  $\beta$ -catenin an

attractive candidate for more analysis to be conducted on its roles in squamous cell skin carcinogenesis.