
This is the author’s final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher’s version if you wish to cite from it.

http://eprints.gla.ac.uk/163447/

Deposited on: 05 June 2018

Enlighten – Research publications by members of the University of Glasgow

http://eprints.gla.ac.uk
Accelerated differentiation and p21/p53 responses to ROCK-mediated p-AKT/p-GSK3β/β-catenin overexpression prevent papillomas in transgenic mice

Siti F Masre,1,3 Nia Linkov1 Michael F. Olson2 and David A Greenhalgh.1,4

Section of Dermatology and Molecular Carcinogenesis, College of Medical, Veterinary and Life Sciences, Glasgow University, Scotland G31 2ER.

ROCK2 roles in epidermal differentiation and initiation of carcinogenesis have been investigated in mice expressing a cre-responsive, RU486-inducible, 4HT-activated ROCK2 transgene [K14.creP/IslROCKer]. RU486/4HT-mediated ROCKer activation induced hyperplasia similar to epidermal expression of rasHa [HK1.ras], however ROCKer did not elicit papillomas. Consistent with normal, supra-basal ROCK2 roles in differentiation that influence tissue rigidity stiffness in barrier maintenance, additional basal-layer ROCKer activation induced epidermal hyperplasia with elements of premature differentiation. Unlike HK1.ras activation, K14.creP/IslROCKer hyperplasia exhibited premature keratin K1 expression in the expanded basal layers; but reduced hyperproliferative-associated keratin K6, with premature appearance of late-stage markers loricrin and filaggrin; whereas HK1.ras hyperplasia exhibited uniform K6, delayed K1/oricrin and filaggrin loss. Resultant ROCKer hyperplasia also displayed suprabasal-to-basal increases in activated p-AKT1, which inactivated basal layer GSK3β [p-GSK3βser9] leading to persistent, elevated β-catenin signalling; thus potentially increasing proliferation [via Wnt] and epidermal rigidity via focal adhesions. Increased Tenascin C-positive cells in K14.creP/IslROCKer dermis also suggest matrix alterations responding to ROCKer contributed to tissue rigidity and facilitate carcinogenesis initiation. However, despite additional ROCKer-associated NF-κB expression, the anomalous p-AKT1/p-GSK3β/β-catenin axis appears to triggered compensatory persistent p53/p21 expression in epidermal basal layers, absent in HK1.ras hyperplasia, which may help explain the lack of ROCKer-mediated papillomatogenesis when coupled to the accelerated differentiation responses.