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Accelerated differentiation and p21/p53 responses to *ROCK*-mediated p-AKT/p-GSK3β/β-catenin overexpression prevent papillomas in transgenic mice

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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/lslROCK^{er}*]. RU486/4HT-mediated ROCK^{er} activation induced hyperplasia similar to epidermal expression of *ras^{Ha}* [*HK1.ras*], however ROCK^{er} did not elicit papillomas. Consistent with normal, supra-basal ROCK2 roles in differentiation that influence tissue rigidity stiffness in barrier maintenance, additional basal-layer ROCK^{er} activation induced epidermal hyperplasia with elements of premature differentiation. Unlike *HK1.ras* activation, *K14.creP/lslROCK^{er}* 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/loricrin and filaggrin loss. Resultant ROCK^{er} hyperplasia also displayed suprabasal-to-basal increases in activated p-AKT1, which inactivated basal layer GSK3β [p-GSK3β^{ser9}] 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/lslROCK^{er}* dermis also suggest matrix alterations responding to ROCK^{er} contributed to tissue rigidity and facilitate carcinogenesis initiation. However, despite additional ROCK^{er}-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 ROCK^{er}-mediated papillomatogenesis when coupled to the accelerated differentiation responses.