Fos co-operation with 14-3-3σ [Stratifin] induces malignant conversion in transgenic mouse skin carcinogenesis: a paradigm for SCC of follicular origin.

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To study mechanisms driving/inhibiting skin carcinogenesis, transgenic mice have been established that express activated *H-ras* or *fos* oncogenes and RU486-inducible ablation of *PTEN-mediated AKT inactivation* [*Δ5PTEN*]. Tri-genic *HK1.ras-fos-Δ5Pten* mice exhibit papillomas that convert to well-differentiated SCC following p53 loss associated with a suprabasal-to-basal increases in Mdm2 activation (p-Mdm2^{166}). Given that 1433σ/Stratifin stabilises p53 levels by binding to Mdm2 and its resultant removal by auto-ubiquitination, this study investigated whether *Stratifin* over-expression could inhibit malignant conversion via maintanance of elevated p53 levels; a mechanism observed in bi-genic *HK1.fos-Δ5PTEN* and *HK1.ras-Δ5PTEN* mice. Initially mice expressing *Stratifin* in epidermis and hair follicles from a Keratin 14 promoter [*K14strat*] were crossed with *HK1fos* mice [*HK1fos-strat*]. However, instead of the predicted inhibition of benign phenotypes, *HK1fos-strat* mice exhibited a rapid tumourigenesis which quickly converted to malignancy; whereas *HK1fos* controls exhibited pre-neoplastic hyperplasia [over ~9mo] and *K14strat* exhibited only mild epidermal hypoplasia. Histological analysis revealed that early [2-3 weeks] *HK1.fos-strat* epidermis exhibited hyperplasia/hyperkeratosis which rapidly progressed to overt tumours that exhibited a novel histotype. *HK1fos-strat* epidermis displayed loss of correct stratification, accompanied by a pronounced disorder to supra-basal differentiation; with expansion of a distinct, multi-layered basal layer being another unique feature. By 4-5 weeks, overt tumours had appeared that lacked or exhibited a highly disrupted granular layer, with faint keratohyalin granules spread throughout highly disordered upper differentiating layers, as determined by immunefluorescence analysis of keratins K1/K10/K14 and loricrin and filaggrin. However, in older *HK1.fos-strat* tumours [~7 weeks] the paramount feature was a significant tricholemmal keratinisation. These *HK1.fos-strat* tumours also exhibited loss of Keratin 1 expression, indicative of malignant conversion, with extensive pleomorphism and neoangiogenesis with erythrocyte extravasation. While many of these traits were shared with *HK1.ras-fos-Δ5PTEN* and human cutaneous SCCs, the tricholemmal keratinisation differs quite markedly and appears similar to human cutaneous SCC of follicular origin (fSCC, tricholemmal carcinoma). These adnexal neoplasms arise in HF walls and are a relatively underdiagnosed tumour type. In addition to histological similarities Keratin 17, normally expressed in follicular ORS, was expressed in *HK1.fos-strat* fSCCs; appearing as small rings of cells, as observed in human fSCCs; whereas normal and *HK1.fos* skin exhibit K17 confined to follicular ORS and was absent in *HK1.ras-fos* papillomas, *HK1.fos-Δ5PTEN* keratoacanthomas or *HK1.ras-fos-Δ5PTEN* SCCs. Collectively, these data suggest *HK1.fos-strat* tumours are a putative paradigm for human SCC of follicular origin.