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GRK2 acts as tumor suppressor in squamous cell carcinomas

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GRK2 emerges as a key signaling node able to integrate different signaling pathways involved in cancer progression in a tumor and cell-type specific way (Nogués et al, 2017). Our results show that this kinase may play an inhibitory role in the progression of Squamous Cell Carcinomas (SCC). GRK2 protein expression is clearly reduced on the invasive front of skin SCC and on undifferentiated, high-grade SCC tumors of human stratified epithelia. Interestingly, Kaplan-Meier analysis generated from different datasets of those tumors indicate that patients with low levels of mRNA expression of the GRK2 gene (Adrbk1 gene) are prone to increased recurrence and metastasis, suggesting that GRK2 down-modulation might favor SCC tumor progression. GRK2 gene expression is significantly lower in SCC cell lines with a mesenchymal phenotype compared to those with an epithelial phenotype. In contrast, the expression of Snail1 (Snal1 gene), a transcription factor known to be a key Epithelial-Mesenchymal Transition (EMT) inducer and to be present at the invasive front and the periphery of different types of human SCC, displayed the reverse trend, suggesting a functional antagonism between both proteins. Consistently, we find that GRK2 overexpression counteracts the mesenchymal phenotype induced by Snail1 in epithelial cells, and that GRK2 directly interacts and phosphorylates Snail1, thus attenuating its functionality. Importantly, down-regulation of endogenous GRK2 expression in head and neck carcinoma cells is sufficient to trigger EMT features and to foster a motile and invasive phenotype, suggesting that the downregulation of GRK2 observed in clinical samples might contribute to tumor malignancy. Furthermore, induced GRK2 ablation in mice promotes skin hyperplasia and proliferatioin, induces spontaneous papillomas in the tongue and makes animals more sensitive to oral carcinogens. Overall, these data suggest that GRK2 expression levels play an important role in the control of epidermal cell proliferation and differentiation status in vivo, and that GRK2 downregulation favors the development of tumoral features in stratified epithelia.