Understanding the tumour-suppressing activity of rapamycin in epidermis

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Epidermal squamous cell carcinoma (SCC) is one of the most common Caucasian skin cancers and is particularly prevalent in immunosuppressed patients. Use of rapamycin as an immuno-suppressant results in reduced SCC and is currently in phase III clinical trials for skin cancer after renal transplantation. The mechanism behind rapamycin-mediated SCC reduction remains unknown. Epidermal SCC is associated with changes in AKT phosphorylation. AKT2, associated with less differentiated keratinocytes, is upregulated in SCC and in response to UV in epidermis. In contrast, AKT1, associated with differentiated keratinocytes, is downregulated in response to UV and SCC, suggesting a tumour-suppressor role for AKT1. We show that rapamycin increases AKT1 phosphorylation in epidermis, but has little effect on AKT2, suggesting a mechanism for rapamycin’s anti-tumour activity in skin. In skin culture we find that rapamycin selectively upregulates AKT1, but has little effect on AKT2. Rapamycin-induced AKT1 phosphorylation is due to inhibition of the mTORC1-regulated negative feedback loop to the insulin receptor substrate-1 at the plasma membrane. We show that this feedback loop is active in keratinocytes, with rapamycin inhibiting the mTORC1-dependent regulation of IRS-1, increasing IRS-1 stability and downstream signaling to AKT1. We propose that rapamycin increases AKT1 phosphorylation leading to increased tumour-suppressing AKT1 activity and protection against epidermal tumourigenesis.