Preclinical Investigation of anti-CD147 and EGFR Signaling in Cutaneous Squamous Cell Carcinoma

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BACKGROUND:
Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy.

Up to 80% of cSCC occurs in the head and neck and a portion of these cancers are refractory to simple excision, with long term survival as low as 25%.

CD147 is a transmembrane glycoprotein that is over expressed in SCC and has been shown to correlate with overall prognosis, metastasis, and invasion. We demonstrate for the first time that blocking CD147 in vitro and in vivo, EGFR expression is decreased in cSCC. This suggests a novel link between CD147 and EGFR signaling cascades.

METHODS:
Cutaneous squamous cell carcinoma cell lines, Colo-16, SRB-1, and SRB-12, were treated with a range of chimeric anti-CD147 mAb (0, 50, 100, 200 µg/mL) or transduced with a small interfering RNA (siRNA) against CD147. In vitro cell proliferation, migration, and protein expression was then quantified. A murine flank tumor model was then used to assess in vivo response to anti-CD147 treatment.

RESULTS:
In response to anti-CD147 mAb treatment, there was a significant decrease in proliferation, with an average of 78% of control (P-value for Colo-16, SRB-1, and SRB-12: 0.06, 0.06, 0.003). The wound assay demonstrated a decrease in cell migration, averaging a 43% reduction in closure when compared to untreated (P-value for Colo-16, SRB-1, and SRB-12: < 0.001). Colo-16 cells silenced for CD147 expression demonstrated similar reduction in proliferation. In vivo phenotype was then assessed by using a murine flank tumor model. Both the anti-CD147 treatment group and the silenced CD147 cell line showed decreased tumor growth and EGFR expression on histologic evaluation when compared to control. In vitro phenotype, in response to anti-CD147 therapy, resulted in a reduction in EGFR expression. A significant decrease in EGFR expression by immunofluorescence and western analysis was observed in response to loss of CD147 signaling, which was mirrored by a decrease in downstream expression of BAD and AKT.

CONCLUSION:
Loss of CD147 function results in a suppression of the malignant phenotype in vitro and in vivo which may be a result of decreased EGFR expression and downstream AKT pathway activation.