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A New Inducible RNAi Model for Cancer Target Validation In Vivo

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Background

Human xenograft tumor models are widely used for evaluation of potential cancer targets, by assessing the anti-tumor effects of specific agents, such as siRNA. siRNA is usually stably introduced into tumor cells prior to transplantation. However, oncogene silencing results in reduced cell growth/survival *in vitro* and/or failure to establish tumors *in vivo*, thus hindering tumor response-based efficacy evaluation that is more clinically relevant. We therefore explored a new tumor response model based on regulated RNAi.

Methods

A unique RNAi vector was generated to express shRNA only after induction with doxycylcine. Using this vector, we created a novel xenograft tumor model, in which tumors are established under non-induced conditions, followed by induced target inactivation upon oral dosing of the inducer. Three genes were evaluated, a known oncogene (mTOR), and two novel cancer targets (HE7 and HE26), by assessing the tumor response to their silencing.

Results

We demonstrate a significant response of staged tumor regression to silencing of all three target genes. For early staged tumors, inactivation of each of the three targets caused dramatic tumor regression (100% regressed and 50% became tumor-free for both mTOR and HE7, and 100% for HE26). Advanced staged tumors also demonstrated significant responses (100% regression for mTOR, and 75% for HE7, 85% HE26).

Conclusion

Our results demonstrate the utility of this unique and powerful model for efficacy evaluation of cancer targets; our data also provide robust *in vivo* efficacy validations of HE7 and HE26 as novel cancer therapeutic targets.