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LUNG CANCER

Whack a gli hedgehog

Treatment options of lung squamous-cell carcinoma (LSCC) are scarce, and there is an urgent need for effective targeted therapies. Genetic alterations in the Hedgehog (HH) signalling pathway have been described in LSCC, which might offer different possibilities regarding targeted treatment of this disease. To that end, Mark Onaitis and colleagues analysed the RNA expression data sets of two independent cohorts of patients with LSCC to study the activation of HH signalling. "This would allow us to evaluate what kind of genetic features were shared by patients harbouring hyperactive HH-GLI signalling", explains Onaitis.

The analysis showed high levels of expression of the HH target gene *GLI2* in both cohorts, suggesting that *GLI2* is the major signalling transducer in a proportion of LSCCs. They then used human LSCC cell lines to study the effects of blocking HH-GLI signalling by knocking down the expression of GLI2 and the receptor SMO with short hairpin RNAs (shRNAs) and with small-molecule inhibitors. Inhibition of SMO with shRNA and the inhibitor GDC-0449 only had a minor effect on cell survival, whereas inhibition of GLI2 with both shRNA and the inhibitor GANT61 led to significant growth inhibition and apoptosis.

"Once the inhibitor showed satisfactory efficacy *in vitro*, we went on to determine its efficacy *in vivo* by using xenografts in immunodeficient mice," continues Onaitis.

GANT61 demonstrated specific *in vivo* anti-tumour activity. Onaitis explains these findings: "different from canonical HH-GLI pathway activation, our data demonstrated a SMO-independent regulation of GLI in LSCC." Onaitis and his team are currently investigating other clinically available agents that may have the potential to target GLI proteins.

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Original article Huang, L. *et al*. HEDGEHOG-GLI signaling inhibition suppresses tumor growth in squamous lung cancer. *Clin. Cancer Res*. doi:10.1158/1078-0432.CCR-13-2195