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Hakai overexpression induces tumour growth, invasion and metastasis in vivo

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Loss of E-cadherin at cell-cell contacts is one of the best-characterized hallmarks of epithelial-to-mesenchymal transition (EMT), an important process that occur at early stages of tumour progression, whereby cells acquire motility and invasive capabilities. Hakai is an E3 ubiquitin-ligase that binds to E-cadherin in a phosphorylated-dependent manner and induces its ubiquitination and degradation; thus modulating cell adhesions. It has been previously shown that Hakai overexpression induces EMT *in vitro,* suggesting an important role of Hakai in tumour development and metastasis. Here, by immunochemistry we show that Hakai expression is higher in benign human colon adenomas compared to healthy tissues. Moreover, Hakai expression gradually increases in different TNM stages (I-IV) from colon adenocarcinomas compared to human colon healthy tissues. On the other hand, we studied the role of Hakai on tumorogenesis, invasion and metastasis *in vivo*, by injecting non-tumour MDCK cells stably transfected with Hakai (Hakai-MDCK cells) into the flank of nude mice. Hakai-MDCK cells dramatically induce *in vivo* tumour growth, leading high proliferative, invasive and mesenchymal tumours. More importantly, presence of micrometastasis in the lung of the nude mice animals were detected while inoculating Hakai-MDCK cells. These results demonstrate for first time the role of Hakai in tumorogenesis, invasion and metastasis *in vivo* suggesting that Hakai could be considered as a potential new therapeutic target.