The mesenchymal-epithelial transition factor (c-Met) represents an important target for cancer therapy. Aberrant activation of c-Met is associated with oncogenic transformation in several human tumor types, where tumor cell growth depends on constitutive activation of this tyrosine kinase receptor through binding to its high-affinity ligand, hepatocyte growth factor (HGF). A c-Met/HGF experimental cancer model is critical to evaluate c-Met targeting therapies such as tyrosine kinase inhibitors (TKIs) or antibodies. Patient-derived xenografts (PDX) usually lose human stroma over time, which is the main source of HGF; moreover HGF produced by murine stroma is incapable of triggering paracrine signaling because of a lack of cross reactivity with the human c-Met expressed by the tumor. Some PDX grow independently of paracrine c-Met/HGF signaling, thanks to the presence of c-Met activating mutations or gene amplifications that provide constitutive c-Met activation, and autocrine signaling. These PDX models can be used to evaluate the antitumor efficacy of TKIs; however, they are not suitable to assess biologic agents such as antibodies, which work by disrupting the receptor-ligand interaction. Here we tested whether a PDX model with autocrine c-Met/HGF signaling could be used to evaluate antibody therapies against human c-Met. We identified a unique hepatocellular carcinoma (HCC) PDX, the LI0801 model, which relies on autocrine c-Met/HGF signaling for tumor growth, and we confirmed that a human c-Met antibody results in significant tumor response in this model.

**INTRODUCTION**

The mesenchymal-epithelial transition factor (c-Met) represents an important target for cancer therapy. Aberrant activation of c-Met is associated with oncogenic transformation in several human tumor types, where tumor cell growth depends on constitutive activation of this tyrosine kinase receptor through binding to its high-affinity ligand, hepatocyte growth factor (HGF). A c-Met/HGF experimental cancer model is critical to evaluate c-Met targeting therapies such as tyrosine kinase inhibitors (TKIs) or antibodies. Patient-derived xenografts (PDX) usually lose human stroma over time, which is the main source of HGF; moreover HGF produced by murine stroma is incapable of triggering paracrine signaling because of a lack of cross reactivity with the human c-Met expressed by the tumor. Some PDX grow independently of paracrine c-Met/HGF signaling, thanks to the presence of c-Met activating mutations or gene amplifications that provide constitutive c-Met activation, and autocrine signaling. These PDX models can be used to evaluate the antitumor efficacy of TKIs; however, they are not suitable to assess biologic agents such as antibodies, which work by disrupting the receptor-ligand interaction. Here we tested whether a PDX model with autocrine c-Met/HGF activation could be used to evaluate an antibody therapy against human c-Met. We identified a unique hepatocellular carcinoma (HCC) PDX, the LI0801 model, which relies on autocrine c-Met/HGF signaling for tumor growth, and we confirmed that a human c-Met antibody results in significant tumor response in this model.

**METHODS**

- LI0801 was engrafted subcutaneously in immunocompromised mice; the grafted tumor was derived from a male HCC patient (HBV++, early hepatitis B cirrhosis, chronic cholecystitis, cholelithiasis).
- The tumor expression of human HGF and c-Met was assessed by RNAseq.
- The tumor expression of human vimentin, Met, and HGF was assessed by IHC.
- LI0801 was treated with a novel and highly specific c-Met TKI (M101) and a novel c-Met antibody (M102).

**RESULTS**

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**CONCLUSIONS**

1. LI0801, an HCC PDX, expresses high levels of both HGF and c-Met.
2. LI0801 grows via c-Met/HGF autocrine signaling in absence of human stromal cells.
3. LI0801 is sensitive to both a TKI and a monoclonal antibody targeting human c-Met.
4. Our data suggest that a model of autocrine c-Met/HGF signaling is suitable to evaluate both small molecule TKIs and antibody therapies.