Title of the Contribution:
Role of hypoxia-inducible transcription factor 1alpha for progression and chemosensitivity of murine hepatocellular carcinoma.

Abstract:
Hepatocellular carcinoma (HCC) is a hypervascularized tumor entity with association of arterial vessel density with poor prognosis. The hypoxia-inducible transcription factor HIF-1alpha represents a pivotal regulator of angiogenesis and is thought to determine the angiogenic nature of HCC. However, the precise role of HIF-1alpha during the pathogenesis of HCC remains elusive. We established a functional inactivation of HIF-1alpha in vitro and in vivo via RNAi and Cre/loxP-mediated recombination, respectively, to determine HIF-1alpha’s role for tumor growth and chemosensitivity in transgenic and orthotopic murine HCC models. HIF-1alpha-deficient HCC cells displayed significantly reduced anchorage-independent growth and enhanced sensitivity toward etoposide, while basic cellular proliferation was unaffected. Analysis of gross tumor growth failed to detect reduced growth of HIF-1alpha-deficient tumors in the orthotopic and the transgenic HCC model, respectively. In line with the in vitro data, treatment of HIF-1alpha-deficient tumors with etoposide resulted in greater antiproliferative efficacy when compared to wild-type mice. Taken together, our study does not support a pivotal role of HIF-1alpha for tumor growth and angiogenesis in two
murine HCC models. However, our data point toward a significant function of HIF-1alpha in determining chemosensitivity of HCC and therefore warrant validation of HIF-1alpha-inhibitors as adjuvant therapeutic agents in clinical studies of human HCC.