A086 Overexpression of the Scaffolding Protein IQGAP1 Promotes Hepatocellular Carcinoma by Activating YAP1 Signaling

Evan R. Delgado, Hanna Erickson, Junyan Tao, Satdarshan Monga, Andrew Duncan, and Sayeepriyadarshini Anakk

University of Pittsburgh, Pittsburgh, PA; University of Illinois at Urbana-Champaign, Urbana, IL

Introduction: Hepatocellular Carcinoma (HCC) is the 5th most common cause of cancer-related death with an estimated 32,000 annual deaths in the United States. Sixty-85% of HCCs are characterized by elevated IQGAP1 protein expression. IQGAP1 is a scaffold protein that binds signaling molecules associated with cellular proliferation to regulate or enhance their activity. While overexpression of IQGAP1 is associated with HCC, other studies indicate IQGAP1 loss enhances tumorigenic signals. Clearly, maintaining IQGAP1 expression is critical for normal tissue homeostasis. **Methods:** We asked if IQGAP1 contributes HCC growth. To do this, we used hydrodynamic tail vein injections with the Sleeping Beauty transposase to model HCC. Here, HCCs are generated in wild-type, adult mice that are 69% genetically similar to human HCC when human activated (S45Y) β-catenin and MET (B+M) are expressed in hepatocytes. We included the overexpression of IQGAP1 and subsequently investigated downstream pro-growth and survival mechanisms that are regulated by IQGAP1. We also asked if IQGAP1 loss will impact HCC tumorigenesis. Here, we used the diethylnitrosamine (DEN) chemical carcinogenesis model to induce HCC in mice lacking *Iqgap1* expression. Following tumorigenesis, we again investigated changes in mechanisms upon loss of IQGAP1 expression. **Results:** Consistent with the literature, we found IQGAP1 promotes Wnt/□-catenin signaling *in vitro*. However, we found that IQGAP1 overexpression alone is insufficient to drive Wnt/□-catenin signaling and HCC *in vivo*. Similarly, *Iqgap1* loss in the DEN model only modestly increased HCC tumor burden and proliferation marked by Ki-67 staining compared to control mice. Including IQGAP1 in the B+M (B+M+I) transposon system resulted in 2-fold higher LW/BW ratio compared to B+M after 8.5 weeks indicating increased tumor burden. Expectedly, overexpression of IQGAP1 in the B+M model does not promote Wnt/β-catenin activity. However, we found that IQGAP1 overexpression in the B+M model enhances YAP1 signaling. We found that IQGAP1 overexpression enhances YAP1 activity *in vitro*, and nuclear translocation *in vivo*. Finally, we found expression of NUAK2, a YAP1 target gene associated with HCC carcinogenesis, is increased in B+M+I tissues compared to B+M. **Conclusion:** Together, our data identifies a unique mechanism regulated by IQGAP1 that contributes to HCC oncogenesis. Our findings expand the potential for personalized therapeutic strategies for HCC.