Abstract

Obesity is accompanied with a low-grade inflammation, which drives the risk to develop hepatocellular carcinoma (HCC). In this context, macrophages in the obese adipose tissue release cytokines e.g. IL-6 into the circulation. Ultimately, this causes systemic and chronic elevated IL-6 levels in obese individuals. IL-6 acts via the IL-6 receptor and the co-receptor GP130. Downstream signaling activates STAT3 that in turn negatively feeds back via the inhibitor SOCS3 to tightly control IL-6 signaling. Under obese conditions, basal phosphorylated STAT3 levels are elevated in hepatocytes, but the responsiveness to acute IL-6 is diminished. A condition we refer to as IL-6 resistance. In this study different mouse models were generated to better understand the role of IL-6 resistance in HCC. Elevated levels of basal activated STAT3 and increased expression of *Socs3* verified hepatic IL-6 resistance in obese mice. To prevent hepatic IL-6 resistance, a liver specific *Socs3 knockout* mouse was generated that surprisingly failed to prevent the development of an IL-6 resistance, presumably due to compensatory *Socs1* expression. While insulin sensitivity was still improved in 11 weeks old DEN-injected hepatic *Socs3 knockout* mice, these mice developed IL-6 resistance at later stages and ultimately developed similar HCC burden compared to their controls. To further understand the contribution of compensatory SOCS1 in IL-6 resistance, we currently aim at generating a conditional *knockout* and reporter allele of *Socs1* that will be intercrossed with the *Socs3* conditional allele to prevent IL-6 resistance. To induce hepatic IL-6 resistance genetically, a mouse model of constitutively active GP130 (LGP130) was used. *Lgp130* was expressed in hepatocytes and these mice were subjected to DEN-induced hepatocarcinogenesis. These mice developed a similar number, but significantly larger tumors, thus revealing a role of IL-6 resistance in tumor progression rather than development. Hepatic IL-6 resistance exhibited polarizing effects on liver macrophages via CSF-1 and inducible depletion of the *Csf-1r* in macrophages ameliorated HCC progression in obese mice presumably via triggering macrophage polarization towards an M2 state.

To further dissect hepatic IL-6 resistance on HCC progression, a novel ROSA26 allele was generated, allowing for hepatocyte-specific overexpression of *Socs3* that is currently under investigation. Collectively, this study successfully introduces novel genetically engineered mouse models to examine the role of IL-6 resistance in HCC development and progression.