Abstract

Obesity is characterized by a systemic low-grade inflammation, primarily driven by immune cells in the expanding white adipose tissue that release inflammatory cytokines such as IL-6. This chronic inflammation has been demonstrated to cause the sequential progression from steatosis to NASH to HCC. At the molecular level, IL-6 engages the IL-6Rα, prompting the assembly of a complex with two GP130 molecules to induce phosphorylation of STAT3, subsequently promoting gene expression including that of *Socs3*. SOCS3 inhibits the IL-6 signal transmission by a negative feedback loop to ensure its precise regulation. Under obesity, chronically elevated IL-6 levels contribute to a blunted response to acute IL-6 signals in the liver at least partially due to increased *Socs3* expression, a phenomenon termed “IL-6 resistance”. To dissect the effects of hepatic IL-6 resistance in lean mice, a transgenic hepatocyte specific LGP130 construct was employed, which harbors external leucine zippers to promote constant dimerization. Using a DEN-induced HCC mouse model, both dietary and genetic IL-6 resistance drive HCC development. Moreover, LGP130 expression altered fatty acid metabolism and myeloid cell differentiation, key processes in HCC pathogenesis. On the one hand, LGP130 expression in hepatocytes curbed fatty acid accumulation and decreased PGC-1α as well as associated metabolic pathways, including gluconeogenesis resulting in impaired glucose homeostasis during fasting. On the other, hepatic LGP130 expression attracted monocyte-derived macrophages with a fibrotic phenotype, that fosters HCC development. Mechanistically, increased hepatic *Csf1* in models of IL-6 resistance enhanced macrophage infiltration and supported M2 macrophage polarization, both conditions favor tumor growth. However, inducible *Csf1r* deficiency in IL-6 resistant mouse models significantly mitigated HCC progression by reducing fibrotic macrophage invasion and fibrosis by preventing M2 polarization. Furthermore, restoration of insulin sensitivity was observed in lean mice expressing LGP130, possibly due to elevated IL-1ra expression that blocks excessive IL-1 signaling found in these mice.

Conclusively, this study shows how obesity-induced hepatic IL-6 resistance promotes HCC, i.e. by fostering a tumor microenvironment ideally suited for alternative activation of macrophages and their recruitment. Our findings thus highlight a novel link between obesity and HCC pathogenesis, implicating a distinct fibrotic macrophage population present in IL-6 resistant livers.