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Loss of LRP1 expression in alveolar epithelial type 2 cells affects hepatic tissue metabolism.

The low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) is a lipoprotein receptor involved in multiple cellular functions. To investigate its role in alveolar epithelial type 2 cells (T2C), which are specialized in pulmonary surfactant synthesis, our lab generated an inducible, T2C-specific LRP1 knockout model (SPC-LRP1$^{-/-}$). Loss of LRP1 in T2C impacted surfactant homeostasis in 6-month-old mice. Notably, LRP1 loss in T2C also had extrapulmonary effects. In 11–13-week-old mice, SPC-LRP1$^{-/-}$ mice showed increased hepatic ceramide, triglyceride and cholesterol accumulation, activation of fatty acid synthesis pathways, and reduced β-oxidation, collectively resembling non-alcoholic fatty liver disease (NAFLD). To explore this further, we assessed hepatic mitochondrial function. Respiratory complex I, II, and IV activity remained unchanged between WT and SPC-LRP1$^{-/-}$ mice. However, we observed a sexual dimorphism in complex II and IV activity, with females exhibiting higher activity than males in both (WT and SPC-LRP1$^{-/-}$) groups. Interestingly, ATP synthase activity was elevated in SPC-LRP1$^{-/-}$ mice. This, along with reduced FA β-oxidation, could indicate a shift in mitochondrial efficiency to maintain energy homeostasis in response to metabolic stress. Mitochondrial malondialdehyde levels and glutathione peroxidase activity remained unchanged, suggesting lipid peroxidation was at physiological levels. These findings support the existing notion of a lung-liver connection, where T2C dysfunction may contribute to systemic metabolic disturbances, highlighting the need for further investigation into the roles of T2C in extrapulmonary metabolic regulation.