The pathogenesis of type 1 diabetes (T1D) involves the interaction of the immune system with pancreatic islets, featured by inflammation in both macrophages and β-cells. The enzyme 12-lipoxygenase (12-LOX) is expressed in macrophages and β-cells, produces the eicosanoid 12(S)-HETE and promotes inflammation. GPR31 has recently been identified as a 12(S)-HETE receptor. GPR31 protein levels increase in human islets after cytokine-induced inflammation. To elucidate the role of GPR31 in the 12-LOX pathway and during diabetic inflammation, we generated Gpr31b-/- mice on the C57BL/6J background. Gpr31b-/- mice are viable, with normal body weight, glucose tolerance, and β-cell mass. Upon low dose streptozotocin treatment to induce β-cell inflammation, Gpr31b-/- mice remained normoglycemic unlike wildtype littermates and maintained near normal β-cell mass. To examine GPR31 in islet inflammation, RNA sequencing was performed on isolated mouse islets treated with a cytokine cocktail (IL-1β, IFN-γ, TNF-α). Both wildtype and Gpr31b-/- islets showed expected increases in Nos2 and Il1b after cytokine treatment. By contrast, Gpr31b-/- islets, showed changes in Gene Ontology pathways related to ER stress, oxidative stress, protein targeting, and MAPK activity compared to wildtype islets after cytokine treatment. To test a role for GPR31 in macrophage function, we first interrogated its role in the generation of proinflammatory macrophages upon polarization in vitro to the M1-like state using LPS and IFN-γ; under these conditions, we found no differences between Gpr31b-/- and wildtype macrophages, as assessed by flow cytometric analysis, suggesting that GPR31 does not play a role in macrophage polarization. Next, we tested if GPR31 is required for the ability of macrophages to migrate. To do this, bone marrow derived macrophages were isolated from Gpr31b-/- and wildtype littermates and in vitro migration assays were performed using Transwell chambers. We observed a significant decrease in migration of the Gpr31b-/- macrophages compared to wildtype macrophages. Taken together, our data support the concept that GPR31 promotes proinflammatory responses in both macrophages and pancreatic islets.

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