Free fatty acid receptor 2 and free fatty acid receptor 3 (FFA2/3) are two highly similar G protein-coupled receptors belonging to the free fatty acid receptor family. Their ligands are short-chain fatty acids (SCFAs), which are key nutrients that play a diverse role in physiological function, including the regulation of metabolic homeostasis and glycemic control. FFA2/3 are broadly expressed in a multitude of tissues including the intestine, pancreas, adipose and central nervous system, where they contribute to metabolic homeostasis via a summation of tissue-specific effects. Consequently, FFA2/3 have been identified as a potential drug target for metabolic diseases including obesity and type-2 diabetes.

Both FFA2 and FFA3 are highly expressed within the intestinal epithelium – the major site of SCFA generation – and have been identified in hormone-secreting enteroendocrine cells as well as intestinal epithelial cells. However, due conflicting data, the respective roles of FFA2/3 within the intestine and their effects on physiology and metabolism are still largely unclear. Previous in vivo studies involving this receptor have largely relied on global knockout mouse models, making it difficult to isolate their effects in the intestine. To overcome this challenge, we generated a novel intestine-specific knockout mouse model for FFA2 and FFA3 individually, utilizing Cre-mediated recombination under the expression of the villin promoter. Here, we report the first in vivo characterization of FFA2/3 in the intestine and reveal novel insights into receptor function.

Following model validation, we conducted a general metabolic assessment of male Villin-Cre-FFA2 (Vil-FFA2) and Villin-Cre-FFA3 (Vil-FFA3) mice on standard chow and observed no major congenital or time-dependent defects. Because dietary changes are known to alter gut microbial composition, and thereby SCFA production, a pilot study was performed on male Vil-FFA2 and Vil-FFA3 mice and their littermate controls to probe for a phenotype on a high-fat, high-sugar "western diet." Mice were placed on either a low-fat control diet (CD) or western diet (WD) at 10 weeks of age and metabolically profiled for 25 weeks. We found that both Vil-FFA2 and Vil-FFA3 mouse strains were largely protected from diet-induced obesity and had significantly lower fat mass as well as adipose hypertrophy. Additionally, both mouse strains had reduced intestinal inflammation and improved glucose homeostasis. These differences were driven by lower food intake in the Vil-FFA2 strain only. Our findings suggest a novel role of FFA2/3 in mediating the metabolic consequences of a western diet – a state of high inflammation, dysbiosis and metabolic stress. Moreover, these data support an intestine-specific role of FFA2/3 in whole-body metabolic homeostasis and in the development of adiposity and hyperglycemia.

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Intestinal FFA2 and FFA3 Mediate Obesogenic Effects in Mice on a Western Diet

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