Overconsumption of energy-dense, rich in lipids foods promotes the development of obesity, diabetes, and atherosclerosis. Moreover, lipid-rich diets increase incidents of inflammatory bowel disease (IBD) and are a significant risk factor for the development of colorectal cancer. Absorption of lipids in the intestine is a complex, multistep process, initiated by the micellization of lipids by bile acids, their digestion in the lumen of the intestine mainly by pancreatic lipase, uptake of fatty acids (FAs) and glycerol by the enterocytes followed by re-synthesis of the triglycerides (TGs) at the endoplasmic reticulum (ER). Upon resynthesizing, TGs might be targeted for secretion to the general circulation in the specialized vesicles called chylomicrons or stored in lipid droplets (LDs) in the epithelial cells of the intestine. Recently we have got interested in the identification of molecular mechanisms regulating intestinal lipid absorption machinery. In our previous study, we have already identified one signaling molecule, protein kinase D2, inhibition of which in the intestine protects from the development of obesity. In the current project, we plan to identify other mechanisms mediating lipid handling by the epithelial cells. We will focus especially on pathways regulating lipid storage in LDs. We hope that the identification of the molecular pathways regulating lipid metabolism in the intestine will not only increase our understanding of this process, but will also result in the identification of novel targets for pharmacological intervention to treat obesity, diabetes, atherosclerosis as well as IBD.