

# Translational Diabetes



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## Gut mucosal immunity in metabolic disease

Diabetes is a serious and growing health problem, affecting 463 million people worldwide in 2019. Chronic inflammation is a hallmark in the pathogenesis of type 2 diabetes and obesity. However, the initiating mechanisms of glucose dysregulation and inflammation in obesity remain poorly understood.

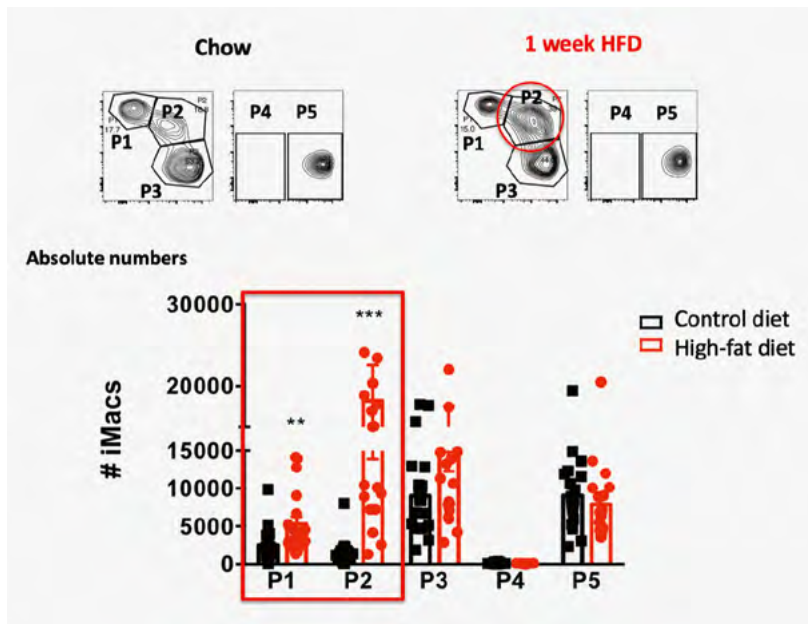
Our research focuses on gut mucosal immunity as a potential starting point of inflammation and glucose dysregulation in metabolic disease. Thereby, we are interested in elucidating the role of the mucosal immune system, especially intestinal macrophages. Intestinal macrophages constitute the largest macrophage compartment within the body and could serve as crucial “sensors” of environmental or external factors (i. e., food intake or environmental toxins such as air pollutants or cigarette smoke particles) for the host’s immune system. We are interested in how intestinal macrophages respond to such environmental stressors and how their response ultimately affects glucose homeostasis and systemic inflammation.

We found that pro-inflammatory/ monocyte-derived colonic macrophages are elevated in mice fed a high fat diet, suggesting a link between colon macrophage numbers and glucose homeostasis. Indeed, we were able to establish a direct link between colon macrophages and glucose metabolism as colon-specific macrophage depletion ameliorated glycemic control and beta-cell function.

Besides classical risk factors like unhealthy food or sedentary lifestyle, also environmental toxins like air pollution or cigarette smoke increase the risk for type 2 diabetes. We showed that air pollution particles mediate diabetes via the gastrointestinal tract rather than via lung exposure as previously thought. Oral exposure to pollutants occurs via mucociliary clearance of particles from the airways with subsequent swallowing of the particles. Particles reaching the gastrointestinal tract caused a distinct inflammatory shift of colon macrophages. This local gut inflammation was associated with impaired insulin secretion and glucose intolerance. Similarly, we are assessing how cigarette smoke particles and e-liquids from e-cigarettes impact on mucosal gut immunity and glucose homeostasis. Also, we are studying the differential effects of air pollution particles on atherosclerosis when they are administered via lung or gut exposure.

In addition, we are also interested in therapeutic aspects of gut mucosal immunity. As weight-loss surgeries are associated with a rapid improvement in glucose homeostasis, we aim to address the question whether weight loss has beneficial effects on gut mucosal immunity and hence glucose tolerance.

In sum, the aim of our laboratory is to better understand the changes of gut mucosal immunity upon environmental stimuli and how this connects with glucose intolerance and systemic inflammation in metabolic disease to potentially find immune-modulatory treatments.



**Fig. 1: Pro-inflammatory colon macrophages are elevated following high-fat diet.**

Top panel: Representative flow cytometry of colon macrophage subpopulations P1-P5 subpopulations in a mouse fed standard chow or 1 week high-fat diet.

Bottom panel: Absolute numbers (#) of pro-inflammatory (P1, P2, P3) and anti-inflammatory/resident colon macrophage subpopulations (P4, P5) in mice fed standard chow or high-fat diet.

## Connection to Clinical Practice

Prof. Dr. Petr Hruz, Prof. Dr. Jan Niess<sup>1</sup>

Prof. Dr. Ralph Peterli<sup>2</sup>

PD Dr. Bettina Wöllnerhansen<sup>2</sup>

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### Human intestinal macrophages in metabolic disease

In order to translate our findings to human disease, we compare human gut biopsies of patients with different environmental “toxins” (i.e., normal weight versus overweight individuals or smokers versus non-smokers). We found an inflammatory shift in intestinal macrophages in obese individuals, similar to our findings in obese mice. To assess whether these changes in gut innate immunity are reversible, we plan to study intestinal macrophages from individuals before and after weight loss surgery. The ultimate goal is to potentially find immunomodulatory treatments at the interface between the environment and the host’s metabolism.

### Selected Publications

Schneider R, Kraljevic M, Peterli R, Rohm TV, Klasen JM, Cavelti-Weder C and Delko T (2020). GLP-1 Analogues as a Complementary Therapy in Patients after Metabolic Surgery: a Systematic Review and Qualitative Synthesis. *Obes Surg* 30, 3561–3569.

AlAsfoor S, Rohm TV, Bosch AJT, Dervos T, Calabrese D, Matter MS, Weber A and Cavelti-Weder C (2018). Imatinib reduces non-alcoholic fatty liver disease in obese mice by targeting inflammatory and lipogenic pathways in macrophages and liver. *Sci Rep* 8, 15331.

Cavelti-Weder C, Zumsteg A, Li W and Zhou, Q (2017). Reprogramming of Pancreatic Acinar Cells to Functional Beta Cells by *In vivo* Transduction of a Polycistronic Construct Containing Pdx1, Ngn3, MafA in Mice. *Curr Protoc Stem Cell Biol* 40, 4A 10 11–14A 10 12.

Cavelti-Weder C, Li W, Zumsteg A, Stemann-Andersen M, Zhang Y, Yamada T, Wang M, Lu J, Jermendy A, Bee YM *et al.* (2016a). Hyperglycaemia attenuates *in vivo* reprogramming of pancreatic exocrine cells to beta cells in mice. *Diabetologia* 59, 522–532.

Cavelti-Weder C, Timper K, Seelig E, Keller C, Osranek M, Lassing U, Spohn G, Maurer P, Muller P, Jennings GT *et al.* (2016b). Development of an Interleukin-1beta Vaccine in Patients with Type 2 Diabetes. *Mol Ther* 24, 1003–1012.