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Proinflammatory cytokines and their effect on murine small intestinal organoid secretion

Abstract: Intestinal organoids are stem cell derived, 3D cell cultures reflecting the morphology and function of the native intestinal epithelium, e.g. transport processes or maintenance of the epithelial barrier. During intestinal inflammation, these functions can be disturbed by proinflammatory cytokines like tumor necrosis factor α (TNF α) leading to a leaky barrier and higher net secretion of electrolytes (mainly Cl⁻) and water into the gut lumen. To elucidate the still incompletely understood effects of proinflammatory cytokines on the intestinal epithelium, murine small intestinal organoids were incubated with TNF α or a cytokine mix over several days.

Both, TNF α and the cytokine mix, induced a swelling of the organoids characterized by a rounded shape and flattened epithelium due to an influx of fluid into the lumen. This could be rather explained by changes in the Ca²⁺-dependent Cl⁻ secretion than by an impaired epithelial barrier. Inhibition of the Na⁺-K⁺-2Cl⁻ symporter 1 (NKCC1) by bumetanide reduced the cytokine-induced organoid swelling. Changes in cytosolic Ca²⁺ lead to the assumption that TNF α modulates the Ca²⁺ entry from the extracellular side and not the release from intracellular Ca²⁺ stores, when organoids were stimulated with the Ca²⁺-dependent secretagogue, carbachol. In contrast, the cytokine mix seems to affect both Ca²⁺ entry as well as release from intracellular Ca²⁺ stores confirmed by an increased Ca²⁺ signaling and upregulation of different transporters and mediators involved in this pathway.

Taken together, this study shows that proinflammatory cytokines have direct effects on the intestinal epithelium by increasing the Ca²⁺-dependent Cl⁻ secretion.

Keywords: Intestinal organoids, cytokines, Ca²⁺ signaling, secretion, epithelium

Biography: Dr. Jasmin Ballout studied veterinary medicine at the Justus Liebig University in Giessen, Germany. In 2019 she finished her doctoral thesis about neuro-immune interactions in the gastrointestinal tract in the context of inflammatory bowel diseases (IBD) at the institute for veterinary physiology and biochemistry, JLU Giessen. Currently, she is working as Postdoc in the group of Professor Martin Diener focusing on intestinal organoids as inflammatory model or purinergic and short-chain fatty acid signaling in the intestine.