

Location, location, location – even gut immune response is site-specific

Researchers at Würzburg University are using mini-organs to model the digestive tract in the laboratory. These so-called organoids provide insights into the inflammatory processes that play a role in diseases such Crohn's and ulcerative colitis.

Why is it that some chronic inflammatory bowel diseases, such as Crohn's, affect both the small intestine and the colon, while others, like ulcerative colitis, are restricted to the colon? In order to solve clinical puzzles such as this one, among others, researchers from the University of Würzburg created miniature versions of the digestive tract in the lab. One of their discoveries: the digestive tract contains an inherent segmentation that could shed new light onto these common inflammatory conditions.

Scientists are now able to generate miniature versions of practically any organ of our bodies - including skin, brain and intestine. These three-dimensional structures are generated from stem cells and are called "organoids". With a diameter of around 0.5 millimeter, organoids may only be the size of a grain of mustard, but they show a remarkable similarity to the real organs. "Despite their miniscule size, organoids simulate the organ they are derived from extremely well" says Dr. Sina Bartfeld, who led the study at the Research Center for Infectious Diseases at the Institute for Molecular Infection Biology. "Organoids contain the same types of cells as the real organ. The stem cells from which the organoids are generated contain a kind of pre-programmed tissue identity. The stem cell "knows" which organ it comes from and even in culture it produces the kinds of cells that are present in this organ in our bodies."

In collaboration with surgeon Armin Wiegeling from the University Hospital of Würzburg, Dr. Bartfeld's team generated organoids from stomach, small intestine and colon. They discovered an unexpectedly large molecular complexity, as revealed by RNA sequencing, which reflects the gene activity of the cells.

One of their findings was that organoids from the different segments of the digestive tract switch on specific gene-programs, depending on their tissue identity. "It's intuitive that gastric and intestinal cells have to produce different digestive enzymes – but we were surprised to discover that particular binding sites of the immune system are also part of this tissue identity", says Bartfeld.

The particular organization of the immune binding sites may play a role in the organ-specific inflammatory diseases. It could even be relevant for the development of cancer, where chronic inflammation has also been implicated. Whether this is the case and how inflammation could contribute to carcinogenesis requires further research, for which organoids form a novel basis.

Not only can organoids be generated rapidly and in large numbers in the laboratory, they have the added advantage that they consist of human tissue and form an approximate representation of a human organ. Since there are substantial differences between humans and animals, organoids can help to reduce animal experiments and illuminate uniquely human diseases. They also play an increasingly important role in drug development.

Organoids demonstrate the amazing organization of the gut – also regarding the recognition of bacteria and viruses

In addition, organoids open up entirely new ways of investigating basic molecular processes in a biologically realistic model – such as the digestive system, which is also the focus of Dr. Bartfeld's research team in Würzburg. The epithelial cells that line our digestive tract have an important barrier function, which prevents bacteria from entering our bodies. These could be pathogens, such as disease-causing bacteria or viruses. At the same time, the intestine is colonized by billions of beneficial bacteria, the so-called microbiota, which help us to digest food. The epithelial cells thus have to be able to sense both friendly and hostile bacteria or viruses and respond appropriately. This is accomplished via special immune binding sites, called pattern recognition receptors.

These receptors recognize specific molecules produced by the different bacteria in the intestine. If the epithelial cells recognize molecules produced by dangerous pathogens, as opposed to beneficial bacteria, they have to raise the alarm and induce an immune response. So far it was unclear how the epithelium is able to differentiate between friend and foe. "It is extremely difficult to untangle the complex interaction between immune cells, epithelial cells and microbes" so Dr. Bartfeld. "However, since our organoids contain only epithelial cells, we can use them to specifically investigate the contribution of the epithelium in this interaction."

During their study, the scientists discovered that each pattern recognition receptor has its own, segment-specific gene activity pattern. "The stomach as well as each segment of the intestine has its own specific repertoire of pattern recognition receptors" explains Özge Kayisoglu, first author of the study. "Thus, the immune response of the epithelium is location-specific. In this way, the stomach reacts to different bacterial compounds than the small intestine or the colon." These differences in the immune response may contribute to segment-specific diseases like ulcerative colitis or Crohn's disease.

What induces this differential reaction to bacterial compounds? Initially, the obvious assumption was that the immune receptors are regulated in response to colonization with beneficial bacteria. To test this hypothesis, the researchers generated organoids that had never come into contact with bacteria. "The data showed that the microbiota does have an effect – but we were surprised to find that in large part, immune recognition of the epithelium is in fact genetically determined during development and independent of the environment," says Bartfeld.

Collectively, their findings represent an important step in illuminating inflammatory processes. They show that each section of the digestive tract has its own specific combination of immune recognition receptors. Dysfunctions of this innate immunity may promote the development of inflammatory diseases.

Original publication

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Location-specific cell identity rather than exposure to GI microbiota defines many innate immune signalling cascades in the gut epithelium

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