Medical Xpress

Navigating the digestive tract: Study offers first detailed map of the small intestine

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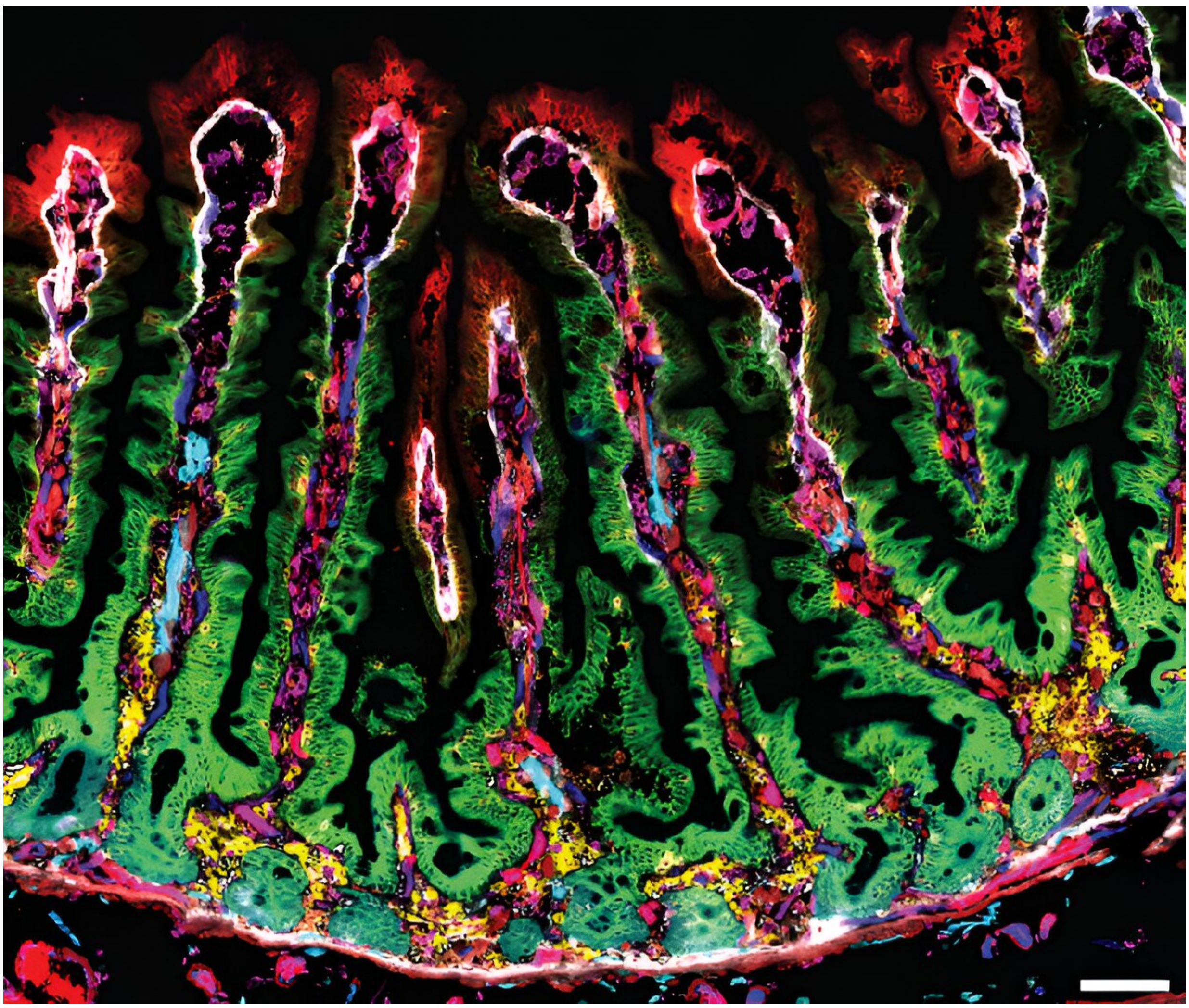


An image of tissue from the human small intestine obtained with the help of fluorescent dyes that made it possible to mark numerous proteins in parallel, thereby mapping out the various proteins produced in each part of the intestinal villi. Credit: Weizmann Institute of Science

Tourists visiting an unfamiliar city would have a hard time finding their way around if they were using nothing but a topological map, no matter how detailed. Most tourist maps, therefore, highlight sights of interest and prominent landmarks.

As far back as the 16th century, we were mapping out the murky territory of the human small intestine in anatomy books. We know, for example, that this digestive tract is—on average—about 6 meters long and that it is covered with millions of villi, tiny finger-like projections that increase the surface area of the tract thirtyfold and that are separated by crypt-like crevices.

Until now, however, it has been unclear where the sights of interest and prominent landmarks are in this complex configuration of crypts and villi. In a new study, reported in *Nature*, Weizmann Institute of Science researchers and experts from Sheba Medical Center's General Surgery Department have compiled the first detailed map of the various activity areas in the human small intestine, revealing what makes it so effective at absorbing nutrients and protecting the body from infection.

Conditions along the small intestine differ completely from one point to another, from the crypts lining the inner walls to the tips of the protruding villi. While the area closest to the wall of the small intestine enjoys a plentiful supply of blood and oxygen, the environment at the tips of the villi is oxygen poor and saturated with nutrients and bacteria.

In 2018, a research team headed by Prof. Shalev Itzkovitz from Weizmann's Molecular Cell Biology Department showed that villi cells in the small intestines of mice adapt to a changing environment and perform defined functions depending on their relative location on the villi.

"Up until that point, we had only worked with mice," says Dr. Yotam Harnik, who completed his doctoral studies in Itzkovitz's lab, recounting the origins of the project to construct a genetic atlas of the human small intestine.

"I was eating lunch on the lawn of the Weizmann campus one day, talking to Dr. Oran Yakubovsky, a surgical resident from Sheba who had started his Ph.D. program in our lab six months earlier. He asked me why we don't take human intestinal tissue from operating theaters. One of the problems with doing that is that surgeons don't often cut out a significant part of someone's intestine when it's healthy."

"We decided to analyze human intestinal tissue, using samples from Whipple procedures, in which the head of the pancreas is removed because of pancreatic pathologies," Yakubovsky explains.

"In this procedure, surgeons also remove the entire duodenum, the first part of the small intestine. One of the advantages of this procedure from a research perspective is that the intestinal tissue, which is removed for anatomical reasons, is considered healthy and can be used to study the normal intestine. We were able to cooperate with the General Surgery Department at Sheba, ensuring that each sample, in its entirety, was frozen quickly."

At the same time, the Weizmann Institute acquired new technology that allows researchers to effectively map spatial genetic expression in tissue, and to analyze—to a resolution of 50 microns—which genes are expressed in every region and to what extent.

Slow-release fats

The atlas that the researchers compiled, under the leadership of Harnik and Yakubovsky—both from Itzkovitz's lab, in cooperation with Dr. Rouven Hoefflin from Prof. Itay Tirosh's lab in Weizmann's Molecular Cell Biology Department—sheds light on some of the long-standing mysteries surrounding the workings of the small intestine.

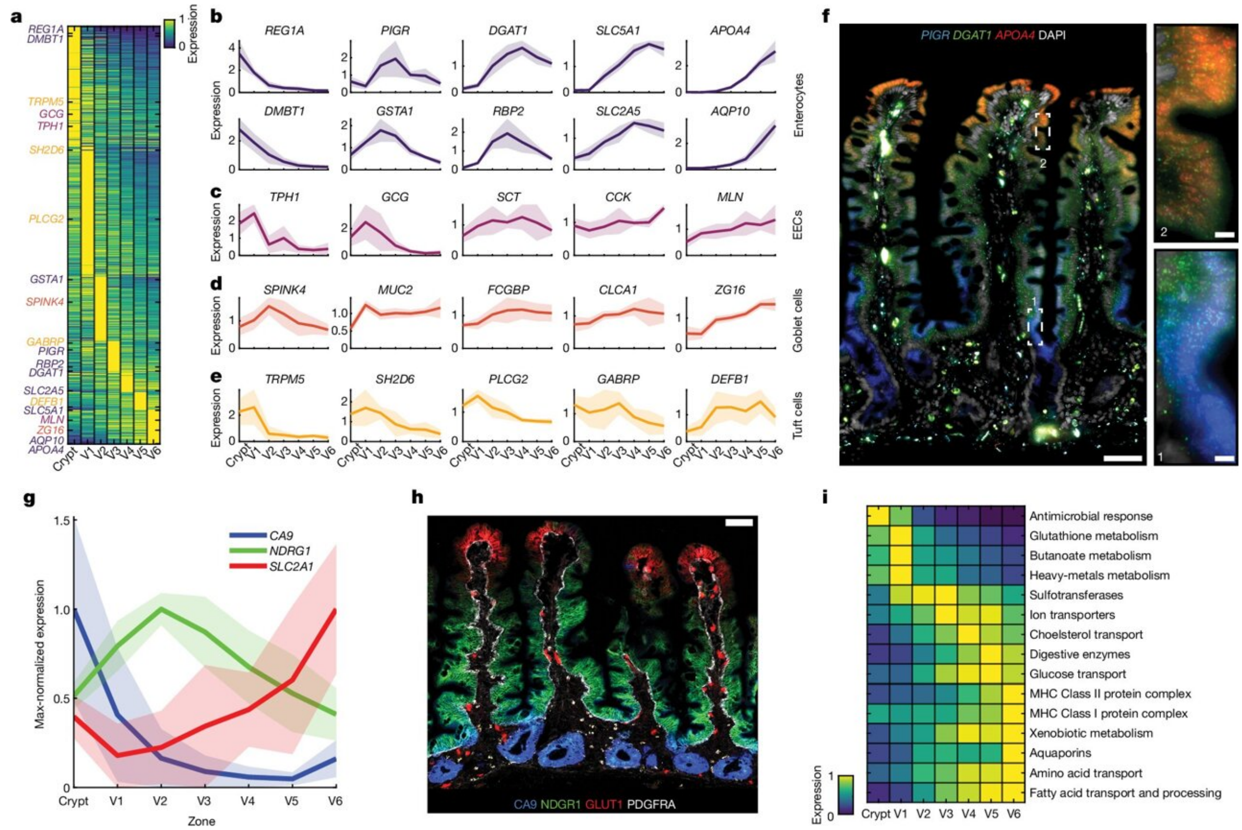
As far back as the 1950s, scientists had discovered that there is a delay of up to two days before fats from food are absorbed into the blood, which prevents a spike in blood fat levels, but how exactly this works had remained unclear. The atlas of the human intestine reveals that the digestion of fat by the human villi resembles an assembly line.

Cells at the bottom of the villi encase fat from food in droplets of fat and it is only several hours later, when those cells advance along the villi and reach the tip, that they load the fat onto "freight trucks," huge particles that transport it via the lymphatic system to blood vessels, and from there to storage in the body.

Regulation of the iron balance in our bodies is also like an assembly line: Iron is absorbed in the crypts and at the bottom of the villi; when the cells reach the tips of the villi (and depending on the iron level in the body) they either release their iron reservoir into the blood or take it with them to their deaths in the intestinal cavity.

The atlas also reveals that the absorption and production of the enzymes needed to digest other important nutrients—amino acids, short proteins and sugars—only occur at the tips of the villi, while the cells at the foot of these protrusions specialize in absorbing vitamins and minerals.

As for the immune defense provided by the small intestine, the researchers found that cells at the tip of the villi secrete antimicrobial proteins that attack the bacteria directly and also send a call for help to the immune system's most aggressive cells. The tips of human villi, therefore, were found to be rich in inflammation-promoting immune cells.



Zonated epithelial gene expression programs along the crypt–villus axis. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07793-3

The long and winding tract

Anatomy textbooks have traditionally described villi in a healthy human small intestine as straight, finger-like protrusions. While compiling their atlas, however, the researchers identified villi that branch off from other villi, something that—until then—had only been observed in cancerous growths. The scientists believe that this branching serves to increase the surface area of the small intestine even further and to improve absorption. The findings were obtained using a new method that allows researchers to document the spatial structure of tissue in three dimensions without disrupting the tissue's integrity.

"Our atlas provides answers to some basic research questions, but it can also be applied to clinical questions," Itzkovitz says. "Now that we have mapped a healthy small intestine, we can start to further our understanding of the changes that it undergoes when it is diseased, when we age, when certain drugs are taken or when we are on a specific diet.

"This study, like others that we are currently conducting with the General Surgery Department at Sheba, is only possible because senior members of that department, headed by Dr. Ido Nachmany, appreciate the importance of basic research. This framework allows physician-researchers at Weizmann to translate questions that come up in the clinic into studies that could provide answers."

Nachmany, the director of Sheba's General Surgery Department, adds, "Cooperation between the Weizmann Institute and the General Surgery Department at Sheba has yielded a series of fascinating studies on the most fundamental aspects of the physiological and anatomical workings of human tissues.

"The collaboration between the two worlds—basic research and clinical medicine—is a wonderful achievement, and it is reflected in this study in *Nature*. We are working to strengthen that connection and hope that more surgical residents will spend significant time engaged in research at the institute. We are convinced that this will have profound benefits for both worlds."

More information: Yotam Harnik et al, A spatial expression atlas of the adult human proximal small intestine, *Nature* (2024). DOI: 10.1038/s41586-024-07793-3

Provided by Weizmann Institute of Science