FIGHTING FOOD ALLERGIES WITH ALGORITHMS

Broad researcher Sam Riesenfeld wields machine learning to show how the nervous and immune systems work together to regulate allergic reactions.

This is the tale of a researcher whose computational models have helped uncover an important connection between neurology and immunology in food allergy.

For years, scientists believed that an overactive immune system was the only culprit behind food allergies, a public health threat in the U.S., where one in 13 children under the age of 18 is affected. But emerging evidence from the Broad's Food Allergy Science Initiative (FASI) is challenging conventional wisdom.

Recently, FASI scientists have demonstrated that the immune system—in tandem with the nervous system—drives adverse reactions to food. Specifically, their research shows that communication between neurons and immune cells known as innate lymphoid cells (ILCs) plays a central role. ILCs, which maintain a stable environment in the lungs, also express receptors for peptides produced by the nervous system—suggesting that the activation of neurons may alter the function of these immune cells.

This finding not only overturns a long-held hypothesis but also points to the importance of bringing together two fields usually kept apart—immunology and neurobiology—in the pursuit of food allergy. Indeed, the leaders of FASI—an initiative launched, supported, and sustained by generous philanthropy—now believe that only by marrying the two disciplines will we be able to crack this problem and someday find effective treatments.

"Prior to this research, it was not known that neurons and ILCs communicated at all, much less in the context of allergic response," said Samantha Riesenfeld, the FASI computational biologist whose models helped analyze how ILCs in the lung trigger an inflammatory response rather than protect the tissue. Others on the FASI team found the same pathways were present in allergic response in the gut.

Riesenfeld's analyses go beyond cell-type classification to understand how ILCs are transformed by signals from other cell types—including neurons and epithelial cells. Using data produced by single-cell RNA sequencing, her computational and statistical approaches analyze tens of thousands of ILCs from both inflamed tissue in mice experiencing allergic response and regular tissue in unstimulated mice. She then applies machine-learning methods to infer from the data which pathways may be used by neurons to drive gene-expression changes in ILCs. These changes may, in turn, provide clues about what other cells are involved and how their behavior differs during allergic response. Her goal is to build models that "encode the complexity of biological systems across cell types, cell states, and time, and apply those models to understand how the immune system regulates inflammatory responses."

Riesenfeld's findings will help the FASI team elucidate how allergens drive disturbances in the lung and gut tissue, leading to experiments testing therapeutic interventions. "Once we have a map of the cells and genes involved in the process of inducing food allergies," said Broad institute member Vijay Kuchroo, one of FASI's scientific leaders and the Samuel L. Wasserstrom Professor of Neurology at Harvard Medical School, "we can start interfering with neuropeptides to not only block the disease but also unwanted effects like vomiting or chronic coughing."

Before joining Aviv Regev's lab at the Broad in 2013, Riesenfeld was a postdoctoral fellow at the Gladstone Institutes, a biomedical nonprofit based in San Francisco. She came to the Broad, she said, because it is "a palace of computational biology," a place where scientists are unusually savvy about computation and math yet still biologically driven. "If there's an idea that makes sense to try, people find a way to do it—collaboratively."

When she isn't straddling biology and computation, Riesenfeld finds herself bridging other divides. "I grew up in the Mountain West, came as an undergrad to Harvard, left for my Ph.D. at U.C. Berkeley, and came back, and am now headed to the Midwest," she said. "I learned Italian as a postdoc because my husband's parents don't speak much English and we spend a lot of time with them, mingling their traditions with my Jewish heritage. Crossing cultures has been a theme."

Riesenfeld, who will be joining the faculty of the Pritzker School of Molecular Engineering and the Section of Genetic Medicine at the University of Chicago this fall, is also the mother of two boys, Elia, 6, and Ari, 3. "Juggling parenting and my career is one of the hardest things I've ever had to do," she said. "There is no way I would've been motivated enough to stick with my postdoc work if I didn't love it."

—Anna Fiorentino ■