Q&A: What human diseases can teach us about the immune system

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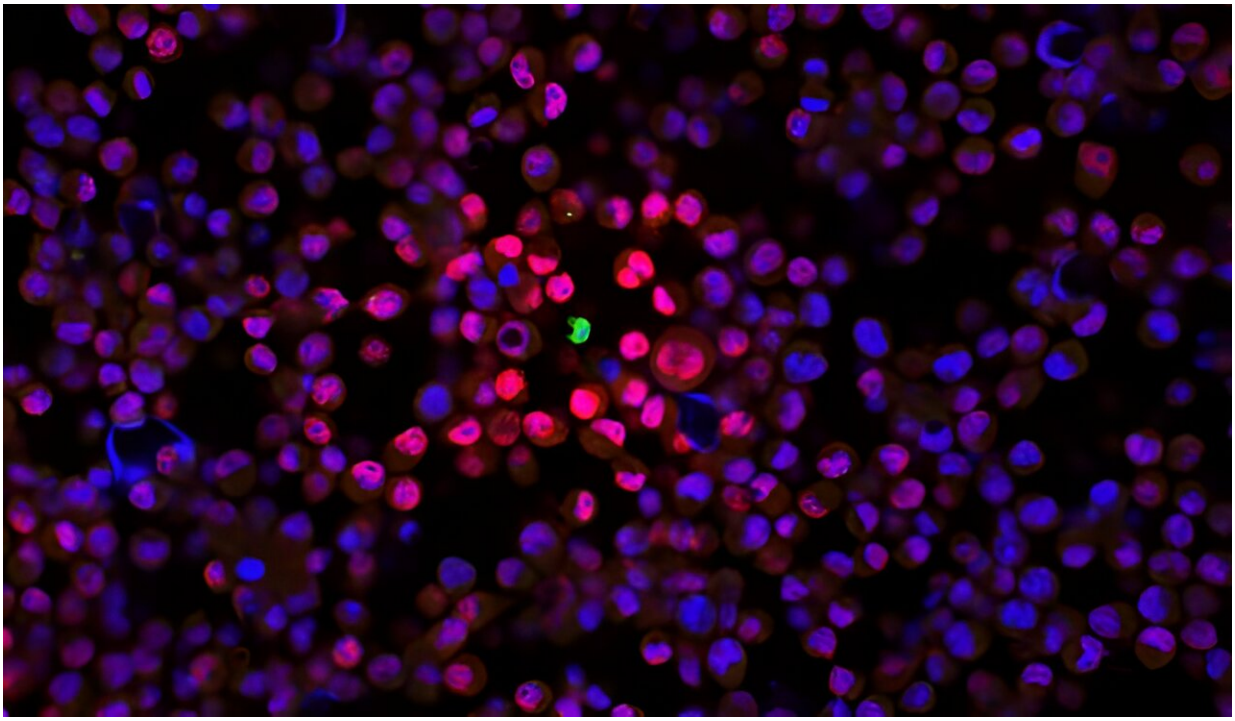

A microscope image of melanoma cells. The green T cell in the center has been activated and is producing interferon-gamma (pink/red), a signaling molecule necessary for certain cancer immunotherapies to work. The Oyler-Yaniv lab is studying how interferon-gamma spreads through dense tissues in the body. Credit: Oyler-Yaniv lab

The immune system is a crucial part of our survival, regularly fending off wide-ranging attacks on the body, both internal and external.

Unsurprisingly, the elegant defense system that protects us from viruses, bacterial infections, cancer, and other threats is immensely complicated. Each time it mounts a response, it must quickly and carefully orchestrate communication across vast numbers of cells and molecules.

Jennifer Oyler-Yaniv is working to figure out how, exactly, the immune system does this—and when and why it fails.

"There's always the next question, the next thing we don't understand. As a scientist, I have full creative freedom to get obsessed with problems," said Oyler-Yaniv, who is an assistant professor of systems biology in the Blavatnik Institute at Harvard Medical School (HMS).

In an ironic twist, Oyler-Yaniv launched her lab at HMS—which she co-leads with her partner, Alon Oyler-Yaniv—at the height of the COVID-19 pandemic, when immunology was garnering new levels of attention from scientists and the public alike.

Straddling the worlds of immunology and systems biology, the Oyler-Yaniv lab is using cancer as a model system to uncover the basic principles of how cells in the immune system communicate.

Her lab recently published a paper in the *Proceedings of the National Academy of Sciences*.

In a conversation with Harvard Medicine News, Oyler-Yaniv discussed her interest in immunology, her approach to research, and her insights about the immune system and cancer.

How would you describe the essence of your work?

We're an immunology lab that asks quantitative questions about the immune system. Broadly, we're interested in how signaling molecules

travel through tissues in the body, and how their behavior changes once they get to the target cells they're going to act on.

Specifically, we study cytokines, which are signaling molecules that enable cells in the immune system to communicate with each other. Cytokines are essential for the immune system to clear pathogens and kill tumors, but they can cause damage to the body when they act on cells not involved in the immune response. Because of that, their spatial dynamics must be very tightly regulated.

Our lab has two big wings. One wing is focused on understanding the biophysical principles that regulate the spread of cytokines through three-dimensional, dense tissues. We want to understand how these cytokines are spatially distributed in tissues, and what factors affect their distribution.

We are interested in this topic from a basic immunology perspective, and for its clinical applications to cancer. On the other side, we're interested in how cytokines change their decision-making when they act on cells, including decisions such as whether to die, proliferate, or become dormant. These decisions have important implications for viral infections and cancer.

What sparked your interest in immunology?

My interest in immunology took off during grad school. Immunotherapy was becoming a viable treatment option for people with cancer, and I was at Memorial Sloan Cancer Center, where a lot of the pioneering work was being done. We would see these survival curves where people who were very sick with cancer and expected to die enrolled in a clinical trial and ended up responding to immunotherapy.

It was an incredibly energizing and exciting time to see what the immune

system could do to treat cancer, and being in that environment provided me with a huge momentum to study the immune system. I'm interested in the immune system beyond cancer immunotherapy, but that was the catalyst for what got me so excited about it in the first place.

You are an immunologist. Why did you join a systems biology department?

As a field, systems biology aspires to extract details to find general principles and repeating patterns. That's something I'm very interested in. My lab aims to identify broader patterns in the way groups of tissues or molecules behave to understand general principles of the immune system.

For example, some of our research focuses on how the cytokine interleukin-2 interacts with immune cells called T cells. We are, of course, interested in the biology of that specific interaction, but we also think that it can be a model system to understand how cells communicate more generally. Ultimately, we hope that finding these general principles that can be applied broadly to different diseases and tissues will allow us to form a more unified view of the immune system.

Being in a systems biology department is helpful because we have the perspective of people who care about finding general principles and we are also able to do a lot of mathematical modeling. We use computational tools like machine learning to analyze very large imaging data sets, including data sets from human tumor specimens. A strength of our lab is analyzing those data sets to understand the spatial relationships between different cell types. We also do a lot of live cell microscopy and experiments with basic mouse models of disease, just like every other immunology lab. I think we are in a hybrid space between systems biology and immunology.

Your lab recently published a paper on cytokines in melanoma. What were the central findings?

I've been interested in the pro-inflammatory cytokine interferon-gamma for a long time. Interferon-gamma is an important cytokine in cancer because it is absolutely essential for certain cancer immunotherapies to work. Yet there have been really conflicting studies in mice and humans about the spatial spread of this cytokine through dense tissues—specifically, how far it can spread through a tumor. Some studies claim that this cytokine is released only to its nearest neighbor, and others claim that it can spread over long distances.

We approached this question of spatial spread from a biophysics perspective: We generated dense, three-dimensional tissues in a lab dish that allowed us to have a lot of control over the experimental parameters as we investigated how far this cytokine can travel.

In a previous study, working with interleukin-2 as a model system, we found that the spread of molecules through dense tissue is a competition between diffusion, which spreads them further, and consumption, or uptake of molecules by cells with receptors that bind to them. In the new study, we found this is also true for interferon-gamma in the context of melanoma: We could predict how far interferon-gamma would spread in a tumor based on the amount and distribution of cells producing the cytokine and cells with receptors that bind to it.

One of our key conclusions was that the only way you get widespread penetration of interferon-gamma through a tumor is if you have a lot of cells producing it and those cells are evenly distributed throughout the tissue. We think that this information could help refine biomarkers to identify who is likely to respond to immunotherapy. We are interested in applying this framework to understanding drug penetration with the idea

that drugs are not too different from cytokines in how they spread through a tumor.

When you aren't in the lab, what else do you spend time on at HMS?

I teach a science communication and ideation course to our first-year graduate students, which is one of two required courses. I care a lot about helping students communicate more effectively and helping them acquire confidence in coming up with new ideas. There are a lot of misconceptions in science that an idea just pops into someone's head, when it's really a lot of storytelling and putting pieces of data together. Research is a team effort, and coming up with ideas is hard. I think that we can normalize that for students and also help them develop a positive attitude and a mindset that it will get easier with time.

This is especially important for students who might not have any scientists in their family, so might not be aware of these misconceptions about how creativity works in science. We can also give students some techniques to actually do it—to learn how to come up with ideas, and how to be original and innovative. These are things that are studied and taught in creative fields, but not really in science, so we want to do that.

More information: Edoardo Centofanti et al, The spread of interferon-γ in melanomas is highly spatially confined, driving nongenetic variability in tumor cells, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2304190120

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