

PING-CHIH

HO



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THE IMMUNOMETABOLOMIC DISRUPTOR

He eavesdrops on the metabolic chatter between cancer cells and immune cells. Manipulating this malignant crosstalk could significantly boost the efficacy of immunotherapy.

Growing up in Kaohsiung, a southern port city in Taiwan, Ping-Chih Ho was lucky to have the kind of parents who cultivate curious minds. “They gave me a lot of freedom to learn everything I wanted to learn,” he recalls. As it turned out, a mix of freedom and curiosity would characterize the best moments of Ho’s future career as well.

They would, most notably, propel him to the front of a fledgling field of growing importance to cancer research known as immunometabolomics, which explores how the molecular byproducts of metabolism mediate a conversation between the immune system and the tissues it patrols. That chatter often proves fateful in tumors, which manipulate their metabolic environment to thwart immune attack.

In 2017, Ho’s laboratory reported in *Nature Immunology* that relative levels of two run-of-the-mill metabolites involved in the

breakdown of the amino acid glutamine and the tricarboxylic acid cycle, a metabolic pathway, can have profound effects on the function of immune cells known as macrophages. His team showed how this balance can determine whether macrophages assume a state in which they can gobble up cancer cells and instigate an anti-tumor immune response, or an alternative one that can suppress such responses and support cancer progression. The findings suggest that the classical enzymatic networks that generate those metabolites might be pharmacologically tweaked to boost the effects of cancer immunotherapy.

Lucky break

Soon after getting a master’s degree in biochemistry from National Taiwan University in 2006, Ho met a visiting University of Minnesota researcher, Li-Na Wei, and convinced her to hire him as a technician in her lab. “That was a very big transition,” says

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Ho. “I expected I’d only be there a year.” But Li had other ideas. She invited Ho to join her team as a PhD candidate, which he did in 2008.

Li and her team were studying the dysfunctions of fat cells that contribute to insulin resistance in Type II diabetes, and one of their interests was a transcription co-suppressor—a regulator of gene expression—known as RIP140 that can contribute to metabolic diseases. Some of their experiments had shown that macrophages express RIP140 at relatively high levels; other researchers reported that the factor boosts their inflammatory effects. Li suggested Ho make RIP140 activity in macrophages and fat cells the subject of his doctoral research. Learning about metabolic disorders and probing macrophage immunology, Ho traced the links between signaling networks that drive lipid transport and metabolism and those that induce inflammation.

“This was how I started getting interested in immunology,” he says.

Freedom and curiosity

So interested, indeed, that he decided to become an immunologist. Despite a strong record of publications in journals like *Cell Metabolism* and *Nature Immunology*, Ho had some trouble landing a postdoctoral position in immunology. “Many people believed back then that studying signaling cascades of macrophages is not real immunology and so I appeared to lack the required expertise in cellular immunology,” he says. Fortunately, the Yale University immunologist Susan Kaech, who is today director of Nomis Center for Immunobiology and Microbial Pathogenesis at the Salk Institute, was not one of them. Ho joined her group as a postdoc in 2012.

Kaech had long explored how chronic viral infections induce a paralyzing exhaustion in the immune system’s T cells, which are charged with clearing such infections. She was now interested in probing a similar phenomenon observed in tumors. Less clear was which angle to take. “We had a number of



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discussions and she gave me a lot of freedom to determine what I should work on,” says Ho.

It was already becoming clear at the time that activated T cells, among the fastest growing cells in the body, have metabolic profiles that resemble those of cancer cells. “Since tumor cells and T cells show similar metabolic activity in the same environment,” says Ho, “my gut feeling was that they would be communicating with each other through metabolic crosstalk and that this might be one of the reasons immune cells fail against tumor cells.”

It was an original idea, and it appealed to Kaech. “We were very lucky,” says Ho, “because it looks like we were right.”

The crosstalk they detected arose from a fundamental process known as glycolysis, by which cells break down glucose to generate energy. Normal cells only switch on glycolysis when they’re starved of oxygen. Cancer cells, on the other hand, keep it on regardless—a

phenomenon known as the Warburg effect—because it generates not just energy but also raw materials essential to cell proliferation. Ho, Kaech and their colleagues discovered that the cancer cell’s induction of the Warburg effect coincides with the exhaustion of killer T cells and helper T cells (which orchestrate immune responses). Their study, reported in *Cell* in 2015, detailed why this is the case.

It turns out that a metabolite generated by glycolysis—phosphoenolpyruvate—is a critical switch for T cell activation. After the immune cell’s surface sensor, the T cell receptor (TCR), has been engaged by a cancer antigen, the glycolytic metabolite induces a flood of calcium into the cell. That influx is critical to the T cell attack. Trouble is, cancer cells tend to consume most of the glucose in their microenvironment.

“Without glucose,” says Ho, “the TCR still gets stimulated, but there’s only a transient calcium influx. That is not sufficient to induce



Photo by Eric Déroze

a T cell response, but it is enough to induce T cell exhaustion.”

Most notably, Ho and his team showed that by engineering T cells to produce phosphoenolpyruvate by breaking down alternative nutrients instead of glucose, they could ameliorate the T cell exhaustion. Injecting those T cells into mice with melanoma shrank tumors and extended the survival of the mice. “This was proof of concept that we can rewire a metabolic pathway in T cells to get them to do their job,” says Ho.

Conflict resolution

A month after that paper appeared in *Cell*, Ho arrived in Ludwig Lausanne, starting a research program in his new laboratory

that is integral to the Branch-wide effort to develop personalized cell-based cancer immunotherapies (detailed in the *2017 Research Highlights* report). Ho still primarily focuses on T cells, with the aim of engineering their metabolism to further boost their activity for such therapies. But he has not forgotten the humble macrophage.

With good reason. Most macrophages in tumors are of the M2 variety that suppresses immune responses, rather than the M1 type that eats cancer cells. “We wanted to understand how tumor cells use their metabolic activity to coopt macrophages,” he says. “Understanding that mechanism might allow us to reprogram those macrophages to improve immunotherapy.”

Soon after opening his lab, Ho was discussing with a student and a postdoc a pair of papers that had come up with conflicting answers on the matter. One concluded that the amino acid glutamine promotes the formation of M1 macrophages, the other that it promotes M2s. This was of special interest to the team because many tumors are highly dependent on glutamine and drugs are currently being developed to block an enzyme, glutaminase, that is involved in its metabolism.

The *Nature Immunology* paper published by Ho in 2017 resolved the dispute and showed that both papers were right, in a way. It wasn't so much glutamine itself that determined the fate of the macrophage as the balance between two molecules in the chain of biochemical reactions that process the amino acid.

"The balance between these two metabolites in the cell determines whether the macrophage becomes an M1 type or an M2," says Ho. If a macrophage is fed glutamine and is prone to making succinate from the amino acid, it becomes an M1 cell in attack mode. If, on the other hand, it is set to make α -ketoglutarate, it turns into an M2. The paper also traced the distinct signaling pathways and patterns of genomic activation that contribute to each of these fates, explaining how and why the ratio of these metabolites in macrophages drives such starkly divergent fates.

"If we can artificially change this balance by providing cell-permeable metabolites or targeting a particular metabolic pathway," says Ho, "we might be able to guide macrophages in the direction we want." Such a capability could be invaluable to a variety of immunotherapies, since it is becoming increasingly clear that many of them are compromised by M2-like macrophages and other immunosuppressive cells in tumors.

Ho and his team are now working toward that goal. ■

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