Secret to Tamping Down Graft-Versus-Host-Disease May Lie in Microbial Genetics

Preclinical bone marrow transplant study shows donor immune cells that target recipient microbiome can influence GVHD severity.

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Risk of graft-versus-host disease (GVHD), an often-debilitating and sometimes-deadly bone marrow transplant (BMT) complication, can be reduced by matching key immune genes in a transplant recipient and their donor.

But new work in mouse transplant models from Fred Hutch Cancer Center scientists suggests that researchers seeking new GVHD-tempering strategies should cast an even wider net.

“The key finding was that we shouldn’t just take into account the host-recipient genetics, we should take into account microbiome genetics as well,” said Fred Hutch medical oncologist Albert Yeh, MD, who led the study, published today in Immunity.

Yeh treats BMT patients while researching how to tackle GVHD, which is driven by donor immune cells (called T cells) that respond to a BMT recipient’s healthy tissue as if to foreign invaders. In mouse BMT models, he revealed that, independent of mouse genetics, some donor T cells respond to specific microbial targets.

In this case, these T cells compounded GVHD severity.

“The findings are quite paradigm-changing,” said Fred Hutch hematologist Geoff Hill, MD, senior author and director of Hematopoietic Stem Cell Transplantation at Fred Hutch. “In the transplant field, we always think of the disparities between the donor and host genetics as what’s driving the T-cell response.”

While it’s already well-known that the microbiome shapes GVHD and BMT outcomes, precisely how this occurs remains unclear. Yeh is the first to show that a group of T cells, zeroing in on specific microbial targets, influence GVHD. Both Yeh and Hill cautioned that the work is preliminary, and needs further validation in people, but there remains much to explore in the complex relationship between microbes, microbe-hunting T cells and GVHD severity.

“It opens up a new field,” Hill said.

T cells: BMT’s double-edged sword

Bone marrow transplants, also known as blood stem cell transplants or hematopoietic stem cell transplants (HST), revolutionized blood cancer treatment. After a conditioning regimen wipes out as many blood cancer cells as possible — and also wiping out healthy blood stem cells — transplant recipients receive healthy new donor bone marrow or blood stem cells. These take root in the bone marrow and grow new oxygen-carrying red blood cells and infection-fighting white blood cells.

With the stem cells come mature donor immune cells, including T cells, a specialized type of immune cell critical both to a bone marrow transplant’s success in treating cancer, and the driving force behind GVHD.

T cells use a specialized molecule, called a T-cell receptor, or TCR, to “read” bits of proteins pinned to the surface of cells by a molecular “peg.” These protein-peg complexes act as bulletins of a cell’s health status, and T cells are trained to leave healthy cells alone.

But when a T cell is dumped in a new environment, they can misread these bulletins. These T cells may attack a BMT recipient’s healthy tissue, even as some donor T cells kill off lingering tumor cells and prevent relapse.

To help ensure that donor T cells understand the messages they’re reading, hematologists try to ensure that the “pegs” they’ll see in a recipient match the “pegs” they’re used to seeing in their home turf, the donor. If they are well-matched, T cells are more likely to understand the message that their new host is “self” — and safe.

This is called tissue typing.

But tissue typing isn’t perfect. The pegs, called HLA, for human leukocyte antigen (or MHC, for major histocompatibility complex) are among the most variable genes humans have. And each person has several MHC genes, each with its own dizzying variety. On top of this, the little protein messages cradled by MHC molecules can vary between recipient and donor just enough to send a “danger!” signal to donor T cells (even when MHC genes match perfectly).

Right now, treatments for GVHD, like corticosteroids, muffle the anti-tumor cells along with those driving GVHD.

“It’s the holy grail of transplant: separating GVHD from the graft-vs.-leukemia effect,” Yeh said. “I wanted to understand how to improve GVHD from the standpoint of the individual T cells.”

He hoped that if he could identify the GVHD-promoting T cells, he would be able to devise strategies to remove them, leaving only the leukemia-targeting cells behind.

Donor T cells respond to recipient microbes

Still working from the assumption that recipient and donor genetics would be the key to solving this dilemma, Yeh performed “twin” transplant studies. In these, bone marrow from one donor mouse is split apart and transplanted into two genetically identical recipient mice.

Yeh and Hill expected that, faced with the same genetic milieu, the same T cells that respond to the new environment would expand in each recipient. (TCRs are even more variable than MHCs: each new T cell builds a bespoke TCR that is one of more than a quadrillion possible TCRs.)

By comparing the donor TCRs in each recipient, the scientists expected it would be possible to find the recipient-targeting TCRs that could drive GVHD.

But the T cells confounded them. In each recipient, a pool of T cells with certain TCRs would expand, suggesting that they were responding to something in their new environment.

“Even in completely identical donor and recipients, there’s almost no overlap in which T cells expanded,” Hill said. “This is shocking given how we currently think about alloreactivity [the T-cell response to MHC variants].”

But an individual may have billions of different TCRs floating around — some found on only a single T cell. Yeh, working with Fred Hutch computational biologist Phil Bradley, PhD, developed mathematical models to confirm that the lack of overlap didn’t reflect the chance that each twin had received a different set of rare TCRs.

Yeh found that antibiotic treatment (two weeks prior to one week after transplant), but not total-body irradiation, reduced the pool of T cells that expanded after transplant. Previous work had suggested that the microbiome can influence GVHD through general immune mechanisms. What if the T cells were responding to the microbes through their TCRs?

Yeh took advantage of the fact that mice bred in different facilities have different microbiome makeups. He gave a bone marrow transplant to two sets of recipient mice (with higher and lower levels of a certain bacterium). To the donor bone marrow, he added T cells genetically engineered to carry TCRs that detect the bacterium.

He found that not only did the bacterium-targeting T cells expand more in the mice with higher levels of the bacterium, but also exacerbated GVHD lethality. Yeh further showed that GVHD does not originate with the bacterium-targeting T cells.

“By themselves they don’t do too much,” he said.

Instead, these bacterium-directed T cells give GHVD a helping hand.

They are caught in a unique situation: During the onset of GVHD, the initial assault against recipient tissues breaks down the gut barrier that separates the microbiome from the rest of the body. This allows bacterial components to enter areas bacteria normally can’t venture.

Previous work by Hill's team showed that these components get incorporated into the MHC-protein health bulletins of cells lining the gut. This brings them to the attention of bacterium-targeting T cells, which give GVHD-promoting T cells a helping hand.

In this way, the bacterial genes that encode these T cell-triggering proteins enter the landscape of minor genetic variations that can promote GVHD.

Next: extending the findings to people

"What Albert has shown is that a significant proportion of T cells are expanding in response to microbial targets," Hill said. "It suggests that if you can think about not only microbial exposure, but about whether T cells are pre-formed to various microbes, you may be able to modify T cells, and make a protective response rather than a pathogenic response."

Yeh's next steps will include confirming that a similar phenomenon occurs in human transplant recipients.

"There's no reason to believe it's not present, but it will be much harder to identify," he said. "Likely, not all bugs elicit the same types of T-cell responses. They could induce T cells that are inflammatory or regulatory; certain bacteria clonotypes could thus be protective."

If he can identify specific microbe-reactive T cells in BMT patients, as well as the microbes they target, it will be a first step toward microbiome- or T cell-focused strategies that either put the brakes on GVHD-promoting, microbe-directed T cells, or give protective, microbe-responsive T cells a boost.

"This is a profound change in thinking," Hill said.

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