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Science Matters: Harnessing The Inherent Power Of MAIT Cells

by Mark Ratner

Tapping into the interplay between gut microbiota and an underappreciated subset of T cells could lead to therapies in a range of diseases.

A publication in the May 25th issue of *Science Translational Medicine* (*STM*) suggests that gut microbiota may activate a type of unconventional T cell called MAIT (mucosal-associated invariant T cell) in cancer patients receiving allogeneic hematopoietic cell transplantation (allo-HCT). The paper suggests a link between the presence of MAIT cells, as well as another so-called unconventional T cell, and reduced risk of graft-versus-host disease (GVHD), a serious complication of allogeneic transplantation.

The paper is part of a growing body of recent literature around MAIT cells, whose functions are not clearly understood but where evidence is pointing to their potential role in a variety of immunological and infectious disease settings.

Many studies are now linking the presence of a diverse microbiome capable of making many different ligands and metabolites with good patient outcomes. But why a diverse microbiome in the body supports good outcomes in treatment or throughout natural disease course is not yet well understood, noted Kate Markey, part of the research team at Memorial Sloan-Kettering Cancer Center that did the study published in *STM*.

Previous research has suggested associations between gut microbiota, immune reconstitution, and outcomes after patients with hematopoietic tumors receive an allogeneic transplantation, a procedure in which the immune system where the cancer resides is first ablated with a combination of chemotherapy and radiation, then is replaced with foreign donor cells. “Our work fits with what other people have described in the allo-HCT setting,” Memorial Sloan-Kettering’s Hana Andrlová told *In Vivo* . “It strengthens the protective role of MAIT cells.”

The *STM* study also showed that the activity of another brand of unconventional T cell, the Vδ2

cell, appears to be closely related to that of MAIT cells – they both are microbiome dependent. "We were to first ones to make the association with the Vδ2 cells and the gut microbiome and specific metabolomic characteristics," Andrlová observed. MAIT cells had already been suggested as protective against GVHD in several papers. "We think both MAIT and Vδ2 cells are probably dependent on a similar microbiomic environment, but what exactly they do we can only speculate on," she said.

MAIT cells, however, have a special link to the microbiome. They are the only population of lymphocytes that is entirely dependent on receiving signals from microbiota. MAIT cells are activated by a well-defined, limited number of antigens that are derived from the riboflavin biosynthesis pathway and presented in the context of a broadly expressed MHC class 1-related protein, MR1. These ligands are found in a range of bacteria and fungi. Exposure to these microbiotic signals educates MAIT cells early in life and gives them the ability to generate and expand once they make their way into tissues. When in close contact with microbiota in tissues, the same signals can reactivate these cells.

The study of MAIT cells has increased in recent years with the realization that they could be studied in mice. For a long time, researchers could not find MAIT cells in mice that had been raised in the laboratory and so were not exposed to diverse microbiota. That hindered the ability to do the kinds of mechanistic studies done on other populations of lymphocytes.

"MAIT cells had been neglected by immunologists," opined Yasmine Belkaid, chief of the Metaorganism Immunity Section of the National Institutes of Health's National Institute of Allergy and Infectious Diseases. But in fact, MAIT cells develop very well in mice – provided they have the right signal, which microbiota provide. With that realization, scientists have had more opportunity to use this model system to look for in-depth mechanistic insights.

Studying the microbiome after allo-HCT is relatively new but is a logical place for understanding their impact on MAIT cells.

MAIT cells can be reactivated when they are present in tissue or at an inflammatory site. The post-transplant environment in general is probably the most inflammatory environment that exists. "We are essentially asking that new immune system to run through the whole developmental process that a neonatal immune system would do," explained Markey, who is now at Fred Hutchinson Cancer Center. But in an

Science Matters: Welcome To The Oncobiome

By Mark Ratner

20 Apr 2020
A new publication offers up proof of concept that the genetic signatures of microorganisms

adult with very different physiologic conditions and tissue damage after transplantation.

"Because you see the rebuilding of an immune system, you can have a sense of cause and effect between microbiota, immunity and outcome," Belkaid added. The *STM* paper confirmed in humans the ability of unconventional T cells to expand in the context of a dramatic perturbation, she said, and that the presence of these cells correlates with the presence of the microbiome. It showed, for the first time, an association between MAIT cells, the gut microbiome and specific metabolomic characteristics. "You can imagine based on this kind of work that you could actually dictate that a certain type of microbiota is more likely to push those nonclassical T cell responses," she stated. "Understanding the presence of these microbes can help predict how these cells can be expanded and may be an important way to stratify patients."

found in blood and tumor tissue could improve precision medicine cancer diagnostics. The study also bolsters the notion that targeting the microbiome could lead to innovative cancer therapies.

Read the full article here

The observations build on an emerging theme of deciphering the role of MAIT cells – and other unconventional T cells, for that matter – and how their interactions with gut microbiota can affect a variety of diseases.

Unconventional T cells are immune system components that operate at the boundaries of the innate and adaptive immune response. Their presence builds up early in life as the immune system forms, which may explain the link between diverse intestinal microbiota and better outcomes in a range of diseases. MAIT cells are being studied as potential targets in cancer, both as adjuncts to leukemia stem cell transplantation and also to help improve response to immunotherapy. They have been implicated in tuberculosis and in airway infections (including SARS-CoV-2) as well as in anti-bacterial immunity generally, in fatty liver diseases, in tissue repair and other conditions, and in the context of obesity and diet.

"Liver and lung would be two places where you'd like to think they could be beneficial," Mitchell Kronenberg, chief scientific officer at La Jolla Institute for Immunology, said. MAIT cells in the airways and the lining of the lungs are in close contact with bacteria. The cells also sit in the vasculature of the liver and while that organ is normally fairly sterile, products from the gut drain into the portal circulation.

With colleagues at the Trudeau Institute, Kronenberg has been trying to show that MAIT cell stimulation could be beneficial for tuberculosis pretreatment. "We've gotten results showing that MAIT cells could be protective by stimulating them, followed by inhalation of the TB strain HR37," he said.

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MAIT cells develop as effector cells in the thymus, but they can also be activated by their ligand, or by introducing certain intracellular bacteria – studies have successfully used Salmonella and francisella tularensis (a serious infection and also a potential bioweapon), for example. But in some settings, the experimental work has been confounding. In one study in primates given MAIT cell ligand and a toll-like receptor, the signals seemed to not cause a vast expansion and adaptation, but instead provoke a tolerance-like response. "The primate experiment where the researchers copied the mouse protocol and got the opposite result is sobering," Kronenberg noted.

"We know in mice you can activate MAIT and that it has a potent protective effect in infections, and perhaps is beneficial in other contexts as well," Kronenberg said. In SARS-CoV-2, MAIT cells can become activated and express more activation markers. "It's clear that they are at this threshold of being activated, but not quite over the line," he said. "It's probably more than one thing, not just T cell receptor and antigen but probably secondary signals that they need to be pushed to be activated."

Whether MAIT cells can effectively be activated in humans for therapy is still to be determined, Kronenberg concluded. "But I have to believe these cells do have potential," he said.

Belkaid points out that the confidence that these challenges can be solved also stems from the fact that unconventional T cells come out of the thymus and into tissues "ready to go" and that they are easily activated when using the appropriate ligand. "We have an enormous possibility to explore pretherapeutic or early therapeutic approaches because the ligand is the same in all animal species," she said. "This is quite an opportunity to study how to activate these cells."

On the cautionary side, because MAIT cells are present throughout the body and all have the same T cell receptor, activating them in a systemic way could be detrimental. MAIT cells also produce a large amount of cytokines, and in tissues that are not ready to accept that level of cytokine release, their activation could have very negative consequences. "If you learn how to tame MAIT cells and how to target treatment, they offer an extraordinary opportunity for rapid responses," said Belkaid. "But the immunity they provide has to be transient because if sustained, it could become inflammatory."

The cancer arena may hold the most promise for MAIT cell-based therapy. In another recent publication from Memorial Sloan-Kettering, researchers showed that the composition of the gut microbiome correlates with response and toxicity following anti-CD19 CAR-T therapy. "It is another one that teases out the idea of

Science Matters: With Ferroptosis, Cancer Drug Developers Can Strike While Iron Is Hot

By Mark Ratner

what is going on in the gut and the ligands and metabolites that are produced [there] and how they probably influence those incoming CAR-T cells," noted Markey. "That paper gives us the first hint that it is a direction to think about for other immunotherapies and not just after a transplant," she said.

27 Aug 2019
A series of basic research insights around the cell death process called ferroptosis could form the underpinnings of a new class of treatments aimed at drug resistant tumors.

Read the full article here

Unconventional T cells have taken a back seat to the large volume of recent work around immune regulation and the success of immunotherapies. "It's a boutique field," Belkaid suggested. "But I think because of the rediscovery that these cells are very abundant in the tumor environment, in inflammatory settings, I think they are coming back to the stage."

"In many ways this is still a fairly young field," added Kronenberg. "I haven't yet seen formulations – lipid formulations or nanoparticle formulations that would allow you to deliver antigen and whatever other accessory signal very effectively."

That said, a handful of start-ups are on the cusp of initiating commercial activities around targeting MAIT cells or other T cells that similarly recognize metabolites from the microbial riboflavin pathway presented as antigens in the context of MR1.

Three biotechs presented relevant data at a May 2022 EMBO workshop in Gothenberg, Sweden. *Biomunex Pharmaceuticals SAS* showed that a bispecific antibody can redirect MAIT cells to kill cancer cells in a cell-specific manner that did not engage all T cell subsets. *Enara Bio* discussed development of ENA-0001, an MR1-targeting T cell therapy. (Enara has also entered into a collaboration with *Boehringer Ingelheim GmbH* to apply its discovery platform to identify and validate novel T cell antigens for use in immunotherapies targeting lung and gastrointestinal tumors. *[See Deal]* (Also see "*Boehringer Explores 'Dark Antigens' With Enara In Potential $1bn Deal*" - Scrip, 12 Jan, 2021.)) And *Immunocore, Ltd.* presented an abstract characterizing a high-affinity version of the canonical human MAIT T cell receptor, which it said could be used as a highly sensitive staining reagent to track MR1 antigen expression *in vitro*.