How targeting killer T cells in the lungs could lead to immunity against respiratory viruses

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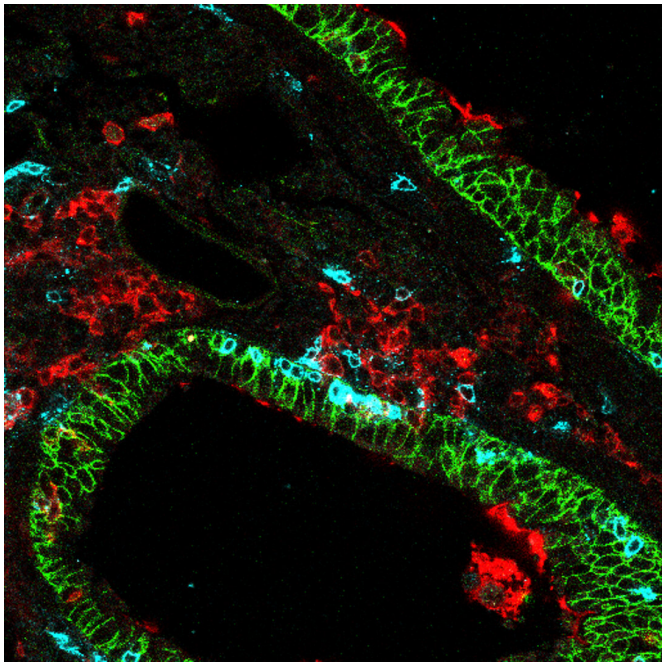

Lung-specific CD8 killer T cells (blue) in lung tissue (green) surrounded by dendritic lung cells (red). Credit: Salk Institute

A significant site of damage during COVID-19 infection is the lungs. Understanding how the lungs' immune cells are responding to viral infections could help scientists develop a vaccine.

Now, a team of researchers led by Salk Professor Susan Kaech has discovered that the cells responsible for long-term immunity in the lungs can be activated more easily than previously thought. The insight, published in the *Journal of Experimental Medicine* on June 11, 2020, could aid in the development of universal vaccines for influenza and the novel coronavirus.

"Inside our lungs exist long-lived killer T cells that recognize specific viruses and protect us against re-infection, should we encounter the virus again. Our results have elucidated the manner by which these cells 'see' the virus upon re-infection and provide rapid immunity," says Kaech, director of Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis. "It also may help us understand long-term immunity as it relates to coronavirus."

When we are first exposed to bacteria or viruses, such as influenza, one type of our immune cells, known as killer T cells, destroy infected cells to prevent the spread of the disease. Once the pathogen is cleared, these experienced killer T cells (also called killer "memory" T cells) remain in our body long-term, and "remember" previous invaders. These killer memory T cells enable our immune systems to more rapidly respond to a second attack and effectively provide long-term protective immunity against the invader, a fundamental concept behind vaccination.

Scientists know a lot about how killer memory T cells get activated in lymphoid organs (such as lymph nodes). Immune messenger cells called dendritic cells present fragments of the virus to the killer memory T cell, similar to a handler presenting a scent to a hound, to license their killer function.

But prior studies had not examined this interaction in vital organs, such as the lung. The lung is a frequent entry site for pathogens such as influenza and coronavirus, so the team set out to confirm whether this long-held dogma applied to killer memory T cells that reside in the lungs.

Kaech and then-graduate student Jun Siong Low, first author of the paper, assumed that dendritic cells would be required to reactivate killer memory T cells to fight a second viral attack. So, they

deleted various types of messenger cells one at a time in mice to see if the killer memory T cells would still recognize a second influenza infection. The researchers used a green florescent reporter protein to make the killer memory T cells glow if they recognized the virus. However, each time the researchers deleted a specific cell type, the killer memory T cells in the lungs continued to glow.

"At first, our results were disappointing because it didn't seem like our experiments were working; the killer memory T cells in the lungs continued to recognize the virus after the deletion of many different messenger cell types," says Low, now a postdoctoral fellow at the Institute for Research in Biomedicine (IRB) at the Università della Svizzera Italiana, in Switzerland. "Soon, we realized that these lung-resident killer memory T cells were special because they were not reliant on any single type of messenger cell. Instead, they could 'see' the second influenza infection through a variety of different messenger cells, including non-immune cells like lung epithelial cells, which was a remarkably exciting finding."

In contrast, when the researchers examined the killer memory T cells in the lymph nodes—glands that swell during infections—they found that the killer memory T cells needed dendritic cells to recognize the second viral attack. This suggests that the anatomical location of the killer memory T cells dictates how they get reactivated, challenging the long-held dogma that killer memory T cells require dendritic cells for reactivation. The results help to reshape the paradigm of killer memory T cell activation.

Because lung-resident killer memory T cells can be quickly reactivated by nearly any cell type at the site of pathogen entry, identifying vaccines that can create these lung-resident killer memory T cells will likely be critical for superior immunity to viral infections of the lungs.

"We will take this knowledge into our next study, where we will examine whether lung-resident killer memory T cells form after a coronavirus infection," says Kaech, holder of the NOMIS Chair. "Since not all infections induce killer memory T cells, we will determine if these cells form after a coronavirus infection and whether they can be protective against future coronavirus infections."

More information: Jun Siong Low et al, *Journal of Experimental Medicine* DOI: 10.1084/jem.20192291

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