Alveolar macrophages help CD8+ T cells go (anti-)viral

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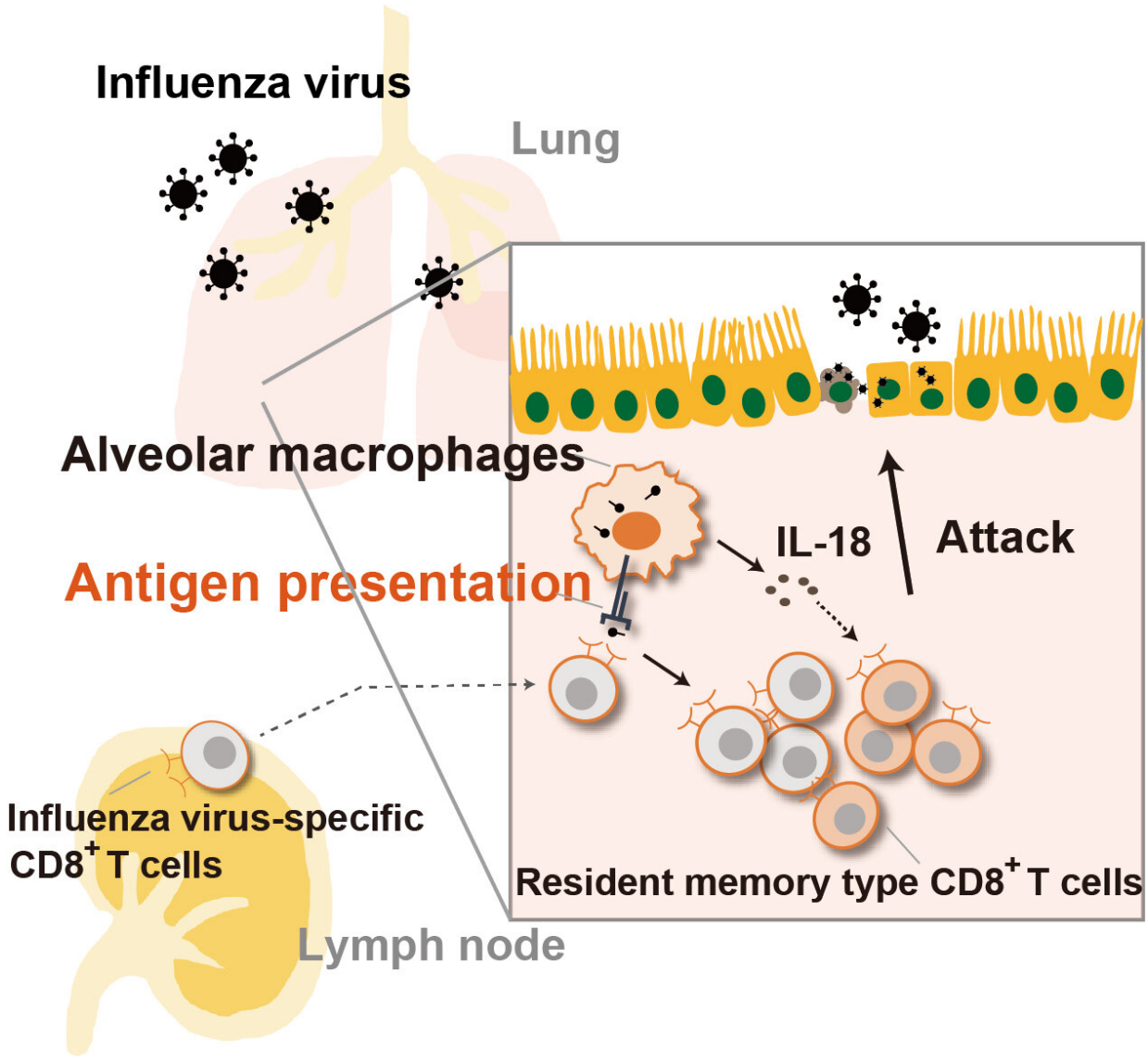

Influenza virus-specific CD8* T cells induced in lymph nodes as a result of

influenza virus infection or vaccination circulate throughout the body. During second influenza virus infection, viral fragments taken up by alveolar macrophages (AMs) are presented as antigens to promote virus-specific CD8* T cells proliferation. The proliferated CD8* T cells suppress viral proliferation. In addition, interleukin-18 (IL-18) released from AMs induces resident memory type CD8*T cells, contributing to long-term host defense. Credit: Nara Institute of Science and Technology

The human immune system is a highly complex network of cells, signals, and responses that is tightly regulated to ensure that the body can fight off infection without damaging its own tissues. Now, researchers from Japan report a new way in which the immune system protects lung tissue from viral infections.

In a study published in *Cell Reports*, researchers from Nara Institute of Science and Technology (NAIST) have revealed that antigen-specific killer T cells (CD8+ T cells) rapidly expand in the lungs when they encounter antigen-presenting alveolar macrophages (AMs) to protect against viral infection.

CD8+ T cells confer protective immunity against infection with respiratory viruses, such as influenza A virus (IAV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by killing infected cells. In order to target the correct cells for killing, naive CD8+ T cells must be primed by contact with antigen-presenting cells (APCs), which mediate the uptake of virus-infected cells and present their antigens, in a process known as cross-presentation. The primed CD8+ T cells then clonally expand and differentiate into effector or long-lived antigen-specific memory T cells.

"Multiple cell types can present antigen to CD8+ T cells in the lungs, although the role of tissue-resident macrophages in this process is

unclear," explains Takumi Kawasaki, lead author of the study. "AMs are the first cells in the lungs that encounter infectious materials, environmental particles, surfactants, and dying cells, and they are important for the host defense against bacterial and fungal infection, so we suspected that they were also important in protecting against respiratory virus infection."

To test this, the researchers explored the mechanisms by which APCs instruct antigen-specific CD8+ T cells in the lungs. First, mice were primed by vaccination with a specific antigen or infection with IAV, and then they were subjected to secondary immunization or re-infection.

"We determined that antigen-presenting AMs present inhaled antigen to memory CD8+ T cells," says senior author of the study, Taro Kawai, "and that this resulted in a rapid expansion of antigen-specific CD8+ T cells in the lungs."

Furthermore, the researchers found that AMs help to develop resident memory-type cell population by producing interleukin 18. Importantly, administration of antigen-loaded AMs to mice induced the proliferation of resident memory-type CD8+ T cells.

"This strategy may improve the efficacy of CD8+ T cell-dependent cellular immunity," says Kawai.

Given that the lung is a major tissue for IAV and SARS-CoV-2 infection, the findings from this study regarding the mechanism of lung-resident memory CD8+ cell expansion are expected to lead to the development of new vaccines that induce cellular immunity. Virus-specific antigen-presenting AMs could be delivered as a type of "cell transplant vaccine" in the future.

More information: Takumi Kawasaki et al, Alveolar macrophages

instruct CD8+ T cell expansion by antigen cross-presentation in lung, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111828