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'Bystander' chronic infections thwart development of immune cell memory

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Studies of vaccine programs in the developing world have revealed that individuals with chronic infections such as malaria and hepatitis tend to be less likely to develop the fullest possible immunity benefits from vaccines for unrelated illnesses. The underlying mechanisms for that impairment, however, are unclear, and distinguishing these so-called "bystander" effects on priming the immune system to fight future assaults versus development of immunological memory has been challenging.

A team from the Perelman School of Medicine at the University of Pennsylvania found that chronic bystander viral or parasitic infections – which are models for human infections like hepatitis, malaria, and parasitic worms – impaired the development of memory T cells in mouse models of long-term infection.

The effect of bystander infections also extended beyond mice. The researchers generated signatures of transcribed genes of cytomegalovirus-specific T cells from people with chronic hepatitis C infection and healthy controls. The gene-expression profiles of these two groups showed a clear impact of bystander chronic infection on T cells, including a difference in expression of many key T-cell memory-related genes. The findings are published this week in *Immunity*.

"Co-infections can result in poor immunity for other invading microbes and also vaccines," says senior author E. John Wherry, PhD, director, Institute for Immunology and associate professor of Microbiology. "We

now understand one of the main reasons: failure to develop immune memory capable of responding upon new infections."

Immune memory, the hallmark of protective immunity against intracellular pathogens, is what keeps humans from being reinfected by a microbe to which they have already been exposed. Some immune cells are long-lived and active against whatever they were originally triggered by.

"If a person in the developing world gets a vaccine, and they harbor unrelated infections, such as malaria, tuberculosis, hepatitis B or C, and other parasitic infections, will this person have effective immune memory to the vaccine?" asks Wherry. "Our study has major relevance for applying vaccines in the developing world where co-infections might radically alter the type and quality of immunity generated by vaccines."

Wherry cites vaccine campaigns for rotavirus and polio virus in the developing world in which people who were vaccinated had only 50 percent efficacy compared to 80 to 90 percent in the developed world for the same vaccine. Vaccine efficacy is the incidence of people who are vaccinated and get disease versus an unvaccinated control group.

The effects of bystander infection on immune memory cell development seen in the current study were independent of initial priming of the immune system by other pathogens and were associated with a molecular signature of chronic inflammation. Chronic inflammation reduced the number of bystander T cells, their memory development, and their ability to protect from a challenge infection.

The team concluded that exposure to prolonged bystander inflammation impairs the transition of effector T cells to memory T cells. In other words, bystander chronic infections prevent the critical ability of the immune response to "stand down" and preserve responsive cells for

future encounters with the same infection.

These data have important implications for vaccines for the developing world where co-infections are common and also for vaccines and immune therapies in patients with chronic inflammatory diseases. Specifically, working to treat co-infections—via anti-parasite treatment in developing countries, for example—prior to vaccines or treatment with anti-inflammatory agents at the right times may improve long-term immunity in some settings.

More information: Cell Reports, Hong et al.: "Path to the clinic: Assessment of iPSC-based cell therapies in vivo in a non-human primate model." www.cell.com/cell-reports/abst … 2211-1247(14)00306-4

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