# Research team sheds light on immune system suppression

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The work was reported in the October 16 issue of the journal *Cell Host & Microbe*. The study described the suppression of this immune response in mice infected with lymphocytic choriomeningitis virus, pointing to potential new avenues for the development of drug treatments for immunosuppressive diseases in humans.

"It's the first demonstration that a virus causes suppression of the interferon response in vivo," says the paper's senior author Michael Oldstone, a Scripps Research professor and a pioneer in immune system studies. "This model explains how a secondary infection can be caused by a normal virus infection and this provides the guide for what to do and where to look in human diseases, which are of course more difficult."

Mammals have two main ways to fight off infections. Adaptive immune responses are those that involve the production of antibodies and T lymphocytes that attack specific infections. In contrast, innate immune responses are genetically encoded and are generally the same regardless of infection type. One key component of the innate immune system is interferon, which plays a range of roles including direct antiviral effects, activating innate natural killer cells and adaptive T lymphocytes, which destroy a wide range of infectious invaders.

To better understand this system, the Scripps Research team, spearheaded by Elina Zuniga, formerly a postdoctoral fellow in the Oldstone lab who is now assistant professor at the University of

California, San Diego, worked with mice infected with lymphocytic choriomeningitis virus, a model Oldstone describes as a Rosetta Stone for understanding viral pathogenesis and immune system recognition of foreign substances like microbes and viruses. The researchers found that the virus suppressed the mouse immune system by interacting with immune cells known as plamacytoid dendritic cells, which are key producers of one of two critical groups of interferons, known as type I.

When plasmacytoid dendritic cells come in contact with viruses and other foreign invaders, they bind with them via membrane proteins known as toll-like receptors. Under normal conditions, this binding triggers massive production of type I interferon that then triggers other immune responses.

But the lymphocytic choriomeningits virus, and presumably other immunosupressor viruses like measles and HIV, disable this system. This then compromises other reactions, most critically activation of the natural killers that would otherwise destroy the virus-infected cells, as well as other invaders.

The researchers showed that once in this infected condition, a secondary opportunistic agent, in this case the herpes virus murine cytomegalovirus, which the mice could have otherwise fought off, grew unchecked. Remarkably, opportunistic infections with herpes viruses are frequently observed in patients infected with HIV and the mechanism described in this study could well be one of the underlying causes.

One critical aspect of the group's findings is that while the initial lymphotcytic choriomeningitis virus effectively blocked interferon production, it did not kill the dendritic cells, instead allowing them to function as long-term hosts. This allows such viruses to persist, causing persistent immunosuppression.

"I think the implications are that many of the diseases we don't know the causes for, be they behavioral, mental, cardiovascular, or endocrine, may well be caused by viruses that persist without destroying the differentiated cells they infect, alter their functions, and by this means alter homeostasis and cause disease," says Oldstone. "Examples would be viruses that persistently infect neurons and cause problems in learning and behavior, viruses that infect oligodendrocytes and cause demyelination, and viruses that infect endocrine cells and alter their production of hormones. There may be some differences, but most certainly there are a lot of commonalities."

Oldstone says that knowing such basic details about how a virus can suppress the mouse immune system could well aid the development of new treatments for the many immunosuppressive conditions such as HIV and measles that plague humans. "I think that our study opens up an avenue for people who work in those human diseases to translate our findings," says Oldstone.

For now, Oldstone's group is focused on identifying the signals and molecules involved in the lymphocytic choriomeningitis virus's crippling of the dendritic cells' interferon production.

Source: Scripps Research Institute