Alcoholics have an abnormal CD8 T cell response to the influenza virus

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It is well known that chronic drinking is associated with an increased incidence and severity of respiratory infections. Previous research had demonstrated that an increase in disease severity to influenza virus (IAV) infections was due, in part, to a failure to mount a robust IAV-specific CD8 T cell response, along with a specific impairment in the ability of these T cells to produce interferon γ (IFNγ). A new rodent study further examines chronic drinking's damage to CD8 T cells, finding that some effector functions of CD8 T cells become limited or reduced while other effector functions are left intact.

Results will be published in the September 2014 online-only issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"It is well known that chronic alcohol consumption compromises the human immune system," explained Kevin L. Legge, associate professor of pathology at the University of Iowa as well as corresponding author for the study. "This fact is underscored when examining the susceptibility of chronic alcoholics to infectious disease. Alcoholic patients have greatly increased risks of infection with extracellular bacteria, intracellular bacteria, and viruses. Numerous reports have documented that alcoholics exhibit higher rates of bacterial pneumonia, sepsis, meningitis, and peritonitis. Among the best-studied examples of this increased predilection to severe respiratory disease following chronic alcohol abuse are bacterial pneumonias. In fact, Benjamin Rush, the Surgeon General of the Continental Army and a signer of the

Declaration of Independence, as early as 1785 described alcoholics as susceptible to yellow fever, tuberculosis, and pneumonia. More recent studies have demonstrated that there is a two- to seven-fold greater incidence in mortality as well as increased morbidity in chronic alcohol-consuming individuals compared to non-alcoholic pneumonia patients."

"It has also been known since the 1800s that alcohol use disorders are associated with increased susceptibility to lung infection – both viral and bacterial, including community acquired pneumonia and tuberculosis – acute respiratory distress syndrome, and chronic obstructive pulmonary disease," added Ilhem Messaoudi, associate professor of biomedical sciences at University of California Riverside. "Therefore, understanding the mechanisms underlying the increased susceptibility to lung infection and injury in individuals with alcohol use disorder is extremely important. Although several studies have demonstrated that this phenomenon is in part due to significant perturbations in the immune system, our understanding of the impact of alcohol abuse on immunity remains incomplete."

"Immunity and long term protection against influenza virus infections is conferred by two components of the adaptive immune response," explained Legge, "namely, antibodies which neutralize the virus preventing infections, and T cells, which find and kill infected cells, thus limiting spreading of the virus to other cells and halting the infection. Our prior work showed that chronic levels of alcohol predispose for an increased severity of disease – both symptoms and lethality – following influenza virus infection. In fact, chronic alcohol changes in a dramatic way what is typically a subclinical infection into a lethal outcome. Our prior studies demonstrated that this change in disease severity is in part due to alcohol's effects on CD8 T cells. Chronic drinking can decrease the number of the CD8 T cells available to defend against the infection, and this decrease in CD8 T cells is more severe the longer the length of alcohol exposure, as well as limit the ability of the remaining CD8 T

cells to use one of their anti-viral tools. In this manner, chronic alcohol attacks the CD8 T cell immune response on two separate levels: limiting the number of cells that can fight the infection, and limiting the ability of the remaining cells to fight."

The researchers gave mice alcohol in their drinking water for eight or 12 weeks. Mice were infected intranasally with IAV; subsequently, the activation and effector functions of IAV-specific CD8 T cells were examined in both the lung-draining lymph nodes and lungs.

"T cells utilize multiple tools – called effector functions – to limit and control pathogens," said Legge. "While our prior study demonstrated the loss in CD8 T cell numbers and ability of the remaining CD8 T cells to make IFN, it was unclear if and how many of the other tools CD8 T cells are known to utilize were effected by chronic alcohol. Here we show that some but not all of the CD8 T cells effector functions are reduced with chronic alcohol abuse. In summary, we show that alcohol may have distinct effects on the effector ability of CD8 T cells, limiting or reducing some functions while leaving other effector functions intact. It is known that triggering of each specific effector pathway requires precise signals. Therefore, further mapping of which effector functions are altered, coupled with examination of pertinent molecules, could yield promising drug targets for reversal of the effects of alcohol on this important adaptive immune cell population."

"It is difficult to uncover mechanisms in the clinical setting because of uncertainty of exact amount consumed as well as other confounding effects," added Messaoudi. "Therefore, using an animal model allows us to specifically uncover defects in immune response without the additional confounding factors. We know that chronic alcohol exposure also results in ablated CD8 T cell responses in mice following infection with an intracellular bacterium Listeria monocytogenes, and defects in CD8 T cell responses have also been identified in a rhesus macaque

model of HIV infection. Taken together, these various studies indicate that CD8 T cells might be exquisitely sensitive to alcohol. Understanding this provides a therapeutic target so that we can now focus our efforts on developing strategies aimed primarily at boosting CD8 T cell function. For instance, new vaccination strategies that are more efficient at eliciting CD8 T cell responses could be developed specifically for this population."

"For humans, this work suggests that there may be a serious hole in the normal adaptive immune response against influenza virus in alcoholics," said Legge. "At this time it is not possible to easily fix the influenza-specific CD8 T cell response. However, one of our prior studies demonstrated that the anti-influenza drug, Oseltamivir, appears effective in limiting influenza virus in a chronic alcohol environment. Results from that study, coupled with those from this study, indicate that Oseltamivir may have promise."