Response to Comment on "Chronic Alcohol Consumption Increases the Severity of Murine Influenza Virus Infections"

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Letters to the Editor

Comment on “Chronic Alcohol Consumption Increases the Severity of Murine Influenza Virus Infections”

I read the paper entitled “Chronic alcohol consumption increases the severity of murine influenza virus infections” by Meyerholz and colleagues (1). The authors demonstrated an important fact that chronic alcohol consumption increased influenza severity. To answer why this happened, they focused on a decrease in CD8+ T cells, which was considered to be the main reason. The result is consistent with the finding that mice lacking CD8+ T cells have increased viral replication and morbidity after infection with influenza PR8 virus (2). However, host response to influenza virus infection is a complicated system that includes an intact immune response. NK cells, dendritic cells, macrophages, etc., and even the innate immune systems decreased by ethanol. CD8+ T cells act together; each one alone is not sufficient to overcome virus. For example, CD4+ T cells and B cells help CD8+ T cells to produce Ab (8). Both activation of CD4+ T cells and CD8 need their costimulators, OX40 and 4-1BBL, respectively (9). Thus, they work in combination to fight virus and single element defect could be compensated by others. It is also important to examine other immune responses, especially Ab production, which appears as early as day 7; they are critical for control of influenza as published recently (10). Indeed, other studies showed that ethanol can inhibit TNF-α (11, 12), NK cells (13), and IFNγ (14). It also decreases IL-12 and increases IL-10 to cause immune suppression (15).

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We fully agree with Dr. Chen that immunity to primary influenza virus challenge and ultimately clearance of the virus and resolution of the infection is complex and multifactorial. These factors include but are not limited to the adaptive arm of the immune response including CD8+ T cells, CD4+ T cells, and B cells as well as innate cells such as NK cells, dendritic cells, macrophages, etc., and even the infected respiratory epithelium and airway surface fluid (1–4).

The purpose of our study was to illustrate the destructive impact of chronic alcohol consumption on pulmonary influenza...
virus infections. The results showed that in addition to a reduction and an altered effector ability in the pulmonary influenza-specific CD8 T cell response, chronic alcohol consumption increased morbidity, mortality, pulmonary virus titers, neutrophilia, and edema. In this article, we chose to focus our initial examinations on influenza-specific CD8 T cells because of their known importance in protecting from the virulent A/PR/8/34 influenza virus strain used in this study (5), as well as their ability to protect upon transfer into lethal influenza virus-infected animals (6). Although innate and other adaptive immune factors are able to control primary infections in the absence of CD8 T cells when less virulent influenza virus strains are used (7), they were unable to adequately control the A/PR/8/34 infection and protect against mortality in this study. To what extent these other antiviral innate and adaptive mechanisms are compromised by chronic alcohol consumption is a key question, and we agree with Dr. Chen that they also need to be explored. Toward this end, ongoing work at the University of Iowa using the same alcohol consumption model has demonstrated the integrity and function of the B cell compartment to be intact at 4 and 8 wk, the time points used in this study, although humoral immunity is diminished with extended periods of ingestion (24–32 wk; T. Waldschmidt, personal communication). Further studies have shown 4 and 8 wk of ethanol intake to alter the activation state of CD8 T cells, increase CD4:CD8 T cell ratios, reduce the numbers of dendritic cells, and alter dendritic cell function and/or migration from peripheral sites (8–10). The negative effect of alcohol consumption on CD8 T cell function highlighted in the paper, as well as significant alterations in dendritic cells, macrophages and inflammatory cytokines (described in Discussion) are consistent with these findings. The detailed examination of innate, CD4 T cell, and humoral immunity after influenza challenge in chronic alcohol mice is part of an active program in the laboratory, as is the analysis of pulmonary epithelial integrity and dysregulation of the pulmonary inflammatory response. Importantly, we share Dr. Chen’s goal of fully understanding the extent of damage that long-term ethanol intake has on the lung environment and pulmonary immune response.


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