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Alcohol and immunology: Summary of the 2012 Alcohol and Immunology Research Interest Group (AIRIG) meeting

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Abstract

On October 27, 2012, the 17th annual Alcohol and Immunology Research Interest Group (AIRIG) meeting was held at the Grand Wailea Hotel in Maui, Hawaii as a satellite meeting to the 2012 Society of Leukocyte Biology conference. This year's meeting focused on the influence of alcohol on signal transduction pathways in various disease and injury models. Three plenary sessions were held where invited speakers shared their research on alcohol-mediated alterations of cell signaling components, immune cell subsets, and inflammation. These studies suggested alcohol has a negative effect on cell signaling machinery and immune cell homeostasis, resulting in disease, disease progression, and increased mortality. Researchers also identified tissue-specific alcohol-linked elevations in markers of inflammation, including cold-shock proteins and microRNAs. Additionally, one study revealed the effects of alcohol on immune cell subsets in a model of allergic asthma.

Keywords

Ethanol; Binge drinking; Inflammation; Leukocytes; Disease; Injury

Introduction

Binge drinking and chronic alcohol consumption increase patient susceptibility to pathogen attack, including opportunistic infections, such as pneumonia in the respiratory system and hepatitis C viral infection in the liver. These drinking patterns also advance the progression of HIV infection, primarily through dysregulated immune responses (Baliunas, Rehm, Irving, & Shuper, 2010; Bhatty, Pruett, Swiatlo, & Nanduri, 2011; Prakash, Mason, Luftig, & Bautista, 2002; Romeo et al., 2007; Zhang, Bagby, Happel, Raasch, & Nelson, 2008). Both clinical and experimental data suggest that alcohol consumption alters the immune system, which influences innate and adaptive immunity (Zhang et al., 2008). The mechanisms by which alcohol alters immune responses are under investigation, but the

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mechanisms likely involve multiple overlapping elements, including aberrant signal transduction pathways and epigenetic modulation, excessive inflammation and oxidative stress, and defective epithelial barriers (Apte et al., 2005; Choudhry et al., 2004; Curtis, Zahs, & Kovacs, 2013; Messingham, Faunce, & Kovacs, 2002; Nath & Szabo, 2009; Purohit et al., 2008; Zahs, Bird, Ramirez, Choudhry, & Kovacs, 2013). These important topics were the basis for the 2012 Alcohol and Immunology Research Interest Group (AIRIG) meeting.

The AIRIG meeting was held on October 27, 2012 at the Grand Wailea Hotel, Maui, Hawaii. This one-day session was a satellite meeting at the 45th Annual Society for Leukocyte Biology Conference and was sponsored by the National Institutes of Alcohol Abuse and Alcoholism, the Society for Leukocyte Biology, and the Alcohol Research Programat Loyola University, Chicago. Meeting organizers were Drs. Elizabeth Kovacs and Mashkoor Choudhry (Loyola University Chicago Health Sciences Campus) and Dr. Pranoti Mandrekar (University of Massachusetts Medical School). The meeting consisted of three plenary sessions that covered research focused on understanding the consequences of alcohol consumption on cell signaling pathways, inflammatory responses, injury and repair, and adaptive immunity. Sixteen posters were also presented in concurrence with a Society for Leukocyte Biology poster session.

Alcohol, injury, and signaling

Dr. M. Katherine Jung opened the meeting with an overview of alcohol modulation of receptor signaling. This was followed by the first plenary session, chaired by Drs. Stephen Pruett (Mississippi State University) and Robin Walker (Howard University College of Medicine), where presenters discussed the effects of alcohol on various disease and injury models. Dr. Patricia Molina, Louisiana State University Health Science Center, provided insight on how alcohol and cannabinoids have differential effects on the host response to human immunodeficiency virus (HIV) infections. Both chronic alcohol abuse and cannabinoid usage are frequent practices in individuals with HIV infection (Lefevre et al., 1995; Prentiss, Power, Balmas, Tzuang, & Israelski, 2004). These substances have been shown to alter disease progression and tissue injury, as well as the longevity of this population (Kino, Mirani, Alesci, & Chrousos, 2003; LeCapitaine et al., 2011; Lee, Karon, Selik, Neal, & Fleming, 2001). Alcohol abuse causes multi-system alterations while cannabinoids affect neurobehavorial and immune responses. Additionally, the host response to HIV infection depends on the mechanism of viral entry and replication. Hence, there are limitations to analyzing individual organs or cellular subsets, and a complete multi-system analysis is required to sufficiently understand disease pathology. Dr. Molina used a model of alcohol and cannabinoid administration in Simian Immunodeficiency Virus (SIV)-infected rhesus macaques. This model allowed an integrated system biology analysis to identify dysregulated cellular and molecular mechanisms contributing to disease progression. Data from this study indicated that chronic alcohol administration negatively affects the development and progression of SIV infection, in part through altered pathophysiological mechanisms including metabolic, nutritional, oxidative, and neuroendocrine pathways. In contrast, although cannabinoid treatment has multisystem effects, it may be beneficial and offer protection in the central nervous and immune systems and in the gut mucosa, which are specific organ systems critical for disease progression. The results from this study led Dr. Molina to hypothesize that the different effects of chronic alcohol abuse and cannabinoid use each have on SIV-infected non-human primates will offer an opportunity to better understand epigenetic, genetic, and proteomic components in the HIV disease model and have translational implications for HIV-infected patients.

Dr. Benyam Yoseph, Emory University School of Medicine, presented data on how chronic alcohol consumption can affect mortality during sepsis. Studies have indicated that patients

admitted to the intensive care unit who consume alcohol on a chronic basis have a 2–4 fold increase in morbidity and mortality than non-alcoholics (Delgado-Rodríguez, Gómez-Ortega, Mariscal-Ortiz, Palma-Pérez, & Sillero-Arenas, 2003). The effect of chronic alcohol exposure on the pathophysiology of sepsis was explored using a mouse model in which mice were fed a liquid ethanol diet for 12 weeks, followed by cecal ligation puncture (CLP) to induce sepsis. Findings revealed that chronic ethanol exposure prior to sepsis reduced villi height and increased gut apoptosis and permeability. Chronic ethanol exposure in septic mice also had diverse effects on cytokine levels in the serum, peritoneal fluid, and bronchoalveolar lavage (BAL) fluid. Compared to levels from nonethanol-exposed septic animals, serum interleukin-6 (IL-6) was lower, while macrophage chemo attractant protein-1 (MCP-1) was higher in the peritoneal fluid. Likewise, transforming growth factor beta (TGFβ) and granulocyte colony stimulating factor (G-CSF) levels were elevated in BAL fluid in comparison to septic mice that did not receive ethanol. Data presented by Dr. Yoseph demonstrates that in a murine model, chronic ethanol abuse prior to sepsis leads to an increase in mortality and highlights ethanol-induced alterations of cytokine production in key organs affected by sepsis.

Dr. Anita Zahs, Loyola University Chicago Health Sciences Campus, presented data examining how the inhibition of myosin light chain kinase (MLCK) affects gut inflammation and tight junction proteins in a mouse model of ethanol exposure and burn injury. Changes in intestinal permeability during various diseases and injuries have been correlated with alterations in MLCK activity (Turner, 2006). In particular, both burn injury and ethanol exposure alone have been shown to increase intestinal MLCK activity (Ma, Nguyen, Bui, Nguyen, & Hoa, 1999; Tinsley, Teasdale, & Yuan, 2004). Since approximately 50% of burn patients are intoxicated at the time of injury (McGill, Kowal-Vern, Fisher, Kahn, & Gamelli, 1995), the role of MLCK activity in intestinal permeability was further examined in a mouse model of binge drinking and burn injury. This combined insult resulted in a 10-fold increase in MLCK activators, tumor necrosis factor alpha (TNFα), and IL-6 in the serum of combined injured mice as early as 2 h after insult, in comparison to shamgroups. At 3 h post insult, both total MLCK and phospho-myosin light chain (pMLC) were elevated in intestinal epithelial cells in comparison to controls, suggesting an increase in MLCK activity. Augmented intestinal permeability was characterized by increases in villus blunting, bacterial translocation, and interleukin-1 beta (IL-1β) levels in the ileum, at 6 h post insult. The altered location of tight junction proteins, including zonula occludens-1 (ZO-1) and occludin, in the villi confirmed a dysfunctional intestinal barrier in mice exposed to combined insult. Furthermore, treatment with a membrane-permeant inhibitor of MLCK (PIK) reduced pMLC, IL-1β, and IL-6 levels, and decreased intestinal permeability, as determined by restored ZO-1 and occludin localization, compared to mice not receiving PIK treatment. These data highlight MLCK-dependent mechanisms that occur shortly after combined insult which directly contribute to intestinal barrier dysfunction and suggest that early interventions to reduce MLCK activation may prevent systemic complications.

Dr. Robin Walker of Howard University College of Medicine gave the last short talk in this session and discussed how chronic alcohol drinking impacts the expression levels of antioxidant genes, which regulate oxidative stress machinery in heart tissue. Chronic alcohol consumption has been correlated with an array of cardiac disorders, including cardiomyopathy and cardiac arrhythmias (Skotzko, Vrinceanu, Krueger, & Freudenberger, 2009). Heavy alcohol exposure can lead to a disruption in muscle contractile units, resulting in irregular myocyte contractility and heart muscle dysfunction (Preedy, Atkinson, Richardson, & Peters, 1993). Oxidative stress has been shown to be the major factor contributing to these alcohol-induced heart conditions (Preedy et al., 1993; Wu, Zhai, & Shi, 2006). Dr. Walker has recently established the importance of the AKT/PI3K pathway in

cardiovascular disease (Walker et al., 2013). Using a rat model of chronic ethanol exposure, current studies analyzed the expression of NRF2, a transcription factor that regulates antioxidant genes. Increasing ethanol concentrations elevated antioxidant *NRF2* and *SOD-3* gene expression. Furthermore, Dr. Walker proposed that NRF2 might function as a molecular switch to control cardiovascular oxidative stress levels during chronic ethanol consumption. The role of NRF2 in oxidative stress during chronic ethanol-induced cardiomyopathy and the link between NRF2 and the AKT/PI3K pathway in cardiac muscle disease is a source of active investigation.

Alcohol abuse and inflammation

The second plenary session focused on alcohol abuse and inflammation and was chaired by Drs. Katherine Radek (Loyola University Chicago Health Sciences Campus) and Mark Asquith (Oregon National Primate Research Center). Dr. Ping Wang, Feinstein Institute for Medical Research, opened this session by sharing some of his laboratory's work on cold shock proteins and alcohol-induced neurosuppression. Alcohol is one of the most commonly abused substances and is associated with both impairments in cognitive function and structural decline in the brain (Harper & Matsumoto, 2005; Hermens et al., 2013). Brain glucose metabolism, in particular, is a key indicator of cerebral function. Changes in structure and function in the brain, including glucose metabolism, can be assessed by brain imaging techniques, such as positron emission tomography (PET). Studies using PET imaging have shown a decrease in brain glucose utilization after acute alcohol exposure, which correlates with diminished brain activity (Volkow et al., 2013). To identify the molecular mechanism behind decreased glucose metabolism, Dr.Wang's laboratory hypothesized that cold inducible RNA-binding protein (CIRP) is the inflammatory mediator responsible for alcohol-induced neurosuppression. To test this hypothesis, wild type and CIRP-knockout mice were administered ethanol, followed by an infusion of fluorescently labeled glucose, 18F-fluorodeoxyglucose (FDG). Brain glucose metabolism was then assessed using a real-time microPET scanner. Ethanol-exposed wild-type mice showed a significant decrease in brain glucose metabolism, while CIRP knockout mice were more resistant. It was also found that ethanol exposure increased CIRP protein levels in the hypothalamus and the cerebrospinal fluid of wild-type mice. Additionally, in vitro experiments using microglia BV2 cells demonstrated an increase in CIRP mRNA and protein levels following ethanol exposure in a dose-dependent manner. These data suggest a mechanism where alcohol intoxication upregulates CIRP, which, in turn, causes reduced brain glucose levels, and is likely associated with central neurosuppression.

Dr. Mark Asquith, Oregon National Primate Research Center, continued this session by describing his work on chronic ethanol consumption and the peripheral and mucosal immune homeostasis in a rhesus macaque model of ethanol self-administration. Previous work using this model demonstrated that chronic ethanol consumption alters the serum cytokine profile (Helms et al., 2012). Dr. Asquith presented data demonstrating coincident altered peripheral and mucosal immune homeostasis. To test immune function after ethanol consumption, rhesus macaques were immunized with modified vaccinia Ankara (MVA) prior to the induction of self-administered ethanol consumption, as well as 6 months after the onset of ethanol self-administration. Animals were euthanized after 12 months of ethanol consumption. Blood and gut biopsies revealed that during the booster vaccination, ethanol inhibited CD4 and CD8 T cell responses to MVA, but not B cell mediated responses to MVA. When peripheral blood mononuclear cells (PBMCs), lung, small and large intestine, and their draining lymph nodes were analyzed, an increasing dose of ethanol resulted in a decrease in PBMC growth factor production and Th1 and Th17 responses in the intestinal mucosa. Additionally, Dr. Asquith correlated these changes with an increase in microRNAs that are associated with regulating PBMC and colonic mucosa cytokine expression.

Dr. Shashi Bala, University of Massachusetts Medical School, presented data on circulating microRNAs (miRNAs) as markers of hepatocyte injury and inflammation in acute and chronic liver disease. MicroRNAs regulate gene expression; the levels of miRNAs in tissue and in the circulatory system change during disease. Circulating miRNAs are also associated with exosomes or proteins and affect cell-to-cell communication (Mo, 2012). Dr. Bala's studies specifically focused on circulating miRNA-122, which regulates metabolic pathways in hepatocytes, and miRNA-155, a known regulator of inflammation. Experimental design included 4 different mouse models to induce liver damage. Wild-type mice were given: 1) chronic ethanol with the Lieber-deCarli diet to induce steatosis and inflammation, 2) acetaminophen to induce hepatocyte necrosis, 3) Toll-like Receptors (TLRs) 9 and 4 ligands to stimulate inflammation and lymphocyte recruitment, or 4) CCl_4 to cause inflammation and fibrosis. Data indicated all 4 models resulted in an increase in alanine aminotransferase (ALT) and serum/plasma miRNA-122 and miRNA-155 levels, with a linear correlation between ALT and miRNA-122. TLR4 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-deficient mice are protected from ethanol-induced liver damage, and ethanol exposure did not result in elevated serum levels of miRNA-122. This suggests that miRNA-122 is a potential marker of hepatocyte damage in liver disease. Additionally, it was found that the association of miRNA-122 and miRNA-155 with either the exosome-rich fraction or the protein-rich fraction in the serum/plasma is dependent on the model of liver disease. Together, these data highlight how measuring circulating miRNAs can be a useful biomarker for distinguishing between hepatocyte damage and inflammation in multiple models of liver injury. The association of miRNAs with exosome and protein fractions requires further analysis to deduce its importance in different models of liver injury.

Dr. Laura Nagy, Cleveland Clinic Foundation, closed this session with a discussion on how ethanol affects inflammatory signaling by adiponectin. Previous studies have shown that chronic alcohol exposure increases inflammatory signaling via TLR4 activation in Kupffer cells (Nagy, 2003). Dr. Nagy's laboratory has identified adiponectin as an anti-inflammatory protein that neutralizes inflammatory cytokines and chemokines produced as a result of chronic ethanol consumption. One mechanism by which adiponectin reduces inflammation is by activating adiponectin receptor 1, which decreases cell surface expression of TLR4, leading to a decrease in MyD88-dependent and independent inflammatory signaling. Adiponectinwas also found to polarize macrophages from the M1, pro-inflammatory phenotype to an M2, anti-inflammatory phenotype, increasing anti-inflammatory mediator production. Overall, these data highlight adiponectin as an effective regulator of inflammatory signaling via TLR4.

Alcohol and adaptive immune signaling

In the final plenary session, chaired by Drs. Paul Drew (University of Arkansas for Medical Sciences) and Juan Rendon (Loyola University Chicago Health Sciences Campus), presenters discussed how alcohol influences the adaptive immune system. The first speaker, Dr. Peter Oldenburg, University of Nebraska Medical Center, shared his laboratory's work on how alcohol affects airway hyperresponsiveness and inflammation in allergic asthma. Characteristics of allergic asthma include bronchial constriction, increased mucus secretion, and elevated airway inflammatory cell recruitment (Bousquet, Chanez, Vignola, Lacoste, & Michel, 1994; Busse, 2010). Interestingly, alcohol has been used as a bronchodilator to treat asthma symptoms (Ayres, Ancic, & Clark, 1982; Cuddy & Li, 2001). Previous studies in Dr. Oldenburg's laboratory have shown ethanol exposure decreases airway hyperresponsiveness in non-allergic mice using a nitric oxide/PKG-mediated pathway (Oldenburg, Wyatt, & Sisson, 2010). Current studies examined pulmonary parameters in a mouse model of allergic asthma and chronic ethanol exposure. In ethanol-exposed, sensitized mice, airway hyperresponsiveness was similar to non-ethanol-exposed, non-sensitized control mice. Non-

sensitized control and ethanolfed mice also had no change in inflammatory cell populations in BAL fluid, macrophages being the primary cell type. However, BAL fluid from ethanol-exposed, sensitized mice resulted in an increase in inflammatory cells, but with a ratio of 65% fewer eosinophils and a 50% increase in the ratio of macrophages compared to non-ethanol-exposed, sensitized mice. This work may suggest a positive role of alcohol in modulating the airway inflammatory response during allergic asthma.

Dr. Erin Lowery, Loyola University Chicago Health Sciences Campus, presented data on how primary graft dysfunction (PGD) in lung transplant patients is increased with donor chronic alcohol abuse. Lung transplant patients have the highest risk of morbidity and mortality, compared to all other solid organ transplants (Yusen, 2009). With a five-year survival rate of only 50%, PGD is the main cause of early mortality, affecting 15–55% of recipients (Christie, Carby, et al., 2005; Lodhi, Lamb, & Meier-Kriesche, 2011). PGD is also the leading cause of death in the early perioperative period and is a risk factor for developing chronic rejection (Christie, Kotloff, et al., 2005). Additionally, alcohol abuse has been linked to pulmonary complications and acute lung injury. Dr. Lowery hypothesized that donor alcohol abuse would result in an increased risk for PGD after lung transplantation. To test this hypothesis, a retrospective cohort study of lung transplant recipients was performed on patients who received lung transplantation at Loyola University Chicago from 2007 to 2010. This study demonstrated that recipients who received a lung allograft from donors with reported alcohol abuse required prolonged mechanical ventilation and resulted in more days spent in the hospital, which can lead to increased risk for acquiring hospital-related infections and pneumonia. PGD was also reported in 100% of these recipients, in comparison to recipients whose donors did not report chronic alcohol abuse. Taken together, these data suggest that chronic alcohol abuse by donors results in a pro-inflammatory environment in the lung that, when combined with the oxidative stress of transplantation, leads to an increased risk of PGD.

Dr. Hui Zhang of Washington State University gave the final presentation of the meeting and discussed the effect of chronic alcohol consumption on NKT cells in tumor immunity. NKT cells are immune regulatory cells whose functions include modulating autoimmune disease and anti-tumor immunity. Chronic alcohol consumption has been linked to an increased risk of cancer and a decrease in the survival rate of cancer patients (Park, Lim, Shin, & Yun, 2006). Current studies explored how chronic ethanol abuse specifically affects NKT cells in a mouse model of subcutaneous B16BL6 melanoma inoculation. Ethanol consumption in non-tumor injected mice resulted in an increase in NKT cells ($NK1.1^+$) and a decrease in $NK1.1^-$ cells (non-NKT cells) in the thymus and liver, but not in the spleen or blood. Ethanol also increased interferon γ-(IFNγ) (Th1) producing NKT cells but decreased proliferating NKT cells in the liver. In ethanol-consuming, tumor-injected mice, NKT cells were increased in the thymus, liver, and blood, with a further increase in the ratio of $NK1.1^+$ to $NK1.1^-$ cells. However, there was a cytokine profile shift from IFNγ-(Th1) producing cells to IL-4-(Th2) producing cells. This study demonstrates that ethanol consumption alone alters NKT cell activation in both immune and non-immune organs. Furthermore, ethanol and melanoma together induce NKT cell anergy resulting in the production of Th2 cytokines and an inhibition of anti-tumor immunity. This model presents a unique opportunity to further understand the mechanism of how alcohol affects anti-tumor immunity.

Summary

The 2012 AIRIG meeting focused on the effect of alcohol on receptors and signal transduction in immunology. Acute, binge, and chronic alcohol intoxication have been shown to disrupt cell signaling pathways, altering immune responses and adversely impacting disease outcomes (Messingham et al., 2002; Nelson & Kolls, 2002). Disease and

injury models discussed at this meeting demonstrated how alcohol consumption could advance disease progression or lead to an increase in mortality. Data shown at the meeting further suggest that alcohol alters kinase activity and transcription factor activation, as well as cold shock protein and microRNA expression. Changes in these signaling components were shown to result in immune dysregulation and amplified inflammation. Alcohol also affects Th1, Th2, Th17, and Kupffer cell responses, as well as the activation of eosinophil, macrophage, and NKT cell subsets. The clinical study presented at this meeting discussed the adverse effect of alcohol consumption in lung transplantation, emphasizing the value of translational research in improving patient outcomes in various disease and injury models. Additionally, these studies revealed that alcohol consumption can also positively affect certain immune responses in allergic asthma. Overall, data presented at this meeting highlight possible mechanisms underlying immune dysregulation in alcohol-associated diseases and injuries, as well as define a possible therapeutic use of alcohol in modulating disease conditions.

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