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The Gut Microbiome: A new frontier for alcohol investigation

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Alcohol consumption is common in the United States, where 52% of adults aged 18 and over are reported to be regular drinkers, defined as consuming at least 12 drinks in the past year (<http://www.cdc.gov/nchs/fastats/alcohol.htm>). Approximately 7.2% of adults (> 18 years) and half as many youth (12–17 years) are reported to have an alcohol use disorder, in which 15% of youth drinkers are estimated to engage in binge drinking. (<http://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm>)

While moderate alcohol consumption in adults is linked with health benefits such as decreased risk of heart disease and its related mortality, ischemic stroke and diabetes, heavy alcohol consumption is pathological and associated with increased morbidity and mortality as well as higher economic burden. (<http://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm>) As intestinal blood supply flows directly to the liver via the portal vein, links between the intestine and liver have been realized with both non-alcoholic and alcoholic associated liver disease. Although the liver is considered the primary site for ethanol metabolism, extrahepatic organs are also equipped to metabolize ethanol, including the intestine and the gut microbiota. The article by Hartmann et al (2015) is particularly timely as it reviews the literature to date surrounding evidence of the crosstalk between the gut microbiome and associated alcoholic liver disease.

Funded by the NIH common fund in 2008, the Human Microbiome Project was established to identify and characterize the human microbiome and its role in human health and disease. Healthy adults (18–40 years) have provided samples from 5 major body sites: skin, oral and nasal cavities, and urogenital and gastrointestinal tracts. Advanced technology utilizing 16S rRNA and metagenomic sequencing has led to the isolation and sequencing of over 1,300 reference strains thus far from the human body (Human Microbiome Consortium, 2012). This has led to an unprecedented amount of data about the complexity of the human microbiome allowing for a baseline for further research into the impacts of the microbiome on health and disease. As a precursor to the Human Microbiome Project, the Human Gut Microbiome Project has widened our appreciation for the bacterial ecosystem that resides within the human intestinal tract. This system is comprised of microorganisms such as bacteria, archaea, fungus and viruses that are distributed throughout the entire gastrointestinal tract (Backhed et al, 2005). Ongoing investigations are revealing the importance of the gut microorganisms in exerting beneficial effects on human health.

Prior to these efforts, much of what is currently known about the role of commensal gut microbiota was discovered by comparing conventionally raised with germ-free (GF) mice. Germ-free mice are physiologically different from conventional mice in that they have

reduced intestinal mucosal cell regeneration, digestive enzyme activity, mucosa-associated lymphoid tissue, lamina propria cellularity, muscle layer thickness and resistance to infection (Hooper et al, 2012). The gut microbiota and its microbial byproducts stimulate the host intestinal immune system by activating the secretion of antimicrobial molecules (Hooper et al, 2012). Interestingly, the presence of a seemingly adequate immune system is not all that is required to prevent virulence, as pathogenic bacteria can establish persistent infection despite the presence of functional immune responsiveness when commensal bacterial composition is compromised (Kamada et al, 2012). This may be due in part to certain bacterial species ability to promote mucin production (Johansson et al, 2008), compete for nutrients (Kamada et al, 2012), or counteract the effects of pathogenic bacteria induced exotoxins (Karczewski et al, 2010). Some commensal microbes produce various antimicrobial substances that inhibit growth of Gram-positive and –negative pathogens as well as control metabolism and toxin production of pathogens (Brown et al, 2013). Quorum sensing is a cell-density dependent gene regulatory mechanism in bacteria which can be employed by pathogenic bacteria to assess relative abundance of other commensal species in the intestine (Yang et al, 2012). Quorum sensing, mediated by chemical compounds called autoinducer, regulates both intra-species and inter-species communication. It appears that a community change in the gut microbiota is associated with a disturbance of a particular quorum sensing system. Also gaining appreciation is the interaction of the gut microbiota with medications and how the microbiota influences the way our bodies perceive medications (Gonzalez et al, 2011).

Understanding the stability of the microbiota within an individual through time is an important step in enabling prediction of disease states and developing therapies to correct dysbiosis (imbalances in the microbial community). Revealed by metagenomic analysis, gut microbiota composition changes throughout early stages of human development and is influenced by the diet (Koenig et al., 2011). As an infant's diet comprises breast milk and formula, this is reflective in that the microbiome is enriched in genes to facilitate lactate utilization. A shift in the functional capacity to preferentially utilize plant-derived glycans occurs prior to the introduction of solid foods. Around 3-years of age, the bacterial composition resembles that of an adult and remains stable until old age when variability in community composition increases (Claesson et al, 2011). However, this consistency assumes that numerous variables, including diet, disease and environment, are also being held constant.

Unlike *in vitro* and *in vivo* animal studies, humans are free-living and exposed to a multitude of environmental and lifestyle factors that are now known to disrupt the stability of the gut microbiota. As an increasing majority of people consume less complex diets, one that is rich in simple carbohydrates and other manufactured ingredients, the gut microbiota shifts in response (Minot et al., 2011). Demonstrated in animals and humans, a shift microbiota composition can occur within 24-hr of a dietary change (Wu et al, 2011). Alcohol should also be considered a dietary component and likewise is known to induce gut dysbiosis and negatively impact gut microbiota fermentation byproducts in animal models (Xie et al, 2013) and is associated with worse liver pathology and outcome in humans ((Zhao et al, 2004; Chen et al, 2011; Bajaj et al, 2014). In addition to consuming a “Western” diet, people consuming alcohol may not only have co-existent co-morbidities associated with metabolic

syndrome and gut dysbiosis, but they also are likely to be prescribed medications additionally known to alter the gut microbiota (e.g., antibiotics, histamine-2 antagonists, proton pump inhibitors, corticosteroids). Hartman et al (2015) review what is currently known about the association between ethanol, gut liver-injury and the gut microbiota. Recent and ongoing research indicates that the model of microbiota-gut-liver axis is central to health, and that when disrupted this association contributes to initiation and maintenance of liver disease and related complications. As alcohol consumption is likely to continue to be a common indulgence, it is imperative that the gut microbiota be considered when investigating pathological effects of alcohol. Learning more about the complex interactions between the host and gut microbiome and considering this relationship with investigations of alcoholic liver disease will facilitate new research directives for this multifaceted disease.

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