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Does genetic loss of immunoglobulin A have no impact on alcoholic liver disease?

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Chronic alcohol abuse leads to liver injury in the manifestation of hepatic steatosis, hepatitis, fibrosis, cirrhosis and cancer (Gao and Bataller, 2011, Wang et al., 2016, Nagy et al., 2016). Alcohol-induced steatohepatitis is characterized by hepatocyte death, liver inflammation and lipid accumulation, and can proceed to late-stage liver diseases which have no successful treatment other than liver transplantation. The pathogenesis of alcoholic liver disease (ALD) has been extensively studied, and one important factor is the gut-liver axis (Szabo, 2015, Chen et al., 2016). Chronic alcohol exposure impairs intestinal epithelial barrier, increases gut permeability, elevates translocation of bacterial endotoxin lipopolysaccharide to portal blood flow, activates toll-like receptor 4 (TLR4) and thus induce liver injury. Alcohol abuse also disrupts intestinal microbiome homeostasis and metabolic composition, which further contributes to liver inflammation (Chen et al., 2016).

Immunoglobulin A (IgA) is an isotype of mammalian antibodies. Despite its existence in blood, most IgAs are found in mucosal membrane and play a critical role in immune function in these areas (gut, respiratory tract, urogenital tract, etc). Human IgA has two subclasses, IgA1 and IgA2, differing in structure and their proportion in serum and secretions (Delacroix et al., 1982). Mouse only has one subclass structurally similar to Human IgA2 (Corthésy, 2013). In comparison to the monomeric serum IgA, the dimeric secretory IgA (sIgA) exists in various secretions (saliva, tears, breast milk, sweat, gastric fluid, etc.) and contains a joining (J) chain and a secretory component (SC). sIgA is the main form responsible for immune functions, and the sIgA secreted into intestinal lumen is the first barrier of intestinal epithelium against enteric toxins and pathogenic microbiome. The known effects of IgA include immune exclusion of pathogens, maintenance of intestinal microbiota composition, and reduction of pro-inflammatory response (Mantis et al., 2011). Elevated serum IgA (Bogdal et al., 1976, Meillet et al., 1997, Teppo and Maury, 1983, Gonzalez-Quintela et al., 1995), liver IgA deposition (Swerdlow et al., 1982) and anti-adduct IgA formation (Koskinas et al., 1992, Latvala et al., 2005) are associated with chronic

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alcohol abuse. However, the exact role of IgA in alcohol-induced injury especially liver injury remains unknown.

In this issue of *Alcoholism Clinical & Experimental Research*, Inamine et al. (Inamine T, 2016) investigated the importance of IgA in the development of experimental ALD using IgA knockout (KO) mice. Despite the well-known protective role of IgA against intestinal bacteria, loss of IgA in mice surprisingly did not have a significant increase in indexes of liver injury and liver steatosis compared to matched wild type (WT) mice, either at the basal level or after 4 weeks' Lieber-DeCarli ethanol diet feeding. As for liver inflammatory cytokines, the level of hepatic IL-1 β was similar, while hepatic levels of TNF α were significantly increased in alcohol-treated IgA KO mice. The levels of hepatic Cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1) and alcohol dehydrogenase, two important enzymes for ethanol metabolism, as well as intestinal permeability, were not different between IgA KO and matched WT mice after alcohol feeding. While ampicillin pretreatment reversed IgA-low phenotype, the IgA KO mice still had similar extent of liver injury, steatosis, inflammation even after a prolonged alcohol exposure for up to 7 weeks. It is well-known that feeding mice with Lieber-DeCarli ethanol diet for 4–8 weeks only causes mild liver injury without noticeable liver inflammation and fibrosis in the liver, the authors also utilized the recent established chronic plus binge alcohol mouse model. Mice treated with chronic plus acute alcohol have increased liver injury and liver inflammation (Bertola et al., 2013). The authors found that liver injury was also comparable between IgA KO and WT mice after chronic plus binge alcohol treatment. These results strongly argue against a protective role of IgA in the pathogenesis of ALD.

While the findings that IgA KO mice are not more susceptible to alcohol are intriguing, it is not completely unexpected. Increasing evidence implicates that caution needs to be used for the interpretation of data obtained from the use of genetic KO mice. Compensatory effects or even secondary effects present in the KO mice due to the chronic loss of a gene often make the data interpretation very complex (Williams et al., 2015, Ni et al., 2012). Indeed, the authors found that IgA KO mice had compensatory increased levels of IgM. However, the evidence provided in this paper only showed a correlation but not cause-and-effect relationship between IgA deficiency and increased IgM, or between increased IgM and unaffected liver injury response. Whether increased IgM indeed protects against bacteria translocation remains unknown. Ideally, it will be helpful to determine liver injury induced by alcohol in IgM KO or IgA and IgM double KO mice. Alternatively, an inducible IgA KO model or acute knockdown of IgA using viral vector-mediated shRNA in vivo delivery should be used, which would be very helpful to minimize the compensatory effects of chronic IgA deficiency. We recently show that acute knockdown of Parkin in the mouse liver using an adenovirus Parkin shRNA overcomes the compensatory protective effects from the Parkin KO mice (Williams et al., 2015). However, it should be noted that while the approach of acute knockdown of a gene or inducible KO mice may be helpful to dissect the molecular mechanisms of the direct action of a particular gene, the phenotypes of chronic KO mice may actually be more physiological relevant. This is because that many patients who have genetic gene mutations would phenocopy of the KO mice. Indeed, many IgA deficient patients also do not have significant symptoms (Yel, 2010). This may be because they have

normal levels of other immunoglobulins like IgG and IgM as an adaptive compensatory response.

Perhaps another notable interesting finding from this study is that the authors did not find significant difference in liver steatosis and injury among male and female mice regardless of the genotype of IgA. A recent study also demonstrated that there was no difference of liver injury among male and female alcohol drinkers (Li et al., 2016). These results argue against the notion that females are more susceptible in ALD than males. National Institutes of Health (NIH) have recently highly emphasized to consider the gender difference in animal studies. More future studies are needed to confirm that gender is not a critical factor in the pathogenesis of ALD, which will tremendously help researchers to significantly cut down the numbers of experimental animals.

As mentioned earlier, intestinal dysbiosis contributes to ALD progression. Though bacteria overgrowth potentiates ALD, the absence of microbiota increases alcohol metabolism and exacerbates acute binge-induced injury and inflammation (Chen et al., 2015a), suggesting that broad antibiotic treatment may have unneglectable side effects. Probiotics treatment promotes an anti-inflammatory response and shows protection against alcohol-induced liver injury (Sung et al., 2016). Besides, other methods of maintaining/restoring the intestinal eubiosis, like supplementation of saturated fatty acids (Chen et al., 2015b) and fecal microbiota transplant, may help to intervene the progression of ALD. A better understanding of microbiota and its regulation will greatly benefit the development of new therapeutic targets of ALD.

In conclusion, this study elegantly showed that chronic loss of IgA can be compensated by increased levels of IgM during the pathogenesis of ALD. This study also suggests that caution needs to be used to interpret data from chronic genetic gene KO mice.

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