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Roles of Inflammation and Gut Microbiota Metabolite Indole in Pathophysiology of Diet-induced Steatohepatitis

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T3: TEXAS A&M TRIADS FOR TRANSFORMATION
A President's Excellence Fund Initiative

Background

Stimulator of interferon genes (STING) is a mediator of innate immunity. Previous research has validated that STING promotes macrophage proinflammatory activation, which in turn contributes to the development of non-alcoholic fatty liver disease (NAFLD), as well as non-alcoholic steatohepatitis as the advanced form of NAFLD. Increasing evidence also has suggested a role for dysregulation of gut microbiota composition in contributing to the pathogenesis of NAFLD.

With the support from a TAMU T3 Grant, the Lab of Dr. Chaodong Wu has been able to examine the relationship between altered composition of gut microbiota and hepatic STING activation in the content of NAFLD phenotype. Upon identifying indole as a microbiota metabolite whose levels were decreased in a mouse model of NALFD, the Wu Lab further examined the extent to which indole alleviates NASH in mice.

Method

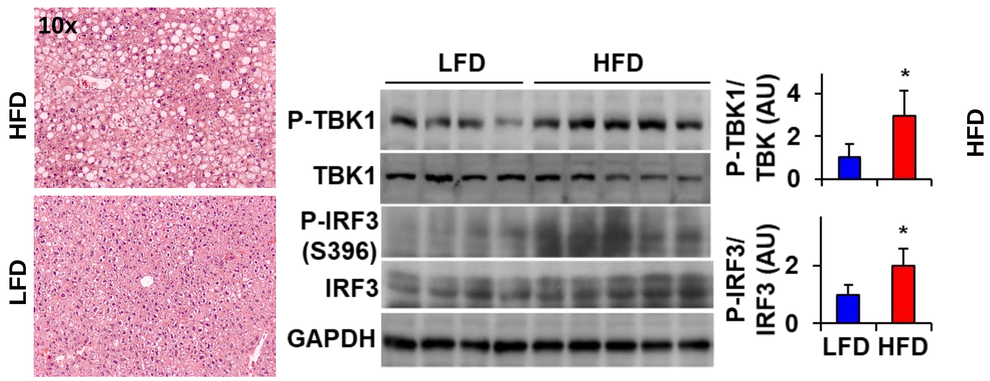
Study 1: Male C57BL/6J mice, at 5 – 6 weeks of age, were fed a high-fat diet (HFD) or low-fat diet (LFD) for 12 weeks and examined for liver STING signaling, as well as NAFLD phenotype. Also, the composition of gut microbiota of the mice was analyzed.

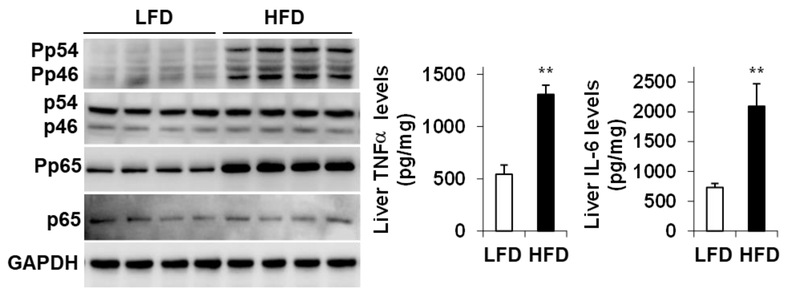
Study 2: At 10 - 12 weeks of age, male WT (C57BL/6J) mice and STING-disrupted mice (STING^{gt}) mice, in which STING was disrupted in all cells, were fed a methionine- and choline-deficient diet (MCD) for 5 weeks and examined for NASH phenotype.

Study 3: Male C57BL/6J mice, at 10 - 12 weeks of age, were fed an MCD for 5 weeks and treated with indole (50 mg/kg/d, dissolved in BSA) or BSA for the last 4 weeks of the feeding period. After the feeding/treatment period, the mice were examined for NASH phenotype.

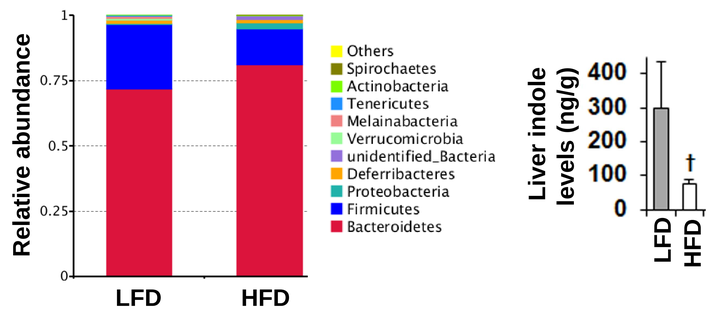
Results

1. STING signaling is increased in livers of mice with diet-induce NAFLD.

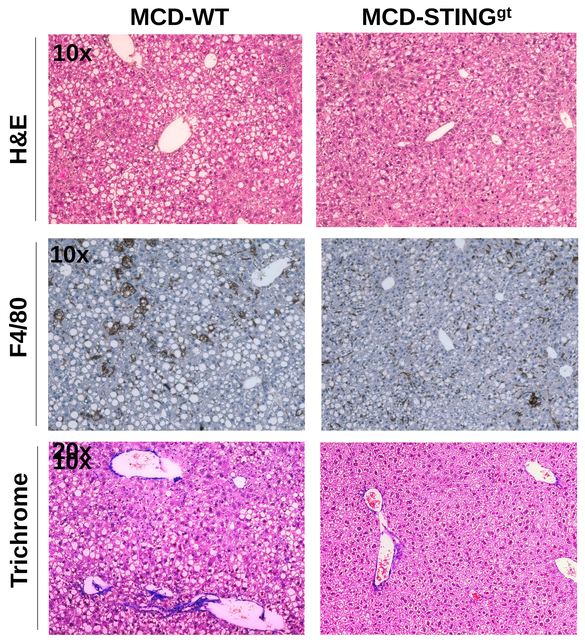




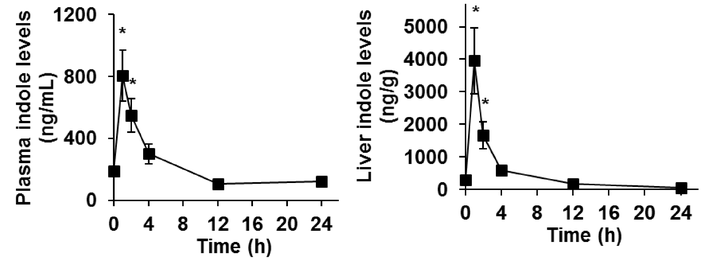
2. In mice with diet-induced NAFLD, the composition of gut microbiota is altered and accompanied with decreased hepatic levels of indole.



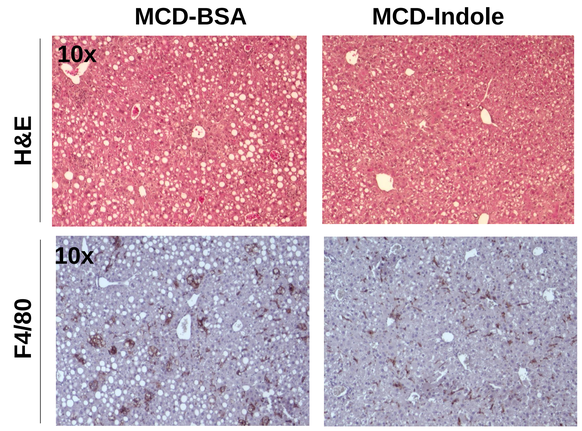
3. STING disruption alleviates the severity of MCD-induced NASH phenotype.



4. PK/PD patterns indicate the liver as a primary target of indole.



5. Indole supplementation alleviates MCD-induced NASH.



Conclusion

Both increased STING and decreased production of microbiota metabolite indole are involved in the pathogenesis of NAFLD.

While it remains to be examined whether STING functions to decrease indole production, it is convincing that indole supplementation alleviates NASH phenotype in mice.

Acknowledgement

This study was supported, in whole or in part, by a TAMU T3 grant., and grants from the American Diabetes Association (1-17-IBS-145) and the NIDDK (DK095862).

Outcomes

This T3 grant contributed, in part, to 2 recent publications from the Wu Lab (*Hepatology* and *J Endocrinol*) and one NIH R01 grant (DK124854 to C.W.).