Xanthophylls Shift the Gut Microbiota and Reduce Inflammation in Mice During Influenza A Virus Infection

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Objectives: Seasonal influenza A virus (IAV) infection impacts both respiratory and intestinal microbiome homeostasis. However, it is not well understood the extent to which the gut-lung axis plays the role in innate immunity and acute inflammation during IAV. Xanthophylls are fat-soluble, oxygenized carotenoids with potent antioxidant properties. We recently reported that xanthophylls can promote gut microbiome homeostasis and is associated with attenuation of intestinal and systemic inflammation. Here, we sought to investigate the protective effects of xanthophylls, e.g., zeaxanthin (Z) and astaxanthin (A) in IAV pneumonia by regulation of the host gut microbiome.

Methods: Six-week-old male and female 129S6 wild type (WT) and beta-carotene oxygenase 2 (BCO2) knockout mice were fed with AIN93M chow diets supplemented with or without Z (0.02% w/w) and A (0.02 w/w) (e.g., A + Z). After 6 weeks of the dietary intervention, mice were intranasally infected with 100 pfu H1N1 PR8 virus. Animal body weight and phenotypes were monitored daily. Animals were sacrificed 6 days post-infection. Blood and lung tissues were collected for experiments. H & E staining, gut microbiota 16S rRNA sequencing, immunohistochemistry, and immunoblotting were used for clinical, histopathological, and other biochemical assessments.

Results: Depletion of BCO2, the xanthophyll cleavage enzyme, made mice more resistant to IAV infection. Administration of A + Z caused A + Z accumulation and enhanced resistance to IAV in BCO2 KO but not WT mice, as demonstrated by histological lung damage and colon and ileum inflammation. Gut microbiome profiling results showed that α–diversity and β–diversity were significantly altered in these experimental groups. In particular, A + Z accumulation is positively associated with Bacteroides abundance. The increases in Bacteroides abundance were even greater in BCO2 KO mice, compared to the WT. Furthermore, Akkermansia abundance was significantly increased in BCO2 KO mice after IAV infection.

Conclusions: Association of xanthophyll accumulation with the gut microbiota shift could protect animals from IAV infection by reducing local inflammation. Bacteroides potentially plays a beneficial role in this process.

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