Index No.: 79/19/Life Sc./26
Title of the Thesis: Effect of pre and postnatal exposure to Arsenic on the Immune and Gastrointestinal Function: study in mice model

ABSTRACT

Arsenic is a highly potent environmental pollutant which affects more than 200 million people globally particularly through ingestion of contaminated food and drinking water. Arsenic has been known to exert deleterious effects not only in adult life but also in prenatal and early life. As Arsenic can easily cross the placenta a fetus becomes particularly vulnerable to toxic effects of the metalloid increasing the risk of infant mortality, and other associated impacts later in life including the maternal-offspring microbiota exchanges and development and maturation of the neonatal microbiome and the gastrointestinal system. This thesis aims to better understand how prenatal arsenic exposure may change the gut microbiome and its consequences on gut function, if any, in later life.

To witness how arsenic exposure in adult life may affect immune and gastrointestinal physiology we undertook initial approach by treating Balb/c mice with 4 ppm and 10 ppm of arsenic trioxide in drinking water respectively for 30 days. Mice exposed to Arsenic (As-mice) showed reduced CD4+ and CD8+ T-cells in spleen, IgG1 and IgG2a in serum and increased susceptibility to enteric *Shigella* infection. Shigella infection in As-mice increased bacterial burden in colon, expression of mucin-2, iNOS and cytokines IL-6 and TNF- α compared to control. This is an interesting observation where we found correlative association between reduced T cells and increased susceptibility to gut infection.

Next we investigated if and how prenatal arsenic exposure affects all three arms of immune system (innate, humoral, and cellular) and if it leads to any long lasting influence in the postnatal host immune repertoire. Pregnant mice were exposed to arsenic trioxide through their drinking water from time of conception until parturition. The 4-week-old pups that had not been exposed to Arsenic after birth were used for functional analyses of gastrointestinal and immune function. We uncovered that prenatal arsenic exposure significantly decreased splenic CD4+T-cells and CD8+ T-cells, while mice also failed to produce and decrease in IL-2 and IFN-γ upon proper stimulation. There were marked significant reductions in inducible early T-cell activation markers CD44 and CD69 while serum IgG2a levels were decreased and thus ultimately leading to decreased immunity as observed by increased susceptibility to septicemic *E. coli* infection. Thus prenatal arsenic exposure induced a generalized defect in immune function that then persisted even in the absence of further Arsenic exposures.

Lastly, we delved into the study to understand if prenatal arsenic exposure affects the gastrointestinal function in post natal life in mice. The prenatally arsenic exposed mice (pAs-mice) showed a striking reduction in *Firmicutes* to *Bacteroidetes* (F/B) ratio coupled with decrease in tight junction protein, occludin resulting in increase in gut permeability, increased infiltration of inflammatory cells in the colon and decrease in common SCFAs in which butyrate reduction was quite prominent. Further studies with supplementing butyrate, to pAs-mice we observed reversal of the arsenic induced changes in the gut. Our investigation on the molecular mechanism revealed that reduction in butyrate production in pAs-mice leads to increase in miR122 expression in gut which in turn decays Occludin mRNA, one of the important tight junction proteins.

Thus in conclusion, we can state that prenatal and postnatal exposure to Arsenic hampers the development of immune system and gastrointestinal system which could lead to increased susceptibility to diseases and other variety of health complications later in life.

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02/02/2023

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