A Novel Mouse Model With Humanized IgA Dynamics: The Hepatobiliary-Specific pIgR KO

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Introduction: Environmental Enteropathy, a subclinical condition of the small intestines thought to result from the interplay of malnutrition and frequent diarrheal infections, is a critical barrier to healthy growth of children worldwide. When challenged with malnutrition or infection, mice with humanized gut IgA dynamics could provide a better model to study its mechanisms. By removing the mouse IgA "liver pump", a hepatobilliary-specific polymeric IgA receptor knockout mouse (HB-pIgR KO) would mimic the human distribution of pIgR and might serve as such a model.

Hypothesis: The HB-pIgR KO will lack liver pIgR expression, while maintaining jejunal pIgR expression and will have little to no bile secretory IgA (sIgA), decreased stool sIgA, and increased serum sIgA levels.

Methods: HB-pIgR KOs ($pIgR^{fl/fl\ *}$, Albumin-cre/+**) were compared with global pIgR KOs ($pIgR^{-/-\ ***}$), wild types (WT) (C57BL/6) and floxed controls (FC) ($pIgR^{fl/fl\ *}$). Animals were developed together with Cyagen Biosciences Inc.*, The Jackson Laboratory**, and MMRRC***. Liver and jejunal samples were analyzed via PCR, Western blot, and immunohistochemistry for tissue specific pIgR knockout. Stool, serum and bile samples were analyzed via ELISA for sIgA content. All samples were collected from adult mice.

Results: PCR (n=3) confirmed liver tissue-specific gene recombination of the pIgR gene in HB-pIgR KOs. Immunohistochemistry staining (n=1) for pIgR showed similar protein concentration and localization in the jejunum of WT, FC, and HB-pIgR KOs and significant knockdown in those of global pIgR KOs. Liver samples showed efficient knockdown in global and HB-pIgR KOs. Western blots (n=5) for pIgR confirmed immunohistochemistry results. ELISA analysis (serum/stool $n \geq 5$; bile $n \geq 3$) showed increased serum sIgA and decreased stool sIgA in global and HB-pIgR KOs compared to WT and FCs respectively ($p \leq 0.05$; HB-pIgR KO stool ns). HB-pIgR KOs trended towards intermediate changes between controls and global pIgR KOs. Global and HB-pIgR KOs trended towards a decrease in bile sIgA.

Conclusions: The HB-pIgR KO shows an expected hepatobilliary tissue-specific pIgR knockout and concurrent changes in serum, stool and bile sIgA levels. Bile results were not significant, likely due to low sample size. Work continues to characterize the microbiome and response to undernutrition and infection in this model.

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