Cleveland Clinic Innovations

Novel IgA Deficient Mouse Model

Inventors: Thaddeus Stappenbeck, MD, PhD & Qiuhe Lu, PhD
Lerner Research Institute, Inflammation and Immunity

PRODUCT
Novel IgA deficient mouse model

INDICATION
Generation of intestinal-only IgA^{LOW} animal model of inflammatory diseases

VALUE PROPOSITION
- Novel commensal bacterium secretes proteases that degrade IgA in the gut
- IgA^{LOW} mouse models can be generated by oral gavage with no genetic manipulation
- Models retain circulating plasma IgA levels and immune function

DEVELOPMENT STAGE
Mouse model available for licensing

In vivo proof of concept established for DSS-induced colitis model

PUBLICATIONS
Zhang, Shanshan et al. “Select symbionts drive high IgA levels in the mouse intestine.” Cell host & microbe vol. 31,10 (2023): 1620-1638.e7.

CONTACT INFORMATION
Saqib Sachani
Assoc. Director, Business Development and Licensing
sachans@ccf.org
216.672.1913
IDF# 2023-050

UNMET NEED

IgA is the most abundant antibody isotype in humans, synthesized at a remarkable rate of 66 mg/kg/day. The soluble, bioactive form of IgA (SIgA) is secreted by plasma cells and transported into the intestinal lumen, where it promotes critical immunomodulatory functions including protection from harmful pathogens and promotion of host microbiome diversity. IgA deficiency or dysregulation has been associated with many autoimmune conditions including asthma, allergies, IBS, Celiac disease, and dermatitis. However, IgA biology has been noted as “particularly confusing” in the literature, due in part to the poor translatability of existing mouse models that rely on whole-organism genetic deletion of IgA or its receptor (pIgR). Interpretation of these models is confounded by loss of IgA function in both the gut and the broader circulating immune system; furthermore, maintaining breeding programs to support these genetic models limits broad utility across labs and indications.

SOLUTION

The Stappenbeck Lab at Cleveland Clinic has identfied a novel commensal bacterial isolate from wild-type B6 mice, coined *Tomasiella immunophila*, that secretes Cys proteases capable of selectively degrading SIgA only within the gut. After a single oral gavage of *T. immunophila,* fecal IgA levels drop precipitously after just two weeks, while serum IgA levels remain unaffected (Figure A). Endothelial cells co-cultured with *T. immunophila*, but not with control bacteria, rapidly degrade antigen-induced SIgA (Figure B). Mice colonized with *T. immunophila* have a gut-specific SIgA knockdown but maintain normal IgA immune functions, including wild-type B cell and plasma cell phenotypes. This *T. immunophila* model allows IgA loss to be studied in diverse disease-relevant mouse models without further genetic manipulation. As an example, the Stappenbeck Lab demonstrated that intestinal IgA depletion by *T. immunophila* has a negative impact in standard DSS-induced colitis models (Figure C). By enabling a tissue-restricted and easy-to-implement animal model, *T. immunophila* should clarify mucosal IgA biology and shed light on therapeutically vulnerable mechanisms underlying IgA pathologies.