Jeremy T. Richardson
L2
Louisiana State University Health Sciences Center, New Orleans, LA

Mentor's Name: J. Jason Collier, PhD
Pennington Biomedical Research Center, Baton Rouge, LA
Louisiana State University, Department of Biological Sciences, Baton Rouge, LA

"The ICR mouse: an MHC matched control for the non-obese diabetic mouse model, pillar of type 1 diabetes research"

Type 1 diabetes (T1D) affects approximately 9 million individuals and accounts for 5-10% of diabetes worldwide. Furthermore, the global incidence of T1D has in recent years starkly increased and is generally attributed to an exacerbated interplay between polygenic and environmental risk factors. The precise etiology of the disease is to this day unknown; However, a growing body of evidence suggests that viruses and other environmental stressors may disrupt an already fragile pancreatic milieu, trigger autoimmune events, and impede restoration to a homeostatic state once the challenge removed. Still, much of the mechanisms leading to abnormal immune cell infiltration of the islets of Langerhans (insulitis), pancreatic β-cell failure, and resultant hyperglycemia remain to be uncovered. The complex and multifactorial nature of the disease has prodded investigators to heavily rely on animal models to study the various facets of autoimmune diabetes. Makino and colleagues developed a mouse strain found to exhibit a high incidence of dysuria while outbreeding mice from the Jcl:ICR (Institute for Cancer Research) strain to study cataract disease. Further inbreeding of hyperglycemic ICR mice over multiple generations gave rise to the non-obese diabetic (NOD) mouse line, a model with spontaneous disease onset that displays autoimmune characteristics. The NOD mouse model immediately became a cornerstone in T1D research due to its remarkable similarities with human disease development and progression. Mice and humans exhibit autoreactive T cell infiltration within pancreatic islets prior to diabetes onset, loss of β-cell mass, share genes attributed with heightened disease risk, and show dysfunction in many of the same biological pathways. Interestingly, genetically inequivalent mouse models are commonly used as controls for NOD mice despite critical differences between autoimmune and non-autoimmune prone mouse strains and the well-established genetic contribution to T1D.

In this study, we directly compared the NOD/ShiLtJ and ICR/Haj mouse lines, which each carry T1D susceptibility genes, to better understand the ICR model as a non-insulitis, non-diabetes developing, and genetically matched appropriate comparison for studies using the NOD mouse line. As the mice aged, they did not differ in body weight or body composition (no statistical difference in fat, lean, or fluid mass). Histological analysis of normoglycemic, age matched NOD and ICR pancreatic tissues revealed insulitis beginning at 6-weeks of age in the NOD tissue, which grew more pronounced with age. In addition, NOD mice displayed more ICAM-1 staining when compared with age matched ICR mice. Moreover, NOD mice demonstrated upregulation of ICAM-1 by pancreatic β-cells at onset of hyperglycemia (compared with normoglycemic aged-matched NOD controls). Our work shows there are valuable insights to be gained regarding the molecular and immunological events contributing to T1D onset and progression that could be missed in strains mismatched at important genetic loci relevant to autoimmunity.