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Poster Submissions

Poster Title

UNCOVERING THE ROLES OF TOLL-LIKE RECEPTOR 7 AND INTERFERON REGULATORY FACTOR 5 IN IMMUNE COMPLEX GLOMERULONEPHRITIS

Authors and their Affiliation

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Horne BK Jr, Cohen-Bucay A, Rifkin IR, and Bonegio RG

Please describe the extent of your work in this research

Control and experimental mouse lines had been previously generated by Ian Rifkin and Ramon Bonegio (my P.I.).

My poster has four figures.

Figure 1: Mouse NTS injections, sacrifice, organ collection, organ processing, cell staining, and Flow Cytometry (at the BU Flow Cytometry Core) were all performed jointly/together by myself and Ramon Bonegio. The Flow Cytometry results analysis was carried out primarily by Ramon Bonegio, with some assistance from myself.

Figure 2: Mouse NTS injections, mouse sacrifice, and organ collection were performed jointly/together by myself and Ramon Bonegio. Histological and pathological analysis of kidney slides (injury, crescent, and necrosis scoring) was performed jointly/together by Abraham Cohen-Bucay and Ramon Bonegio.

Figure 3: Urine collection, albumin ELISA, Creatinine assay, UACR calculations, and UACR results analysis were performed entirely/solely by myself.

Figure 4: Revised proposed model designed by Ian Rifkin and Ramon Bonegio, with input and adjustments made to the model based upon my UACR results. Mouse NTS injections, sacrifice, organ collection, and organ processing for Microarray performed jointly/together by myself and Ramon Bonegio. Actual microarray carried out, and microarray results reported, by Boston University Microarray Core. Additional analysis of the microarray results report from the BU Microarray Core performed by myself, with some assistance from Ramon Bonegio.

Abstract Submission

- **Horne-Cohen-Bucay-et-al-2015-GSI-Abstract.docx**

Would you like your abstract to be considered for an oral presentation (students and post docs only)?

Yes

UNCOVERING THE ROLES OF TOLL-LIKE RECEPTOR 7 AND INTERFERON REGULATORY FACTOR 5 IN IMMUNE COMPLEX GLOMERULONEPHRITIS

Barry K. Horne Jr, Abraham Cohen-Bucay, Ian Rifkin, and Ramon G. Bonegio

Background and Hypothesis

Immune complex glomerulonephritis (IC-GN) can develop in association with infection, autoimmune disease, or malignancy. It is instigated by in situ formation or deposition of immune complexes, and is characterized by: the formation of glomerular crescents, glomerular necrosis, and proteinuria/albuminuria. Interferon regulatory factor 5 (IRF5) acts downstream of Toll-like receptor 7 (TLR7) to trigger inflammatory responses, and IRF5 polymorphisms have been identified as risk factors for lupus nephritis. We therefore hypothesized that deletion of either the TLR7 or IRF5 gene would ameliorate the disease characteristics of IC-GN.

Methods

The control group consisted of FcγRIIB$^{-/-}$ mice derived from a C57BL/6J background. Two experimental groups were created from the same strain: FcγRIIB$^{-/-}$ TLR7$^{-/-}$ and FcγRIIB$^{-/-}$ IRF5$^{-/-}$. We induced nephritis in all groups via tail-vein injection of endotoxin-free sheep IgG1 nephrotoxic serum (NTS). At time points ranging from 5 hours to 5 days after induction (when the heterologous antibody response peaks), we euthanized the mice and compared renal: histology, inflammatory cell infiltrate, gene expression profiles, and albuminuria.

Results

The control mice developed severe glomerulonephritis, characterized by: formation of necrosis and crescents in 28 ± 6 % of glomeruli, prominent mononuclear cell infiltration, and massive albuminuria. In contrast, mice that lacked TLR7 or IRF5 developed much less disease - crescents and necrosis were seen in only 6 ± 2% of glomeruli ($p<0.01$) and mononuclear cell infiltration was significantly decreased.

Interestingly, although the TLR7 and IRF5 knockouts had similar ameliorating effects on renal inflammation and necrosis, *only* the TLR7 knockout had a significant impact on albuminuria.

Conclusions

IRF5 signaling downstream of TLR7 promotes glomerular inflammation and necrosis – but *not* albuminuria – during the heterologous phase of IC-GN. Since the TLR7$^{-/-}$ group showed decreased albuminuria however, we therefore propose a model in which TLR7 engagement triggers inflammation in an IRF5-*dependent* manner, while also inducing albuminuria in an IRF5-*independent* manner. These distinct pathways may be operating in the same cell, or they may be cell-type specific. We therefore conclude that the TLR7/IRF5 pathway is a rational target for the control of inflammation in IC-GN, and that one of TLR7's other downstream pathways may present a novel target for alleviating the concomitant albuminuria.

About the Authors / Contributors

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