



Parallels between antibody-mediated rejection and ischemic kidney injury with respect to B cell activation

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The traditionally understood pathological roles of B cells in organ transplant injury include their differentiation to antibody secreting cells and their function as antigen presenting cells (1,2). However, Cippa and colleagues suggest that the B cell response to dysfunctional tissue repair reflects a common pathway of kidney injury shared by ischemia/reperfusion injury and transplantation (3). These authors initially observed a gene signature indicating elevated B cell activity (immunoglobuline genes) together with fibrosis (COL1A1, DPT, MMP7) and immunity (CD52, CXCL10, CCL21) in one year protocol biopsies from 42 kidney allograft patients. Patients with increased chronic kidney injury (CKI) at 1 year showed gene signatures with higher levels of acute kidney injury and repair (LCN2, SOX9, ALDH2A1) at three months post-transplant but without graft dysfunction. In order to exclude the contribution of alloimmunity to this process due to a low sensitivity of a conventional pathology grading system, they evaluated subclinical rejection episodes by measuring an extensive list of genes. Interestingly, kidney injury preceded B cell immune responses, and early acute injury was associated with expression of genes linked to innate immune responses. They postulated that a B cell response to tissue injury even in the absence of an alloimmune response induces CKI. In order to model these observations, mouse kidneys subjected to a single ischemia reperfusion injury (IRI) were studied for 16–18 months. Injured kidneys with twenty-one minutes of

warm ischemia (without alloreactivity) showed lymphocytic infiltration (large cellular cluster/ectopic GC) with elevated genes related to fibrosis and lymphocyte homing (Ccl21, Cxcl12, Cxcl13) at 6 months. Interestingly, the same gene signature was found at one month from stromal cells during the transition from acute to chronic injury. Following IR injury, memory B cells infiltrated rapidly, expanded, and progressively switched to a plasma cell population (based on transcriptional analysis). Sixteen–18 months later, they observed persistent CD138 negative B cells (not plasma cells). This B cell expresses CD19+/lo CD45R- with CD126 (IL-6R), Cxcr4 (CD184) and Cxcr3 (receptor for Cxcl12). These polyclonal B cells were enriched for a limited number of clones and by both histology and BCR analysis suggested proliferation, selection, and maturation of B cells in germinal centers within the kidney in association with the transition to chronic kidney injury. Given these changes in response to IRI, the observations suggest that in the absence of foreign antigen an intrarenal B cell response produces broadly reactive autoantibodies that parallel development of chronic injury and fibrosis. The B cell response mirrors that observed with alloantibodies and chronic rejection. In other words, B cells play a critical role in late immune-mediated kidney injury and repair responses, and B cell activity in kidney allografts is indistinguishable from dysfunctional kidney repair due to IRI. Unresolved kidney injury therefore may drive chronic activation of the adaptive immune response including B cells and germinal

centers within the kidney, with production of antibodies that further injure the kidney. The stepwise loss of B cell tolerance leading to a common injury phenotype suggests that early intervention in B cell activation will likely be a more successful treatment strategy than targeting the late events of chronic inflammation and fibrosis. An improved understanding of the pathways of B cell activation leading to chronic injury would potentially lead to development of mechanistic approaches to preventing such injury, likely refocusing current attention on early B cell activation events rather than late steps in the response to injury.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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