Increased Complement Gene Expression in Circulating B Cells From Kidney Transplant Recipients With Chronic Antibody-Mediated Rejection

To the Editor: Chronic antibody-mediated rejection (CAMR) is a major cause of kidney allograft failure, commonly triggered by preformed or *de novo* anti-human leukocyte antigen donor-specific antibodies. After binding to graft endothelium, donor-specific antibodies activate the complement cascade that promotes graft injury.[1] Intriguingly, animal data suggest that complement is implicated not only in the final donor-specific antibody effector mechanisms, but also in germinal center B cell maturation[2] and antibody production.[3] Whether complement affects donor-specific antibody production in human kidney transplant recipients is unknown.

Herein, we assessed the strength of the association of 2 key complement-related genes, *C1QA* and *C1QB*, previously identified as differentially expressed in circulating leukocytes from 10 CAMR and 8 matched control kidney transplant recipients (Supplementary Table S1),[4] with B cells, $CD4^+$ T cells, $CD8^+$ T cells, dendritic cells, monocytes, and natural killer cells. We used CellCODE analysis (see Supplementary Material for details), which quantifies the strength of the relationships between canonical gene sets of distinct immune cell types and a gene of interest.[5]

When we used an interaction model to query which cell type was most tightly associated with the differences in *C1QA* and *C1QB* mRNA expression between the CAMR and control groups, the F-statistic derived from these analyses was highest in B cells, indicating that *C1QA* and *C1QB* mRNA expression in the B cell subset drives the differences observed between CAMR versus control patients (Figure 1).

C1QA and *C1QB* encode the A-chain and B-chain polypeptides of serum complement component C1q. Our findings indicate that B cells could represent an important source of C1q. Recent data suggest that C1q crosslinking IgM and IgG on B cell surface may initiate complement activation and subsequent complement receptor signaling required for optimal positive selection of germinal center B cells.[2] Our analyses support the hypothesis that in CAMR patients, this process depends on locally produced, rather than systemic, C1q. They also raise the idea that graft infiltrating B cells, often reported in cases of CAMR, could represent a source of local complement production that promotes graft injury progression.

ACKNOWLEDGMENTS

Data Statement

Results of the microarray experiments are available in the Gene Expression Omnibus (accession number: GSE51675).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Material.

Supplementary References.

Table S1. Demographic, clinical, and histological characteristics of the patients.

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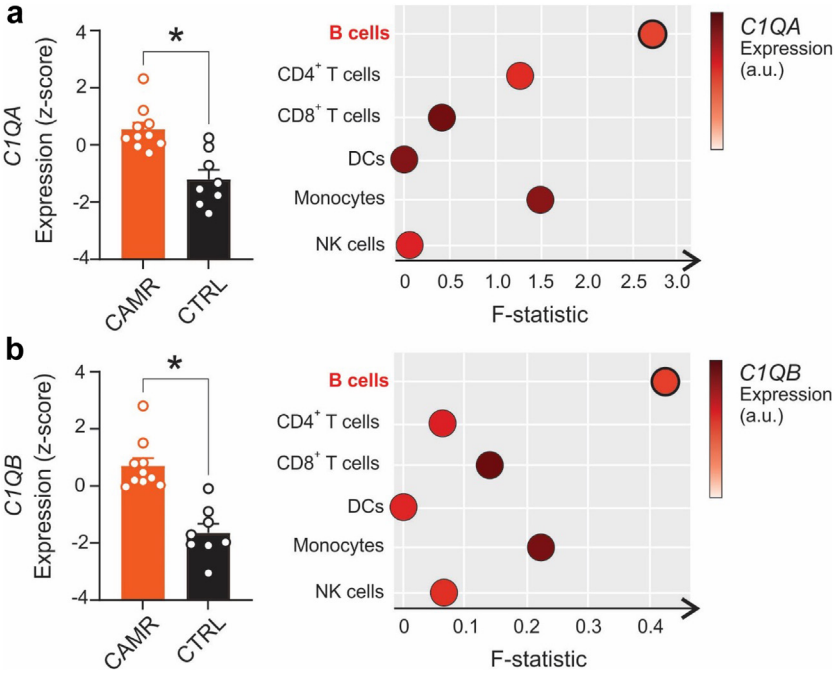

Figure 1. C1q-encoding genes in leukocyte subsets of CAMR and CTRL patients. (**a**) *C1QA* and (**b**) *C1QB* expression (left) and CellCODE analysis (right) to determine the association with different cell subtypes present in PBMCs from patients with CAMR versus CTRL. In CellCODE analyses, data points depict the average relative expression of each gene (color intensity) and its association for each major cell subset with the difference in expression observed (position in the x axis). Higher F-statistic indicates a stronger association. *$P < 0.01$. CAMR, chronic antibody-mediated rejection; CTRL, control.

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