

IgE in Antibody-Mediated Rejection A Novel Pathogenic Mechanism?

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It was nearly half a century ago that Colvin and Dvorak (1) identified infiltrating basophils and mast cells in kidney transplant rejection using simple light microscopy. They astutely recognized this finding to be “analogous to that reported in various delayed hypersensitivity processes in both experimental animals and man” (1). In 2009, following the recognition that antibody-mediated rejection was the most significant threat to long-term kidney allograft survival, Mengel *et al.* (2) used microarray technology to demonstrate that mast cell gene expression in scarred kidney transplant biopsies was associated with reduced graft survival and poor functional recovery.

Interestingly, despite the longstanding role of IgE in the activation of basophils and mast cells in autoimmune kidney diseases (*e.g.*, lupus nephritis) (3), the role of IgE in the pathogenesis of antibody-mediated rejection has not been explored in depth. Now, however, there is a growing body of evidence to support doing so. For example, in 2015, Rascio *et al.* (4) reported that there was upregulated type 1 IFN signaling in chronic antibody-mediated rejection, an intriguing observation given that IgE-mediated IFN- α mechanisms have been clearly shown to facilitate self-destructive responses in autoimmune disease (5). In *CJASN*, Rascio *et al.* (6) build upon their previous work and provide a compelling preliminary evaluation suggesting a role for IgE in antibody-mediated rejection of kidney transplants.

In this retrospective, single-center study, the authors evaluated multiple markers of an IgE-mediated immune response in 56 kidney transplant biopsies with Banff 2013 classified chronic active antibody-mediated rejection (7). These biopsies were compared with 80 kidney transplant biopsies obtained from patients with stable graft function and histology, as well as with 16 kidney transplant biopsies having at least moderate interstitial fibrosis and tubular atrophy. The authors used confocal microscopy to assess intragraft deposition of IgE, tryptase (a mast cell marker), and CD203 (an activated basophil marker). In a subset of patients with available serum samples ($n=40$ of 56 with antibody-mediated rejection, all controls), they measured serum levels of total IgE, circulating basophils, and myxovirus resistance protein 1 (a marker of IFN- α induction). In a further subset of randomly selected patients ($n=10$ with antibody-mediated rejection, ten controls), they used a modified Luminex assay to measure serum anti-HLA IgE levels.

The principal findings include observation of higher intragraft IgE deposition in antibody-mediated rejection biopsies versus controls. The pattern of IgE deposition in antibody-mediated rejection was quantitatively and qualitatively similar to that seen in six biopsies with active lupus nephritis and displayed colocalization with mast cell and basophil markers. The patients with antibody-mediated rejection showed lower serum IgE levels and higher serum basophil and myxovirus resistance protein 1 levels versus controls. Anti-HLA IgE antibodies were only detected in patients with antibody-mediated rejection, although at a very low level (162 ± 18 mean fluorescence intensity). Collectively, these data suggest that an IgE-mediated immune response, with resulting IFN- α induction and mast cell and basophil recruitment, is associated with antibody-mediated rejection in kidney transplants.

Although this is a provocative study suggesting a plausible pathogenic role of IgE in antibody-mediated rejection, there are several limitations that cannot be overlooked.

One limitation is that the majority of the results are predicated on tissue- and serology-based IgE detection methods with reagents whose sensitivity, specificity, and reproducibility have not been validated. It is especially critical that future studies document that the IgE antibodies used do not bind other Ig isotypes. With regard to the modified Luminex assay used in this study to detect serum IgE, even though the authors treated the serum samples with IgG-degrading enzyme of *Streptococcus pyogenes*, a cysteine protease reported to cleave human IgG (8), its effectiveness to limit IgG interference must be confirmed. Furthermore, as intriguing as the detection of anti-HLA IgE antibodies is, the mean fluorescence intensities are barely above background levels and must be interpreted with caution. Additional information on how the anti-IgE reagent was validated will be needed before such tests can be clinically implemented.

In a similar fashion, the results from this study will require validation with an independent cohort of samples. Although the authors included patients with “biopsy-proven chronic active antibody mediated rejection according to Banff 2013 criteria,” a significant proportion of their biopsies had no transplant glomerulopathy, peritubular capillaritis, or glomerulitis and was C4d negative (6). More granular pathologic data

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will be necessary to assure that all biopsies are representative of antibody-mediated rejection. Another recommendation would be to incorporate contemporary Banff criteria into future studies, as recent updates to diagnose antibody-mediated rejection include the incorporation of gene expression testing and elimination of an absolute requirement to detect donor-specific antibodies (9).

Future studies would also benefit from additional controls, namely comparison groups with significant inflammation (e.g., T cell-mediated rejection, BK virus nephropathy) to confirm that the findings are associated with antibody-mediated rejection and not overall inflammatory burden. The latter has not been ruled out because a higher number of circulating basophils identified in the antibody-mediated rejection group in this study is opposite to previous observations in SLE (10). Ideally, a general inflammatory marker, such as CD45, should be incorporated into future confocal microscopy studies to allow for a comparison of the degree of total inflammation as well as Banff i scores and t scores for all sample groups.

In the examples of antibody-mediated rejection and lupus nephritis provided in the work by Rascio *et al.* (6), a significant proportion of IgE deposits appears to be located within the cytoplasm of tubular epithelial cells. Although similar to the pattern of deposition previously reported in lupus nephritis versus normal kidneys (5), this nonetheless may reflect nonspecific tubular reabsorption in individuals with proteinuria compared with those without proteinuria and not necessarily a specific underlying pathophysiologic process. Thus, future studies should confirm the localization of IgE deposits; precisely differentiate tubular, interstitial, glomerular, and vascular deposition; and correlate these results with potential confounding factors, such as the degree of proteinuria. Such attention to detail will help strengthen the tenets put forth in the work by Rascio *et al.* (6).

In conclusion, this is a thought-provoking study that posits a novel pathogenic mechanism for antibody-mediated rejection and provides a framework for further investigation to elucidate novel diagnostic tools and therapeutic strategies. Given the significant threat that antibody-mediated rejection poses to the long-term success of kidney transplantation, further exploration of the potential role of IgE in its development is certainly warranted.

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References

- Colvin RB, Dvorak HF: Letter: Basophils and mast cells in renal allograft rejection. *Lancet* 1: 212–214, 1974
- Mengel M, Reeve J, Bunnag S, Einecke G, Sis B, Mueller T, Kaplan B, Halloran PF: Molecular correlates of scarring in kidney transplants: The emergence of mast cell transcripts. *Am J Transplant* 9: 169–178, 2009
- Charles N, Hardwick D, Daugas E, Illei GG, Rivera J: Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nat Med* 16: 701–707, 2010
- Rascio F, Pontrelli P, Accetturo M, Oranger A, Gigante M, Castellano G, Gigante M, Zito A, Zaza G, Lupo A, Ranieri E, Stallone G, Gesualdo L, Grandaliano G: A type I interferon signature characterizes chronic antibody-mediated rejection in kidney transplantation. *J Pathol* 237: 72–84, 2015
- Henault J, Riggs JM, Karnell JL, Liarski VM, Li J, Shirinian L, Xu L, Casey KA, Smith MA, Khatry DB, Izhak L, Clarke L, Herbst R, Ettinger R, Petri M, Clark MR, Mustelin T, Kolbeck R, Sanjuan MA: Self-reactive IgE exacerbates interferon responses associated with autoimmunity. *Nat Immunol* 17: 196–203, 2016
- Rascio F, Pontrelli P, Netti GS, Manno E, Infante B, Simone S, Castellano G, Ranieri E, Seveso M, Cozzi E, Gesualdo L, Stallone G, Grandaliano G: IgE-mediated immune response and antibody-mediated rejection. *Clin J Am Soc Nephrol* 15: 1474–1483, 2020
- Haas M, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, Castro MCR, David DSR, David-Neto E, Bagnasco SM, Cendales LC, Cornell LD, Demetris AJ, Drachenberg CB, Farver CF, Farris AB 3rd, Gibson IW, Kraus E, Liapis H, Loupy A, Nicleleit V, Randhawa P, Rodriguez ER, Rush D, Smith RN, Tan CD, Wallace WD, Mengel M; Banff meeting report writing committee: Banff 2013 meeting report: Inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions [published correction appears in *Am J Transplant* 15: 2784, 2015 10.1111/ajt.13517]. *Am J Transplant* 14: 272–283, 2014
- von Pawel-Rammingen U, Johansson BP, Björck L: IdeS, a novel streptococcal cysteine proteinase with unique specificity for immunoglobulin G. *EMBO J* 21: 1607–1615, 2002
- Loupy Alexandre, Haas Mark, Roufosse Candice, Naesens Maarten, Adam Benjamin, Afrouzian Marjan, Akalin Enver, Alachkar Nada, Bagnasco Serena, Becker Jan U, Cornell Lynn D, Clahsen-van Groningen Marian C, Demetris Anthony J, Dragun Duska, Duong van Huyen Jean-Paul, Farris Alton B, Fogo Agnes B, Gibson Ian W, Glotz Denis, Gueguen Juliette, Kikic Zeljko, Kozakowski Nicolas, Kraus Edward, Lefebvre Carmen, Liapis Helen, Mannon Roslyn B, Montgomery Robert A, Nankivell Brian J, Nicleleit Volker, Nickerson Peter, Rabant Marion, Racusen Lorraine, Randhawa Parmjeet, Robin Blaise, Rosales Ivy A, Sapir-Pichhadze Ruth, Schinstock Carrie A, Seron Daniel, Singh Harsharan K, Smith Rex N, Stegall Mark D, Zeevi Adriana, Solez Kim, Colvin Robert B, Mengel Michael: The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection. *Am J Transplant*, 2020 10.1111/ajt.15898
- Pellegrini C, Charles N: The deleterious role of basophils in systemic lupus erythematosus. *Curr Opin Immunol* 25: 704–711, 2013

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See related article, “IgE-Mediated Immune Response and Antibody-Mediated Rejection,” on pages 1474–1483.