Bad Memory: CD4 T Cell Presensitization Fosters Antibody-Mediated Kidney Transplant Rejection

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As stated above, the development of AMR or cAMR portends a poor prognosis. Unfortunately, the existing therapies aimed at preventing antibody-mediated damage are only partially or transiently effective. Physical removal of circulating DSA with plasma exchange temporarily removes the offending antibodies but does not decrease antibody production. Treatment with the terminal complement inhibitor eculizumab does ameliorate complement-mediated damage in the acute setting but does not appear to prevent the development of chronic injury presenting as transplant glomerulopathy. A pressing clinical need in this area is the development of immunomodulatory agents that selectively target DSA-secreting cells or the mechanisms responsible for their generation and long-term survival. Importantly, currently available therapies directed against antibody-secreting B cells and plasma cells, such as the anti-CD20 mAB rituximab and the proteasome inhibitor bortezomib, have not been consistently shown to reduce circulating DSA levels and antibody-mediated graft injury. A requirement for further progress toward identifying effective strategies is the development of animal-model systems that allow investigators to accurately dissect the complex immunologic mechanisms underlying the generation of de novo DSA.

In this issue, Gorbacheva et al. report the results of a clever and insightful experimental kidney transplant study in which a clear line is drawn between the presence of donor-specific, memory-phenotype CD4⁺ T cells and the development of a de novo, destructive, antidonor, IgG antibody response. The fully MHC-mismatched mouse model of life-sustaining kidney allotransplantation that was utilized in this study has the distinctive characteristic of being associated, in the naive state, with weak antidonor T cell and antibody responses that are insufficient, in the majority of animals, to cause rejection even in the absence of immunosuppressive therapy. Thus, it might be viewed as representing a somewhat precarious balance between effector and regulatory immune mechanisms—analogous, perhaps, to human kidney transplant recipients in a state of quasi-tolerance after medically directed or unintentional immunosuppression minimization or withdrawal. A key innovation of the study was to transfer CD4⁺ T cells from the spleens of mice that had been sensitized (6 weeks previously) to donor antigen via skin grafts into genetically identical mice that then received kidney allografts. In a control group, splenic CD4⁺ T cells from naive mice were transferred. In this way, the study very precisely isolated the immunologic consequences for the kidney transplant of pre-existing, donor-reactive, (memory) helper T cells in the absence of any other form of antidonor sensitization (i.e., DSA). The central finding was that mice which were “seeded” with donor-specific CD4⁺ memory T cells before transplantation consistently developed a form of rapid allograft rejection...
that bore the histologic hallmarks of AMR and lacked features suggestive of enhanced cellular rejection. This rejection was accompanied by large increases in DSA titers of multiple IgG isotypes compared with control groups. Furthermore, using carefully timed blocking and depletion strategies, the authors demonstrated that the accelerated graft rejection was not significantly mediated by the signature T helper 1 cytokine IFN-γ, CD8− ("cytotoxic") T cells, or persisting CD4+ T cells. Finally, the case for a predominantly humoral mechanism of rejection was further strengthened by the finding that B cell depletion (starting on the day of transplantation) substantially lowered the rejection rate and DSA titers of transplanted mice that had received donor-reactive CD4+ memory T cells.10 As one might expect for a single study, some of the mechanistic questions remain unanswered. For example, the critical site of T cell–B cell interaction and the specific memory T cell effector phenotypes and molecular mediators responsible for enhancing the production of DSA were not investigated. Also, as unfractonated CD4+ splenocytes rather than highly purified memory CD4+ T cells were transferred, a role for additional cell populations cannot be completely ruled out. Finally, in this model it may be possible that adoptively transferred effector T cells, rather than acting directly upon donor-antigen-specific B cells, served to release them from the suppressive effect of an endogenous regulatory cell population.14

Setting aside such finer details, the insight gained from this elegant study clearly has potential relevance to the immunologic complications of human kidney transplantation. First, it may provide further impetus for the development and prospective evaluation of assays to quantify the pretransplant frequency of donor-specific memory-phenotype T cells, for which some prognostic value has previously been reported.15,16 Additionally, the result of the CD4+ T cell depletion experiment carried out by Gorbacheva et al. suggests that even a brief time window (in this case 3–4 days) in which donor-specific memory T cells coexist with donor-antigen-responsive B cells may be sufficient to unleash a highly destructive antibody response.10 This highlights the need for immunosuppressive strategies that more reliably and potently suppress the memory T cell compartment.17 Specifically, agents which target intracellular signaling pathways, costimulatory receptors, metabolic profiles, and adhesion molecules that distinguish memory from naive T cells may prove to have value for better preventing rejection in transplant recipients with high levels of donor-reactive T cell memory.17 Finally, while any extrapolation of the results of Gorbacheva et al. to the late posttransplant period should be made with caution, it is worth noting that human immune monitoring studies are also beginning to reveal links between memory T cell profiles and long-term transplant stability including the occurrence of cAMR.18 One of the fascinating implications of the results of Gorbacheva et al. is that, under some circumstances, alloreactive CD4+ memory T cells may provide a potent stimulus to donor-specific B cells without also mediating a direct cellular assault on the transplanted kidney.10 This type of immunologic outcome could be the result of memory T cell trafficking and localization patterns, a partial regulation of their effector functions, or a T helper differentiation phenotype that favors the enhancement of B cell activation and maturation over that of cytotoxic responses. Through follow-up experiments to precisely track and functionally characterize adoptively transferred donor-specific memory T cells as they interact with B cells and regulatory cells in transplanted animals, it should be possible to gain more detailed answers to questions such as these. Similarly, a continued focus on profiling memory T cell repertoires and their associations with the de novo development of DSA over time in human kidney transplant recipients is likely to reveal whether these observations in mice have an important clinical correlate.

It remains to be seen whether our growing body of knowledge regarding the diversity of donor-reactive T cell phenotypes and their effect on renal allograft survival (including the development of AMR and cAMR) can be honed to an effective, "personalized" approach involving immune monitoring and immunosuppression tailoring. However, as illustrated by the clinically inspired experimental work of Gorbacheva et al., this is a field in which animal-based studies and patient-oriented research are beginning to harmonize and, together, have the potential to positively affect the long-term outcomes of kidney transplant recipients.

DISCLOSURES
None.

REFERENCES


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