Transplant rejection: Mind your T-cell language

To the editor—In the June issue of *Nature Medicine*, Pratt *et al.*[1] report on how local synthesis of the complement component C3 regulates acute renal transplant rejection. They present elegant experiments to show that renal allograft rejection is tempered in the absence of local production of C3. These findings, as described in the accompanying News & Views article[2], underscore the often underappreciated role of the innate immune system in allograft rejection. However, the important question addressed in this study is how the complement system managed to markedly influence the immune process that leads to rejection. Unfortunately, the conclusions in this regard are vague.

The authors seem to imply in the Discussion section that local production of complement affects the priming of T cells by directly increasing the efficiency of T-cell engagement with donor antigen. However, it is not clear what T cells they are referring to. Are they naive T cells or previously primed T cells? Is it the engagement of naive T cells with antigen in the spleen or engagement of previously primed T cells with antigen in the graft? These are important distinctions as naive T cells and activated T cells have disparate homing patterns and activation requirements. Antigen-experienced (primed) T cells, such as effector and memory T cells, enter non-lymphoid tissues during inflammation and engage antigen there, whereas naive T-cell trafficking and antigen engagement seem to be restricted to secondary lymphoid organs[3–5].

The data provided by the authors clearly demonstrate that previously primed T cells express complement receptors and that their proliferation to proximal tubular epithelial cells is defective in the absence of C3 production. However, no mention is made of whether naive T cells share these properties with their activated counterparts. Similarly, data are provided to show that activated T cells that express complement receptors can be found within graft tissue, but no data are provided to examine whether naive T cells enter the allograft. Therefore, we cannot eliminate the possibility that defective priming of naive T cells in the spleens of mice that received C3-deficient allografts is due to defective activation, migration and/or function of graft dendritic cells. The authors imply in their discussion that this possibility is low on their list because "*...in vitro* data suggest that locally produced C3 can exert an effect on T-cell function independently of B7 or MHC expression." The authors, however, disregard the fact that what they studied *in vitro* were activated and not naive T cells. This confusion could have been avoided if precise terminology was used when referring to T cells: Are they naive or are they previously primed? Perhaps it is time for all of us who study transplantation immunology to exemplify the fundamental immunologists and mind our T-cell language.

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Sacks and Pratt reply—Dr. Lakkis rightly points out that in explaining mechanisms by which local complement exerts regulation, we favor direct effects on the T-cell interaction with donor antigen. As this interaction is taking place in the graft and much of our *in vitro* work is based on the use of primed T cells, we recognize that T cells of effector/memory phenotype could well be the T cells involved. However, we do not exclude an effect of complement on unprimed cells entering the graft. Indeed, the recent work of Kreisel *et al.* raises the possibility that first encounter of T cells with donor antigen may take place in the graft[6]. Migration of T cells and maturation in peripheral lymphoid organs might then follow[7]. As Lakkis notes, in experiments with proximal renal tubular epithelial cells (PTECs), it would be of considerable interest to define the responses of naive T cells in such a system. However, the low level of responses to PTECs by naive T cells precludes such analysis.

Although we did not address in detail the question of phenotype of intragraft cells, we agree with Lakkis that these are likely to be of effector/memory type. Expression of the complement receptor detected by antibody to CR1/2 seemed to be restricted to graft-infiltrating cells of the helper T-cell phenotype. However there are other more widely distributed complement receptors on mouse T cells (for example, Crry), and these may have a role in interactions between T cells and graft epithelial cells. Questions remain open regarding the role of complement in activation and migration of donor dendritic cells (DCs), and what effects complement-mediated stimulation of DCs may have on the priming of naive T cells. Although an effect on migrating graft DCs may indeed play a part, donor DCs are short lived, and most of the donor–recipient cell interaction in the later post-transplantation period is likely to be between primed T cells and graft parenchymal tissue.

Finally, we agree with Lakkis that more attention should be given in

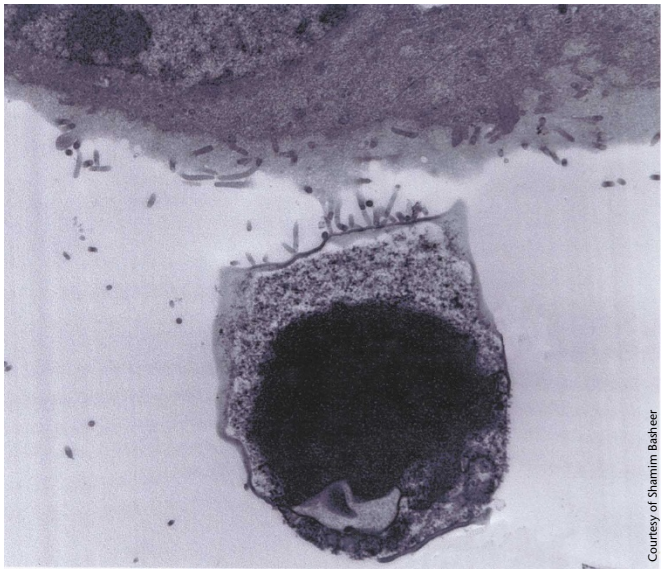

Fig. 1 Cognate interaction between T cell and epithelium