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Editorial

Accommodation: How You See It, How You Don't

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Accommodation refers to a condition in which a transplant sustains little or no injury and functions normally despite the presence of anti-donor antibodies in the circulation of the recipient. We first observed accommodation in the 1980's in the setting of ABO-incompatible kidney transplantation. At that time, 75% of kidneys incompatible for blood group-A or -B were rejected within 3 months. However, Guy Alexandre and a few others found that rejection could be averted and enduring function achieved if the offending antibodies were depleted at the time of surgery. Probing the surprising success we found that in some recipients the anti-blood antibodies returned to the circulation and in all cases the kidneys continued to express the corresponding antigen. We figured then that the grafts might have acquired resistance to injury (1). After observing a similar phenomenon in cardiac xenografts, we applied the term 'accommodation' to denote the possibility that the graft and/or recipient had changed in such a way that what was once lethal was no longer so (2). Notwithstanding occasional reports on highly sensitized recipients (3), accommodation has been seen rarely in recipients presensitized to HLA (perhaps because anti-HLA antibodies include high affinity IgG, presumably reflecting somatic hypermutation characteristic of T cell-dependent and not T cell-independent responses that attack blood group and xenogeneic antigens) and *de novo* produced anti-HLA antibodies presage bad outcomes (4). Whether accommodation can be achieved reliably in presensitzed recipients, how it occurs and why it is not seen more often should compel interest.

In this issue of AJT, Chen et al. (5) report that monkeys previously sensitized by skin transplantation and treated with cobra venom factor (CVF) and with conventional immunosuppression agents can accept kidney grafts. The monkeys had anti-donor antibodies both before and after transplantation and the grafts had normal histology indicating the establishment (or development if you wish) of accommodation. Clearly then, accommodation can be achieved in presensitized primates and that answer should excite clinicians and scientists.

Although Chen and co-workers did not attempt to test how accommodation occurs, their discussion nicely frames this question by commenting that CVF might "bring about" accommodation or "allow it to assert itself" by preventing destruction of the graft. The latter explanation seems most appealing to the authors as they call the CVF used "an extremely potent anti-complement protein". This CVF might allow anti-MHC antibodies to induce protective changes, as described independently from the laboratories of Dalmasso (6), Delikouras (7) and Jindra (8), rather than injury. On the other hand, the CVF used might actually induce accommodation, not by inhibiting complement but rather by activating it. The CVF from *Naja kaouthia* (Naja kaouthia CVF) activates both C3 and C5, generating C3a and C5a and it generates small amounts of terminal complexes that can insert in cell membranes, causing 'reactive lysis' of susceptible cells, like heterologous erythrocytes, and possibly protection of less susceptible cells, such as endothelial cells. The answer to whether it is anti-MHC antibodies and/or activated complement proteins (or something else) that protects grafts from lethal injury could eventuate in new therapeutics in many fields.

If anti-MHC antibodies, which some think are made by most graft recipients, can induce both rejection and accommodation, why is accommodation not seen more often? Chen et al. (5) seem to think the amount of anti-MHC antibody produced explains the outcome—large amounts cause rejection, small amounts accommodation. Consistent with this view they note that monkeys treated with CVF had lower levels of anti-donor antibodies than monkeys not given CVF and take from this result that "... CVF significantly attenuated [the] induced antibody response ...". However, we and others before us have observed that perfused organs and organ grafts can absorb huge amounts of anti-donor antibodies from blood and in some cases anti-donor antibodies may not be seen at all until a graft is rejected or removed (9). Thus, if accommodation allows a graft to continue being perfused it will enable removal of much or all of the anti-MHC antibody produced, while rejection, whether triggered or not by antibodies, will prevent absorption by decreasing the rate blood flows through the graft. One implication of the second potential mechanism is that assays for anti-donor antibodies may well underestimate or entirely miss humoral responses to a graft donor and hence accommodation. If that is so then

we will not see accommodation in many cases when it is present and our original definition of accommodation, the simultaneous presence of anti-donor antibodies and an unblemished graft, should be abandoned. Nor do the results of Chen et al. encourage detection of "protective genes or proteins" as a marker of accommodation because they show (but do not discuss), that these genes and proteins are also seen in rejection. To understand better what accommodation is and how prevalent it may be, we need a better way of seeing it.

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