more apoptosis. The deciphering of downstream signals such as the activity of PI3K in the endothelium in response to relative hypoxia might also shed some light on this provocative result.

Looking forward therapeutically
The observations that loss of the IR and IGF-1R signaling pathways appear to counter the response to relative hypoxia and do not alter vasculogenesis in the absence of relative hypoxia suggest that it is not insulin and IGF-1 signaling in endothelial cells alone that promotes neovascularization in diabetes. It also prompts us to look to other cell types in the retina for a response to diminished insulin action. The experiments of Kondo et al. (6) do not address the role of retinal glia or neurons in vascular regulation. Answers to these questions will directly impact therapeutic choices for diabetic patients. Kondo et al. suggest that, in diabetes, inhibition of retinal insulin or IGF-1 signaling in the eye might be beneficial, however, in the context of what is understood to be systemically reduced insulin signaling in these disease states, therapeutic blocking of insulin signaling appears counterintuitive. Identification of specific molecules at the intersection of the HIF-1 and insulin and IGF-1 signals, as well as a thorough understanding of how the varied cell types in the retina respond to the diabetic state, will necessarily precede therapeutic trials to prevent loss of vision.


Tolerance: Of mice and men

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Little is known about the effect of an individual’s immune history on his or her response to an allogeneic tissue transplant. An important study (see the related article beginning on page 1887) now reveals that individuals harboring virally-induced memory T cells that are cross reactive with donor alloantigen are resistant to conventional strategies designed to induce transplant tolerance.


Enormous progress has been made in the field of transplantation during the past three decades, due in large part to the availability of effective immunosuppressive drugs. Although all of these agents suppress the immune response nonspecifically with respect to antigen, the most effective ones exhibit sufficient selectivity so that rejection can be avoided without undue compromise of the host’s ability to respond to microbial pathogens. Nevertheless, patients on immunosuppressive medications are constantly walking a tightrope between the consequences of too little suppression (i.e., rejection) and of too much suppression (infections or cancer) of their immune system. In addition, even in patients without complications due to their immunosuppression, there is an inexorable loss of transplanted organs due to chronic rejection at a rate of approximately 5% per year (1).

For these reasons, ever since the description of acquired tolerance to allografts in mice by Medawar and colleagues appeared in 1953 (2), a major goal of both clinicians and immunologists in the field of transplantation has been the induction of tolerance in transplant recipients. What has been most frustrating about this quest has been the fact that a very large number of successful approaches to the induction of tolerance have been reported in rodent models, but have failed when attempted in large animals, especially in nonhuman primates and in humans (Table 1). Indeed, as clinical results of organ transplants using standard immunosuppression are so good, at least in the short term, many clinicians are no longer interested in
to tolerance induction is not complete argument that the reason that resistance
tions (5). Adams and colleagues
episodes with intercurrent viral infec-
tional association of clinical rejection
before as a possible reason for the fre-
they point out, has been proposed
infectious cells, a hypothesis, which, as
between the pathogens and the allo-
sure confirmed that the priming led
following viral exposures is that the
ability to overcome tolerance induc-
tion in this protocol is dependent on
the dose of sensitized cells. To sub-
stantiate this hypothesis, they de-
monstrate a dose-dependence of in-
hibition of tolerance induction by
adoptive transfer of sensitized re-
cipient cells to animals that are then
exposed to the tolerance-inducing
regimen. The only caveat to their con-
clusion is that the sensitized cells
used for the adoptive transfer were
from animals sensitized by previous
skin grafts, not by viral exposures,
and whether the effectiveness of these
two cell populations is equivalent in
vivo remains to be demonstrated.

Nevertheless, this study makes a
strong argument for the importance
of previous antigen exposure in
determining the outcome of proto-
cols designed to induce tolerance
through mixed chimerism. The data
clearly support the practice of testing
for potential cellular as well as
humoral sensitization against the
donor prior to carrying out such pro-
tocols clinically, even in cases for
which there has been no known expo-
sure to the donor antigens.

On the other hand, the implications
of these studies for the more
general question of why it is more
difficult to induce tolerance in large
versus small animals, are not entirely
clear. Indeed, the induction of toler-
ance through mixed chimerism is
one of the few methodologies (Table
1) that has been shown to work not

<table>
<thead>
<tr>
<th>Method</th>
<th>Mice</th>
<th>Primates and humans</th>
</tr>
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<tbody>
<tr>
<td>Enhancement</td>
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<td></td>
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<tr>
<td>DST</td>
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<tr>
<td>Peptides</td>
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<tr>
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<tr>
<td>Calcineurin inhibitors</td>
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<tr>
<td>Anti-CD24</td>
<td>+</td>
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<tr>
<td>Anti-CD25</td>
<td>+</td>
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</tr>
<tr>
<td>Total lymphoid irradiation</td>
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<td>+/-</td>
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<tr>
<td>Costimulatory blockade</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Chimerism</td>
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</tbody>
</table>

ALS, antilymphocyte serum; DST, donor-specific transfusion.

testing new approaches to tolerance
induction unless their effectiveness
has already been demonstrated in
large animal models.

But why should there be such a dif-
ference in the ability to induce toler-
ance in mice versus large animal
species? Since it is much easier and
far less expensive to carry out experi-
ments in mice than in large animals,
an answer to this question could have
important practical as well as theo-
retical implications. In this issue of
the JCI, Adams et al. (3) propose a
potential reason for the discrepancy.
In an elegant series of experiments,
they show that sequential exposure
to sublethal infections by certain
pathogenic viruses makes mice more
resistant to tolerance induction by a
protocol previously shown by this
group to result reproducibly in
mixed chimerism and tolerance in
mice (4). This protocol involves
treatment of recipients with a short
course of costimulatory blockade,
busulfan, and a donor bone marrow
infusion. Assays for alloantigen-primed
T cells in vitro following viral expo-
sure confirmed that the priming led
to cells with specificity cross-reactive
between the pathogens and the allo-
genic cells, a hypothesis, which, as
they point out, has been proposed
before as a possible reason for the fre-
quency association of clinical rejection
episodes with intercurrent viral infec-
tions (5). Adams and colleagues
argue that the reason that resistance
to tolerance induction is not complete

only in mice, but also in large animals
(6, 7) and most recently in humans (8,
9). Furthermore, the most obvious
difference between small and large
animal species with regard to toler-
ance induction is in the response to
vascularized organ allografts (10).
Skin graft survival is the hardest to
prolong (11) unless the grafts are
placed after a vascularized graft from
the same donor strain, which sug-
gests that vascularized grafts are
themselves tolerogenic (12). Thus, an
alternative study design, utilizing a
protocol for induction of tolerance
to a vascularized organ allograft,
might have been more suitable for
answering this general question.

Among the differences between
rodents and large animals that have
been suggested to account for this
discrepant behavior in response to
vascularized grafts are the markedly
different tissue expression patterns
of class II MHC antigens (13). These
antigens, which are the most potent
stimulators of the helper pathway in
rejection reactions, are notably absent
from the vascular endothelial cells of
rodents, but expressed constitutively
in all large animals that have been
studied, including humans. Indeed,
in our own laboratory, we have
shown, using intra-MHC recombi-
nant lines of pigs, that matching for
class II antigens permits uniform
induction of tolerance to renal allo-
grafts by a short course of cyclo-
sporin (14), one of the many methods
that allows tolerance induction to
vascularized organ allografts in mice
across full MHC barriers (Table 1).
We have also demonstrated the
importance of an intact thymus to
the induction of tolerance by this
route (15), something that is marked-
ly affected by age, stress, drugs, and
infection — all of which may also be
relevant to the difference between
large and small animal models.

Thus, I congratulate the authors of
this paper for emphasizing the
importance of previous antigen
exposure on the outcome of allo-
genic bone marrow transplantation
and for helping to elucidate the
mechanism of this relationship.
However, I expect that differences in
prior antigen exposure will be only
one of the potential reasons for the marked differences that have been encountered between mice and primates in the ease with which tolerance can be induced.