the future, unique properties of these self-assembled systems may be identified. In the case of the $NbSe_2/TiSe_2$ superlattices, the superconductivity of the system may be revealing. Bulk $NbSe_2$ superconducts below about 7 K, whereas $TiSe_2$ is not known to superconduct. Preliminary results have shown superconductivity in some of these superlattice structures (*7*). Tailoring of optical and magnetic properties will also be possible with this approach, which could yield an unlimited number of new compounds.

References

1. M. Noh, J. Thiel, D. C. Johnson, *Science* **270**, 1181 (1995).
2. E. G. Bauer *et al.*, *J. Mater. Res.* **5**, 852 (1990).
3. K. Ueno, K. Saiki, T. Shimada, A. Koma, *J. Vac. Sci. Technol. A* **8**, 68 (1990); K. Ueno, A. Koma, F. S. Ohuchi, B. A. Parkinson, *Appl. Phys. Lett.* **58**, 472 (1991); F. S. Ohuchi, B. A. Parkinson, K. Ueno, A. Koma, *J. Appl. Phys.* **68**, 2168 (1991).
4. C. Auriel, A. Meerschaut, R. Roesky, J. Rouxel, *Eur. J. Solid State Inorg. Chem.* **29**, 1079 (1992).
5. G. A. Weigers, A. Meetsma, R. J. Haange, J. L. de Boer, *Mater. Res. Bull.* **23**, 1551 (1988).
6. G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **254**, 1312 (1991).
7. D. C. Johnson, paper 635 at the 188th meeting of the Electrochemical Society, Chicago, IL, 8 to 13 October 1995.

Unraveling Immune Privilege

J. Wayne Streilein

Immune privilege, first described more than a century ago, protects tissue grafted to certain sites—the eye, testis, and brain, for example—from rejection. At first, immunologists accepted (and were satisfied with) Medawar's original explanation for this phenomenon (*1*). Medawar's view was that immune privilege was actually "immune ignorance"; privileged sites were isolated behind blood-tissue barriers and lacked lymphatic drainage. Antigenic material, trapped inside these sites, remained invisible to the immune system. As it turns out, nothing could be further from the truth.

In the 1970s, it became clear that foreign tissues in privileged sites could eventually evoke antigen-specific systemic immunity (*2*) and that certain privileged sites (such as the testis) had extensive efferent lymphatic pathways (*3*). Immune ignorance was no longer a valid explanation of privilege. Rather, the systemic immune apparatus can recognize antigens in privileged sites and cooperates to create and sustain a graft-friendly environment. As part of this renaissance, a report in this issue by Griffith *et al.* (*4*) shows that the constitutive expression of Fas ligand (FasL) on parenchymal cells within a well-studied privileged site—the anterior chamber of the eye—contributes to its privilege. In a recent issue of *Nature*, another group reported a similar finding for Sertoli cells of the testis (*5*).

These two papers illustrate two distinct aspects of immune privilege: privileged sites and privileged tissues. Immune-privileged sites are regions of the body where grafts of foreign tissue survive for extended periods (even indefinitely), compared to conventional (nonprivileged) sites. Griffith *et al.* (*4*) show how FasL may help to maintain the integrity of immune-privileged sites such as the eye. They report that Fas^+ lymphoma cells are triggered to undergo apoptosis when exposed in vitro to explants of cornea and iris–ciliary body from eyes of normal mice, but not from eyes of *gld* mice (which do not express FasL). FasL expression in the anterior chamber equips the site to delete by apoptosis Fas^+ T cells that enter the site, and lack of FasL expression may interfere with immune privilege.

By contrast, immune-privileged tissues resist immune rejection when grafted into conventional (nonprivileged) sites. In the experiment by Bellgrau *et al.*, testis cells grafted from C57BL/6 mice into a nonprivileged site (renal capsule) of BALB/c mice could survive indefinitely, whereas similar grafts prepared from *gld* C57BL/6 mice were rejected. Survival of grafts from normal mice correlated with constitutive expression of FasL on Sertoli cells, and the authors concluded that FasL expression triggers apoptosis in Fas^+, antigen-activated T cells of the recipient that engage the testis graft. Thus, constitutive expression of FasL may be crucial for the maintenance of both immune-privileged sites and immune-privileged tissues.

Immune-privileged sites and tissues
Anterior chamber of the eye
Cornea
Retina
Brain
Hair follicles
Cartilages
Liver
Adrenal cortex
Pregnant uterus
Placenta
Ovary
Testis
Prostate
Tumors
Hamster cheekpouch

Multiple features enable privileged sites to accept foreign grafts: blood-tissue barriers (in the eye and brain); absence of efferent lymphatics (eye); direct drainage of tissue fluid into the blood (eye and brain); integrity of the spleen (eye) (*6*); establishment of a potent immunosuppressive microenvironment containing growth factors [transforming growth factor–β (TGF-β) in the eye, brain, placenta, and testis] (*7*); neuropeptides [α-melanocyte–stimulating hormone, vasoactive intestinal peptide, and calcitonin gene–related peptide (CGRP) in the eye] (*8*); soluble and membrane-bound inhibitors of complement activation and fixation (anterior chamber of the eye) (*9*, *10*); and now FasL expression on cells of the ocular anterior segment (*4*).

Privileged tissues are characterized by other features: intratissue structural barriers, such as extensive tight junctions among parenchymal cells (Sertoli cells and retinal pigment epithelium); elaborate surface expression of hyaluronic acid (placenta and trabecular meshwork of the eye); reduced or absent expression of class I and II major histocompatibility complex molecules (brain, eye, and placenta); expression of class Ib molecules (placenta); release of soluble class I molecules (liver) (*11*); secretion of immunosuppressive cytokines (TGF-β in the cornea) (*12*) and corticosteroids (gonads); and now constitutive expression of FasL on parenchymal cells (testis) (*5*).

The biologic meaning of immune privilege extends well beyond experiments with tissue grafts. Antigenic materials placed in privileged sites, such as the anterior chamber of the eye, evoke a remarkable state of deviant systemic immunity in which the usual mediators of immunogenic inflammation (delayed hypersensitivity T cells and complement-fixing antibodies) are curtailed, while others (cytotoxic T cells and noncomplement-fixing immunoglobulin G antibodies) are enhanced (*13*–*15*). Termed anterior chamber–associated immune deviation (ACAID), this stereotypic systemic response to ocular antigens is dictated by features of the eye itself. After injection of antigen into the eye, intraocular dendritic cells pick up antigen locally and migrate via the blood to the splenic white pulp where antigen-specific regulatory and effector T cells (chiefly class I–restricted $CD8^+$) are activated. ACAID emphasizes that privilege is actively acquired and maintained, and that the immune system itself must participate.

A recent report in *Science* by Tafuri *et al.* (*16*) makes these points quite dramatically. Transgenic CBA female mice with anti-K^b

The author is in the Schepens Eye Research Institute, Harvard Medical School, Boston, MA 02114, USA. E-mail: WayneS@vision.eri.harvard.edu

T cell receptors were mated with allogeneic C57BL/6 males (K^b); expression of K^b on fetal tissues significantly influenced the mother's T cell repertoire and reactivity. Pregnant females with a high frequency of anti-K^b T cells were unable to reject K^b-bearing tumor cells implanted subcutaneously. Upon parturition, alloreactivity was regained, and the tumor cells were eliminated. Thus, immune privilege at the maternal-fetal interface is expressed systemically, is actively acquired, and can be transient (as is pregnancy).

What is the biological importance of immune privilege? The results of Tafuri *et al.* (*16*) suggest that immune privilege is necessary for the success of pregnancy. Immune privilege in the anterior chamber of the eye is critical to the avoidance of stromal keratitis, a blinding disease of the cornea that accompanies ocular infection with herpes simplex virus–type 1 (HSV-1). In mice the incidence and severity of HSV-1 keratitis rises dramatically in eyes in which privilege has been lost (*17*). Similarly, immune privilege protects against experimental autoimmune uveoretinitis evoked by eye-specific autoantigens (*18*). Finally, orthotopic corneal allografts are the most successful of all solid-organ transplants in humans, because the eye is a privileged site and the cornea is a privileged tissue. Corneal grafts placed in eyes that have lost immune privilege suffer acute rejection (*19*). Restoration of privilege to such "high-risk" eyes should allow acceptance of corneal allografts that restore vision. Similar strategies may promote the success of other solid-tissue allografts and prevent autoimmune and immunopathogenic diseases of privileged sites and tissues.

References

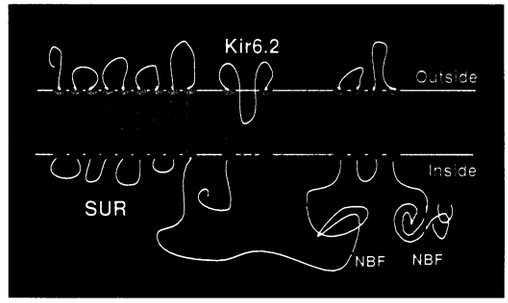
1. P. B. Medawar, *Br. J. Exp. Pathol.* **29**, 58 (1948).
2. H. J. Kaplan and J. W. Streilein, *J. Immunol.* **118**, 809 (1977).
3. W. B. Neaves and R. E. Billingham, *Transplantation* **27**, 127 (1979).
4. T. S. Griffith, T. Brunner, S. M. Fletcher, D. R. Green, T. A. Ferguson, *Science* **270**, 1189 (1995).
5. D. Bellgrau *et al.*, *Nature* **377**, 630 (1995).
6. H. J. Kaplan and J. W. Streilein, *ibid.* **251**, 553 (1974).
7. G. A. Wilbanks and J. W. Streilein, *J. Immunol.* **146**, 2610 (1991).
8. A. W. Taylor and J. W. Streilein, *ibid.* **153**, 1080 (1994).
9. K. Shimada, *Invest. Ophthalmol. Visual Sci.* **9**, 304 (1970).
10. N. S. Bora *et al.*, *ibid.* **34**, 3579 (1993).
11. S. V. Spencer and J. W. Fabre, *Transplantation* **44**, 141 (1987).
12. P. T. Khaw *et al.*, *Invest. Ophthalmol. Visual Sci.* **33**, 3302 (1992).
13. J. Y. Niederkorn and J. W. Streilein, *J. Immunol.* **131**, 2670 (1983).
14. J. W. Streilein, J. Y. Niederkorn, J. A. Shadduck, *J. Exp. Med.* **152**, 1121 (1980).
15. J. W. Streilein, *Curr. Opin. Immunol.* **5**, 428 (1993).
16. A. Tafuri, J. Alferink, P. Moller, G. J. Hammerling, B. Arnold, *Science* **270**, 630 (1995).
17. W. McLeish *et al.*, *Reg. Immunol.* **2**, 235 (1989).
18. Y. Hara *et al.*, *J. Immunol.* **148**, 1685 (1992).
19. Y. Sano, B. R. Ksander, J. W. Streilein, *Invest. Ophthal. Visual Sci.*, in press.

UPDATE

ATP-Sensitive K^+ Channels: Paradigm Lost, Paradigm Regained

Louis H. Philipson

Potassium channels set the resting membrane potential in many kinds of cells and thereby regulate their electrical activity and ion transport. One kind of K^+ channel, K_{ATP}, is inhibited by cytosolic adenosine triphosphate (ATP), thus coupling the metabolic state of the cell to membrane electrical events. The currents carried by these channels have been most thoroughly studied in pancreatic islet ß cells, where they regulate insulin secretion in response to glucose.



Partners. The inward rectifier Kir6.2 combines with the sulfonylurea receptor (SUR) to generate K_{ATP}.

Clues to the molecular identity of the K_{ATP} channels were revealed when the sulfonylurea receptor (SUR) was cloned (*1*) and mutations in SUR were found in several cases of persistent hyperinsulinemia and hypoglycemia of infancy (PHHI) (*2*). Sulfonylureas, the principal treatment for adult onset diabetes, block ß cell K_{ATP} channels. Yet SUR itself does not form the ion-conducting part of the K_{ATP} channel. Instead, as proposed in our previous Perspective (*3*), sulfonylurea-sensitive K_{ATP} is likely formed by an interaction between an inward-rectifier K^+ channel and SUR, which is a member of the ATP-binding cassette protein family. In this issue of *Science*, Inagaki and coworkers have verified this idea and found the right match for SUR—an inward rectifier K^+ channel called Kir6.2 (*4*).

Until now, K^+ channel subunit architecture has been defined by the minimal structure: the P (pore) domain and two flanking transmembrane segments that can be part of a much larger protein (see figure). In the current paradigm, functional channels are formed from tetrameric arrays of homologous subunits (*5*). The parsimonious assumption would be that K_{ATP} would also fit this paradigm. Instead, Inagaki *et al.* have shown that SUR, a protein with no obvious function other than that of binding drugs (*1*, *3*), confers both ion channel activity and K_{ATP}-like pharmacological sensitivities on Kir6.2. A new member of the inward rectifier K^+ channel family, Kir6.2 cannot conduct ions when expressed alone. This dependence on other molecules for optimal activity is an extreme version of a property displayed by some other inward rectifiers—the enhancement of their current by coexpression with similar proteins or G proteins (*6*, *7*).

What is the relation between SUR and its channel? Ten or more inward-rectifier channels may aggregate to form a large complex (*6*); does SUR physically associate with such a complex?

The reconstitution of K_{ATP}-like functions by combining SUR with an inward rectifier of minimal intrinsic activity is more than a curious paradox; it also recalls a model recently described for regulation of the protein critical in cystic fibrosis, CFTR (*8*). Higgins has reviewed evidence suggesting that CFTR and other ATP-binding cassette-containing proteins may be regulators of channels and pumps. We now have our first glimpse of the new paradigm for K_{ATP}.

The author is in the Department of Medicine and is on the Committee on Cell Physiology, University of Chicago, Chicago, IL 60637, USA. E-mail: l-philipson@uchicago.edu

References

1. L. Aguilar-Bryan *et al.*, *Science* **268**, 423 (1995).
2. P. M. Thomas *et al.*, *ibid.*, p. 426.
3. L. H. Philipson and D. F. Steiner, *ibid.*, p. 372.
4. N. Inagaki *et al.*, *ibid.* **270**, 1166 (1995).
5. L. Salkoff and T. Jegla, *Neuron* **15**, 489 (1995).
6. G. Krapivinsky *et al.*, *Nature* **374**, 135 (1995).
7. P. Kofuji, N. Davidson, H. A. Lester, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 6542 (1995); Y. Kubo *et al.*, *Nature* **364**, 802 (1993).
8. C. F. Higgins, *Cell* **82**, 693 (1995).