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Amniotic membrane as a biological dressing in the management of burns

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This report details observations in 90 patients with dermal depth burns treated using amniotic membrane. The patients were divided into three subgroups: superficial dermal, intermediate dermal and deep dermal burns diagnosed clinically. All patients were dressed with amniotic membrane which was changed daily. The amniotic membrane relieved the discomfort of dressing changes, postoperative pain and oozing and allowed rapid epithelialization and early healing in superficial and intermediate depth dermal burns. In deep dermal burns the membrane was dissolved because of slough in the burn wound. After removal of the slough the amniotic membrane helped in rapid regeneration of epithelium and early healing.

Introduction

The role of porcine heterografts and cadaver homografts (Miller et al., 1967; Brown et al., 1953; Artz et al., 1972; Miller and White, 1972) in the management of burns is well established, but the prohibitive cost of the former and the lack of popularity of the latter because of cultural and social constraints in India have restricted their use in our country. Placental membranes which are easily available, and do not require any specialized and expensive processing or storage facilities, are a promising form of treatment.

The role of amniotic membrane for covering partial thickness burns is well established (Pigeon, 1960; Dino et al., 1966; Golocho et al., 1974; Bose, 1979; Piserchia and Akenzua, 1981; Viswanath Rao and Chandrasekharan, 1981; Haberal et al., 1987). It decreases bacterial count in the burn wound (Robson and Krizek, 1973) and contaminated granulation tissue (Eade, 1958) and is effective either for its covering effect (Morris et al., 1966) or by the presence of lysozyme and progesterone (Galask and Snyder, 1970). It is also economical, easily available, alleviates pain and promotes epithelialization (Thomson and Parks, 1981; Haberal et al., 1987).

Dermal burns vary in thickness and clinical characteristics as well as their natural course of healing. We have studied the role of amniotic membrane as a biological dressing in dermal burns of varying thickness to define clearly the type of dermal burns in which it is useful.

Materials and methods

Fetal membranes obtained fresh from caesarean section deliveries were kept in sterile containers at 4°C. No special screening of donors for viral infections was done. Under sterile conditions the chorion was removed and the isolated amnion was washed with four rinses of sterile saline and then rinsed with 0.25 per cent sodium hypochlorite solution (0.000588 g free chlorine per million) and kept at 4°C in small polythene bags containing gentamicin solution and 0.25 per cent sodium hypochlorite solution. Immediate use is preferable although it can be stored for up to 48 h. This study included 90 pateints with dermal depth burns divided into Group I, controls, and Group II, amniotic membrane-treated patients. Each group was further split into three subgroups of 15 patients each and comprised patients with: (1) superficial depth dermal burns, (2) intermediate depth dermal burns and (3) deep dermal burns. Many years of close observation of the clinical characteristics and natural course of dermal burns provided the following criteria for identifying each of the above categories:

1. Superficial dermal burns are painful and sensitive to pin prick. They develop blisters and are moist. They heal in 11–14 days.
2. Intermediate depth dermal burns are painful, sensitive to pin prick and appear moist. They do not develop blisters. Their surface appearance is a diffuse pink with mottled white areas. They heal in 21–28 days, if sepsis is under control.
3. Deep dermal burns are relatively dry, painless, insensitive to pin prick and appear diffuse white with mottled pink areas. They generally heal in 31–42 days if not infected, otherwise they become converted to full skin loss burns.

All wounds were initially débrided and cleaned using 0.5 per cent Savlon and saline. In Group I, the wounds were dressed with 1 per cent silver sulphadiazine cream and the dressings were changed daily until complete healing had occurred or they had been converted to deep burns. In Group II patients, after thorough cleaning of the wound, the amniotic membrane was applied and covered with gauze pads and bandaged. The dressing was changed every 24 h, if the amniotic membrane appeared to have dissolved it was reapplied, if it appeared intact it was allowed to remain and only the outer gauze was changed, subsequent dressings were changed every third day. The burn wounds were observed until complete healing took place.

These patients and their wounds were observed for (a) symptomatic relief of pain, oozing, discomfort during

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dressing changes and in the intervening period, (b) any increase in the amount of discharge or sepsis, (c) total time taken for complete healing and (d) subsequent development of scar hypertrophy.

Results

Control patients

Superficial dermal burns In all patients the dressing changes were painful and the discomfort lasted for 15–30 min. There was no increase in sepsis or in the amount of discharge from the wound surface. The burn wound healed in 11–14 days (*Table I*).

Intermediate depth dermal burns In all patients the dressing changes were painful and the pain persisted for at least 30 min. Slight oozing continued but there was no increase in the incidence of sepsis. The burn wound healed in 21–28 days in all patients and the healed areas developed hypertrophic scars (*Table II*).

Deep dermal burns The dressing changes were painful and the ensuing discomfort persisted for at least 30 min. The oozing continued and the burn wound always became infected; in four patients the burn wound became converted to full skin thickness to a varying extent. In the 11 patients in which this did not happen the wound healed in 31–42 days (*Table III*). The healed areas always developed hypertrophic scars and contractures.

Amniotic membrane-treated patients

Superficial dermal burn In these patients the dressing changes and the post-dressing period were comfortable and free of pain. The amniotic membrane did not dissolve and persisted as a dried, translucent parchment-like membrane adherent to the underlying tissues. There was no oozing from the wound. This was left undisturbed. Healing occurred in 8–11 days (*Table I*).

Intermediate dermal burns In these patients a daily reapplication of amniotic membrane was necessary as the amniotic membrane was seen to have dissolved in the early postburn period. After 1 week of dressing changes the membrane persisted in a parchment-like form. The dressing changes and the intervening period were painless and comfortable. The oozing was significantly reduced. Healing occurred in 14–18 days (*Table II*) and the healed areas did not show scar hypertrophy (*Figs.* 1,2).

Deep dermal burns The dressing changes and the intervening period were comfortable, free from pain and the oozing was reduced. The amniotic membrane had dissolved in all patients and the burn wound showed a sloughing epithelium, consequently daily dressings were continued. About 30 per cent of the patients showed conversion of the

Table I. Comparison of healing time in controls vs. amniotic membrane group in superficial dermal burns

Group	Healing time (days) Range	Mean ± s.d.	Significance
Control group	11–14	12.5 ± 1.1	$P<0.001$
Amniotic membrane group	8–11	9.3 ± 1.2	

Table II. Comparison of healing time in control vs. amniotic membrane group in intermediate depth dermal burns

Group	Healing time (days) Range	Mean ± s.d.	Significance
Control group	21–28	23.9 ± 2.4	$P<0.01$
Amniotic membrane group	14–13	15.7 ± 1.4	

Table III. Comparison of healing time in control vs. amniotic membrane group in deep dermal burns

Group	Healing time (days) Range	Mean ± s.d.	Significance
Control group	34–42	37.5 ± 3.2	$P<0.01$
Amniotic membrane group	24–30	27.5 ± 2.5	

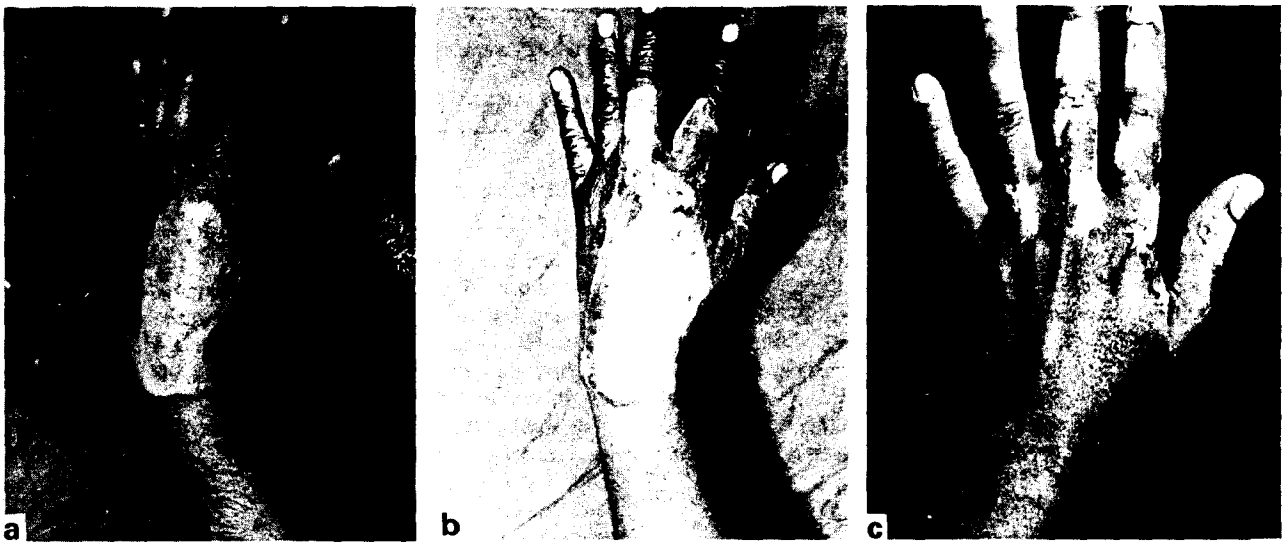

Figure 1. Intermediate depth dermal burn. **a**, Before application of amniotic membrane. **b**, After application of amniotic membrane. **c**, After healing.

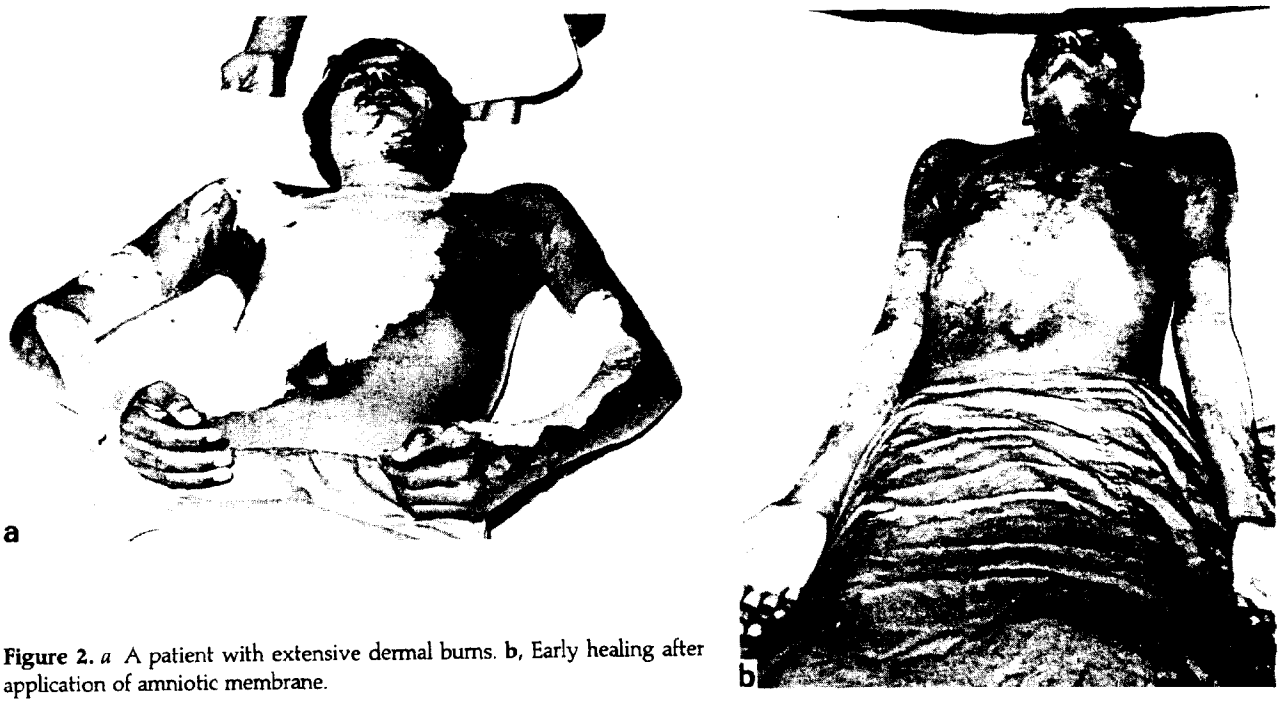

Figure 2. *a* A patient with extensive dermal burns. **b**, Early healing after application of amniotic membrane.

wound depth to full skin loss. In other patients the superficial slough of dead/necrotic tissue gradually separated, leaving islands of hair follicles from which skin regenerated in 24–30 days (*Table III*).

In this category of deep dermal burns additional patients were observed but the type of management was altered. When, on dressing change in the early period, slough became evident, daily dressing with 1 per cent silver sulphadiazine were started and continued until the slough had separated (about 14–21 days), the wounds then showed surviving islands of epithelium around hair follicles. At this stage daily dressing with amniotic membrane was started. This lead to complete epithelialization of the burn wound in an average of 28 days but also the development of hypertrophic scars.

Discussion

Dermal burns are painful, ooze a lot soaking the dressings and are prone to sepsis. The dressing changes are painful and time consuming. The use of amniotic membrane as a biological dressing eliminates pain, reduces oozing and soakage of dressings. The dressings do not stick to the burn wound, consequently, the dressing changes and the post-dressing period are painless and the patients are comfortable. The amniotic membrane promotes early healing in superficial dermal and intermediate dermal burns by facilitating regeneration of epithelium from remnants of skin appendages and protecting it from damage by repeated dressing changes. In deep dermal burns, where the burn wound is covered with dead tissue, the amniotic membrane dissolves. However, when the superficial slough is removed and islands of epithelium from the surviving remnants of dermal appendages (i.e. hair follicles and sweat gland) are seen, the application of amniotic membrane not only protects these epithelial remnants from sepsis and the trauma of repeated dressing changes, but facilitates regeneration of epithelium which spreads to cover the surrounding raw area by providing a proper environment. The healing time is significantly reduced, overall morbidity is minimized and the patients are more comfortable.

The use of amniotic membrane should be limited to superficial and intermediate depth dermal burns or when protection of regenerating epithelium is required in deep dermal burns. The amniotic membrane is easily available free of cost in any large hospital, and needs minimal expenditure on storage. The treatment is cheaper than other methods, the patients are made more comfortable and the overall morbidity is reduced. This is especially so when compared to the use of expensive topical agents. All this can be achieved if proper selection of patients based on the clinical characteristics of a burn wound is carried out.

Conclusions

Application of amniotic membrane reduces discomfort and pain of dressing changes and the patient feels comfortable. It reduces the amount of oozing from the burn wound and protects regenerating epithelium from the trauma of dressings.

Amnion promotes regeneration of skin from surviving remnants of skin appendages and ensures early healing. This early healing discourages excessive granulation tissue formation and reduces scar hypertrophy.

Amnion does not 'take', it only acts as a protective biological dressing. It does not survive on dead tissue and granulating areas and dissolves.

In superficial and intermediate depth dermal burns primary dressing with amniotic membrane promotes early healing. In deeper dermal burns amniotic membrane is useful in promoting early regeneration of epithelium and healing after the superficial slough is removed.

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Letter to the Editor

Burn wound infection

Dear Sir,

The article on burn wound infection by Professor Karyoute (Burn wound infection in 100 patients treated in the burn unit at Jordan University Hospital (1989) *Burns* **15**, 117–119) provides useful and interesting information and it would be helpful if more burns centres published this type of data, thus enabling the microbial problems in different centres to be compared and contrasted.

It so happens that since 1982 the pattern of burn wound colonization in Birmingham has further changed, such that *Acinetobacter anitratus* is now the most prevalent Gram-negative bacillus (Lawrence, 1987), and we hope to prepare a further report shortly.

Criticism of a good paper may appear invidious but we wondered how Professor Karyoute justified the apparent widespread use of Sofra-Tulle. This comprises 1 per cent framycetin sulphate dispersed in white soft paraffin spread on gauze. The topical use of aminoglycosides can result in deafness, although the manufacturer's of Sofra-Tulle claim no appreciable absorption from wounds not exceeding 30 per cent body surface area (ABPI Data Sheet Compendium, 1989–90). It was not clear from the paper whether Sofra-Tulle was used on such burns. However, apart from toxicity, plasmid-mediated resistance to aminoglycosides as a group is well known, and it is widely accepted that topical antibiotics are to be avoided because of the rapidity of emergence of resistant bacteria (Greenwood, 1983). We note that Professor Karyoute reports a moderate incidence of resistance to gentamicin, tobramicin and amikacin but makes no mention of framycetin. Other topical agents, e.g. silver sulphadiazine or silver nitrate, are effective and do not share these problems.

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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.

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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

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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.

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UPDATE

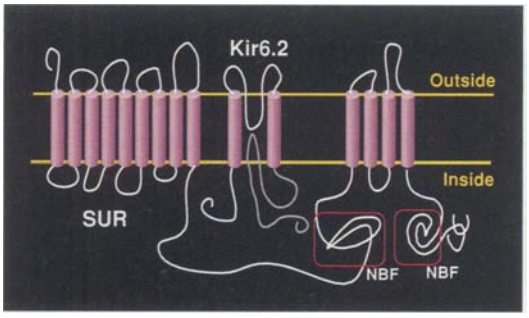
ATP-Sensitive K^+ Channels: Paradigm Lost, Paradigm Regained

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.

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*).



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

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}.

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