

Research sheds new light on corneal graft rejection in atopic patients

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in London

A SERIES of elegant mouse experiments conducted in the US opens promising avenues of research for corneal graft survival in atopic patients. The research also sheds new light on the immunological mechanisms underlying corneal graft rejection.

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The research also produced very early-stage evidence that anti-interferon gamma treatment combined with dampening the expression of the vascular cell adhesion molecule (VCAM) may possibly enhance corneal graft survival in atopic patients, delegates to the Moorfields Bicentenary Scientific Meeting heard.

Jerry Niederkorn PhD, director of ophthalmic research at the University of Texas Southwestern Medical Centre, Dallas, Texas, told EuroTimes that he launched the research when ophthalmologist colleagues lamented the low level of corneal graft survival in atopic patients.

"Current immunological thinking believes that when challenged, the immune system chooses to go down either a Th-1 pathway, which produces interferon gamma, or a Th-2 pathway, which produces such cytokines as interleukin (IL)-4, IL-5, IL-10 and IL-13," he said.

Given that the Th-1 pathway may be responsible for organ graft rejection, a Th-2 response may in turn impede a Th-1 response and enhance the chances of graft survival, he explained.

But numerous reports show that allergy is a risk factor in corneal grafts in keratoconus patients, even though 90% of grafts in non-atopic keratoconus patients are successful, said Dr Niederkorn.

Experiments in mouse model

To explore the role of allergy in graft rejection, Dr Niederkorn and colleagues used a well-established mouse model in which BALB/c mice are made allergic to ragweed pollen. Researchers applied ragweed pollen to induce allergic conjunctivitis. They subsequently performed a corneal allograft to the eye that suffered allergic insult. Another well established mouse strain, C57BL/6 (B6), provided donor corneas.

"This model clinically and histologically resembles corneal allografts in humans. And typically 50% of the grafts survive and remain clear well beyond 100 days," said Dr Niederkorn.

But in his experiments, the B6 allografts failed in the atopic BALB/c mice, in all cases, and at a much more rapid rate than grafts in non-atopic BALB/c mice.

Interestingly, when researcher applied a BALB/c corneal autograft to an atopic BALB/c host, the autograft remained clear, indicating that the allergic response itself did not damage the corneal transplant.

Histological analysis showed that mice mounted a delay-type hypersensitivity response, but cells

were predominately eosinophilic and not mononuclear. But, surprisingly, the tests also showed that interferon gamma, a cytokine thought to impede allergic responses, was expressed at high levels in the atopic mouse.

"It seems that the immunological dogma stating that Th-2 and Th-1 responses are mutually exclusive needs to be reconsidered in light of these results," said Dr Niederkorn.

Unilateral allergy influences graft rejection in fellow eye

To test whether the eosinophilic inflammation was responsible for graft rejection, Dr Niederkorn conducted a new series of tests. Researchers induced an allergic conjunctivitis in the right eye, but applied the B6 corneal allograft to the left eye.

"The graft still rejected at a higher incidence and tempo, indicating that the problem was caused by a systemic allergic response. The eosinophils that were found in the allergic eye were not mediating graft rejection, and thus, were a red herring."

Dr Niederkorn performed another series of tests, this time

performing allografts on the 'hot eye' of atopic mice, but combining the graft with anti-IFN-g treatment, to test whether this Th-1 immunity was responsible for rejection. These experiments showed that the speed and incidence of rejection was unchanged in non-atopic mice, but was reduced in mice with allergic conjunctivitis.

Dr Niederkorn and colleagues theorised that IFN-g may play a 'gate-keeper' role by up-regulating VCAM expression. Anti-IFN-g treatment impedes much VCAM expression, but perhaps not all expression. The team hypothesised that by combining anti-IFN-g with VCAM-dampening (via VLA-4 mAb therapy), corneal graft survival might improve.

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In a subsequent series of experiments, Dr Niederkorn's team used a combination of anti-IFN-g and anti-VCAM treatment before and after applying B6 corneal allografts onto BALB/c mice. Here graft rejection was at a lower tempo and incidence than in untreated atopic mice, or in atopic mice treated with anti-IFN-g only. Dr Niederkorn stressed, however, that these were early results in series of just 20 mice.

Findings raise new questions

Dr Niederkorn told delegates that this series of experiments showed that mice with allergic conjunctivitis reject corneal grafts faster and at a higher incidence than non-allergic mice. Furthermore, histocompatible, grafts are not rejected in mice with allergic conjunctivitis. Atopic mice produce Th-2 cytokines and interferon gamma. Atopic mice also mount a delayed hypersensitivity response to donor alloantigens, but inflammatory lesions are predominantly eosinophilic and



Jerry Niederkorn

not mononuclear. Both Th-1 and Th-2 cells are found in corneal allografts in atopic mice.

He also said that future directions of research needed to examine the mechanism of rejection.

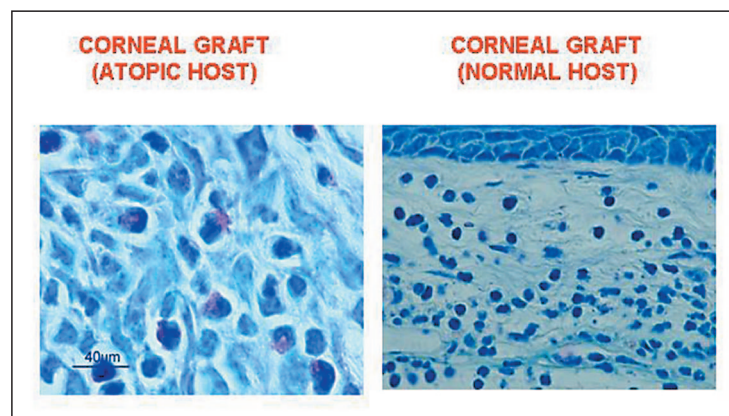
"What role, if any, do eosinophils play in rejection? I believe they're a red herring. Can we reduce rejection in atopics by treating with anti-histamines or other drugs? Why are the tempo and the incidence of graft rejection greater in allergic eyes? What is the role of IFN-g and VCAM? Will topical IFN-g have a salutary effect on corneal graft rejection? We've had 50 years of immunological research on corneal allograft rejection in laboratory animals, yet we still don't understand the basic mechanism that mediates rejection," he said.

Dr Niederkorn will also look at the role of these types of immune response in non-ophthalmic graft rejection, planning initially to examine skin graft rejection in atopic mice. This research could have important implications both for transplant science and immunology in general.

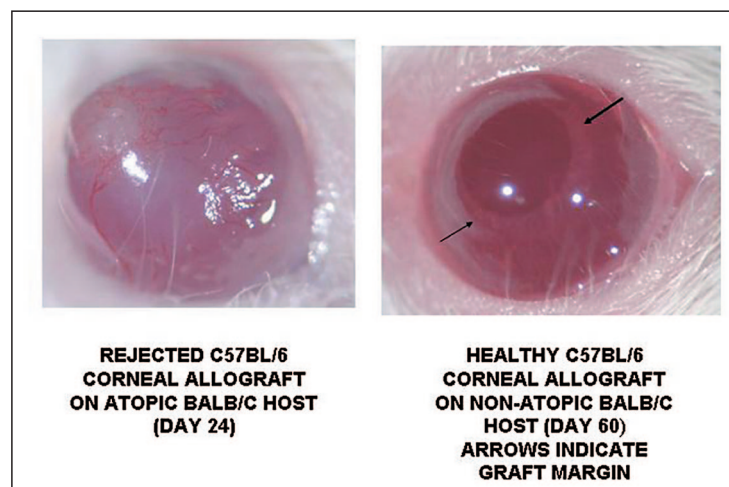
"The work is of interest to corneal transplant surgeons, as we encounter early and vigorous rejection post-transplantation in some of the keratoconus patients with allergic conjunctival and cutaneous disease. This is a newly recognised pathway to corneal allograft rejection, with implications for rejection treatment and prophylaxis in this patient group. In corneal transplant rejection, there is more than one road to Rome," said Frank Larkin MD, consultant ophthalmologist and corneal transplant specialist at Moorfields.

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Inflammatory infiltrate in corneal allografts.



Corneal allografts are swiftly rejected in 100% of the atopic Balb/c mice, while only 50% of the corneal allografts are rejected in non-atopic Balb/c mice.

Courtesy of Jerry Niederkorn PhD