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Transplant Surgeons can Xenograft Kidneys from untreated Pigs without Rejection

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Abstract

The histocompatibility system exists for defence against viruses. It is responsible for the rejection of allograft. The immune system attempts to counter the explosive speed of viral replication by directing the defensive immune attack by cytotoxic T cells on to histocompatibility antigens on the infected cell's surface. This enables destruction of the virus factories before the cytotoxic T cells are swamped by the myriad numbers of new virions, a thousand coming from each infected cell every 10 hours.

The histocompatibility system mistakes alloantigen on grafts for virus-infected host cells that need swift destruction. For surgical transplantation, Henry Kaplan discovered that immune ablation of the recipient followed by inoculation with donor bone marrow prevents rejection of allogeneic grafts. Sykes has improved Kaplan's technique by adding recipient bone marrow cells to the donor ones injected for reconstitution of the recipient after immune ablation. Kaplan's technique, used on untreated pigs, should be the standard procedure for transplantation.

Keywords: The histocompatibility system; Virus infection; Graft rejection; Transplantation; Use of allogeneic and autologous bone marrow; Xenografting

Introduction

Oncologists, wishing to study tumours by transplanting them from their source to another laboratory animal, found that the tumours were rejected. Medawar [1] observed that the rejection of foreign skin grafts on a woman was accelerated on the second occasion, correctly concluding that an immunological process was involved.

In 1952 the first successful kidney transplant was performed between identical twins [2], demonstrating the genetic basis of rejection. The genes involved will be described below.

The Histocompatibility System

To emulate identical twins for acceptance of foreign grafts, oncologists used brother-sister mating of rodents to produce inbred strains. This led to discovery of the histocompatibility (tissue compatibility) system, governed by a major genetic complex, named the major histocompatibility complex (MHC) [3]. These genes code for surface antigens on all nucleated cells. The MHC is present in all species of vertebrates, including man. Why does it exist?

Functions of the MHC

The MHC does not exist to frustrate Transplant Surgeons. It is essential for survival of virus infections, and protects, imperfectly, against autoimmune disease [4]. In a famous experiment Zinkernagel and Doherty [5] found that a cell infected by a virus extrudes a viral peptide on to its surface histocompatibility antigens, where it can be attacked by a complementary cytotoxic T cell clone, if one exists. As shown in Tables 1, the explosive speed of viral replication necessitates swift destruction of the virus factories that the infected cells become, with 1,000 virions emerging from each infected cell every 10 hours [6] and each new virion infecting another host cell. The histocompatibility antigens, on every nucleated host cell, present the extruded viral peptide to cytotoxic T cells, which places the immune reaction on the cell surface, enabling destruction of the virus factories before the myriad of virions swamp the cytotoxic T cells and kill the host.

Mechanism of Immune Tolerance

Parents can react to each other's histocompatibility antigens. They impart to their offspring all the genes necessary for this. Therefore, some mechanism must prevent reaction with self histocompatibility antigens [8]. Burnet [9] proposed that immunocytes in the foetus are deleted by contact with complementary antigen.

Nossal [10], with superb technology, showed that the switch from deletion to reactivity is not a stage in the life of an animal, but a stage in the life of every developing lymphocyte. This explains the continuing influence of histocompatibility antigens on the immune repertoire. Confusing sub-maximal immune response with tolerance, Nossal failed to appreciate his discovery.

Transplantation

Chimera manufacture

Henry Kaplan, a radiotherapist and researcher, who revolutionised treatment of Hodgkin's disease [11], found that animals can be made haematological chimeras [12] by total lymphoid irradiation followed by inoculation with allogeneic bone marrow, after which they will accept allogeneic skin, heart and bone marrow grafts from the donor of the bone marrow.

Clinical achievement of graft-tolerant and host-tolerant chimeras

In 2008, *Alexander, et al.* [13] brilliantly saved the life of a girl with liver failure from acute fulminant viral hepatitis. After receiving a mismatched liver allograft, and ingenious treatments, she eventually became a haematopoietic chimera, completely tolerant of her mismatched liver allograft.

The procedure for regularly achieving the needed graft-tolerant,

Table 1: The race between virus and cytotoxic T cell [4].

The contestants	Replication time	Progeny
Influenza virus	10 hours[6]	1,000 virions
Cytotoxic T cell	18 hours	2 T cells

The race:	Virions:	T cells:	Virion/T cell ratio:
Day 0	1	10^6	$1/10^6$
Day 1	1 x $1{,}000^{2.4}$	10^6 x 21.3	6/1
Day 2	2.5 x 10^{14}	10^6 x 6.3	107/1
Day 3	4 x 10^{21}	10^6 x 1.6	$10^{14}/1$

The result: The virus wins, the patient dies.
The Conclusion:
Cytotoxic T cell clones need to be
1. Large, preformed [7], no time for expansion.
2. Specific for conjoint virus-MHC antigenic target [5], so as not to be muffled by the myriad numbers of free virions.

host-tolerant chimera is clearly performance of immune ablation of the graft recipient, followed by inoculation with both autologous and donor bone marrow, before performing the allo-transplantation.

Improvement of Transplantation

Megan Sykes [14] describes Kaplan's procedure as induction of Full Chimerism. For successful transplantation in rodents, she found it inferior to induction of mixed Chimerism, in which Immuno-ablation of the recipient is followed by reconstitution with bone marrow cells from the graft recipient (autologous) as well as from the graft donor (allogeneic). Use of this protocol should enable xenografting from pigs, offering instant and unlimited supply of grafts for man.

False fear of pig tissues now gone

A long–standing fear that pig grafts would introduce dangerous retroviruses into man has now been allayed [15]. This has led to the establishment of many companies attempting to modify pigs to prevent rejection problems [15].

Unmodified pigs can be used

In the light of Kaplan's great discovery that after immune ablation of the recipient, infusion of donor bone marrow cells makes the recipient a haematological chimera, tolerant of host and donor tissues, completely unmodified pigs can be safely used for xenografting kidneys and other organs into man [16]. Application of xenografting from pigs is needed urgently, and will be a major advance on current HLA-matched human organ grafting, with need for long periods of dialysis while awaiting availability of an HLA matched donor.

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References

1. Gibson T, Medawar PB. The fate of skin homografts in man. J Anat. 1943; 77(4): 299-310.4.
2. Hume DM, Merrill JP, Miller BF. Homologous transplantation of the human kidney. J Clin Invest 1952; 31: 640.
3. Margulies DH, The major histocompatibility complex. In Paul WE, editors Fundamental Immunology. 4th ed. Lippincot- Raven, Philadelphia; 1999. 263-286.
4. Adams DD. Protection from autoimmune disease as the third function of the major histocompatibility gene complex. Lancet 1987; 2(8553): 245-249.
5. Zinkernagel RM, Doherty PC. Restriction of in vitro T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semi-allogeneic system. Nature 1974; 248(5450): 701-702.
6. Fenner F, White DO. Medical Virology. 4th Ed. Academic Press. London. 1975.
7. Simonsen N. On the nature and measurement of antigenic strength. Transplant Rev. 1970; 3: 22-35.
8. Davies TF. Autoimmune Endocrine Disease. New York; Wiley; 1983. 1-39.
9. Burnet FM. The clonal selection theory of acquired immunity. Cambridge University Press. London. 1959.
10. Nossal JG, Pike B. Evidence for the clonal abortion theory of B lymphocyte tolerance. J Exp Med 1975; 141(4): 904-917.
11. Kaplan HS. Hodgkin's disease: unfolding concepts concerning its nature, management and prognosis. Cancer. 1980; 45(10): 2439-2474.
12. Slavin S, Reitz B, Bieber CP, Kaplan HS, Strober S. Transplantation tolerance in adult rats using total lymphoid irradiation: permanent survival of skin, heart and marrow allografts. J Exp Med. 1978; 147(3): 700-707.
13. Alexander SI, Smith N, Hu M, et al. Chimerism and tolerance in a recipient of a deceased-donor liver transplant. N Engl J Med. 2008; 358(4): 369-74. doi: 10.1056/NEJMoa0707255.
14. Sykes M. Mixed chimerism and transplant tolerance. Immunity. 2001; 14(4): 417-424.
15. Coglan A. Saved by a pig's heart. New Scientist. 2008; 200(2684): 8-9.
16. Adams DD. Why the histocompatibility system exists and how transplant surgeons can xenograft without rejection. QJM 2011; 104(9): 767-769. doi: 10.1093/qjmed/hcr051.