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THE ROYAL SOCIETY

On immunological memory

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Immunological memory may not represent a special characteristic of lymphocytes but simply reflect low-level responses driven by antigen that is re-encountered or persists within the host. T-cell memory is important to control persistent infections within the individual host and cannot be transmitted to offspring because of MHC polymorphism and MHC-restricted T-cell recognition. In contrast, antibody memory is transmissible from mother to offspring and may function essentially to protect offspring during the phase of physiological immuno-incompetence before, at and shortly after birth. This physiological immuno-incompetence is a result of MHC polymorphism and the dangers of the graft-versus-host and host-versus-graft reaction between mother and embryo, which necessitate immunosuppression of the mother and immuno-incompetence of the offspring. One may argue therefore that immunological memory of transmissible immunological experience is the basis on which MHC-restricted T-cell recognition could develop or coevolve.

Keywords: T-cell memory; antibody memory; protection; immuno-incompetence; newborn

1. INTRODUCTION

The question of what constitutes immunological memory and how it may be maintained is obviously linked to our understanding of specificity. Specificity can be defined as a time- and concentration-dependent capacity of B or T cells to discriminate between infectious agents that exert evolutionary pressures relevant for the survival of the species. This capacity is most directly measured by protection or cross-protection *in vivo*. For serotype-defined viruses that are usually cytopathic, antibodies are the relevant effector molecules, whereas for many non-cytopathic viruses cytotoxic T cells seem to be key for protection. While many specificities of antibodies and T-cell responses are induced, only some are protective, for example, neutralizing antibodies; other antibodies against internal antigens are irrelevant from the standpoint of protection (reviewed in Zinkernagel 1996; Mims 1987).

There is more than one school of thought about immunological memory: (i) memory is antigen dependent; or (ii) memory is a special quality of T or B cells somewhere in between an untriggered and a fully differentiated effector T or plasma cell (Kündig *et al.* 1996; Zinkernagel *et al.* 1996; Zinkernagel 1990; Ahmed 1992; Gray 1993; Gray & Matzinger 1991; Gray & Skarvall 1988). This brief review attempts to discuss immunological memory from an evolutionary point of view (Zinkernagel *et al.* 1996; Zinkernagel 1996).

2. WHY IMMUNOLOGICAL MEMORY?

Host and virus represent two sides of an evolutionary equilibrium. Cytopathic agents usually kill immunological low responders, whereas in general, high responders tend to survive. Again, T-cell memory probably will not improve these conditions unless vaccines had been foreseen by evolution! If an unprimed host survives an initial infection, the host does not really need immunological memory to survive the second infection and vice versa; if the primary infection is fatal, he does not need immunological memory for obvious reasons. Therefore, immunological memory may not have been really important in evolution for the conventional reasons, but nevertheless might have improved overall fitness over time because it improved resistance to disease. In contrast, there is an important immunological reason for immunological memory, which could overcome the physiological immuno-incompetence of newborn vertebrates. This immuno-incompetence at the time of birth can be explained as a consequence of MHC polymorphism that is necessitated by (or made possible through?) MHC restriction of T-cell recognition. This MHC polymorphism causes potential problems for maternal–foetal relationships. The delicate situation between host-versus-graft and graft-versus-host reaction seems to be controlled by lack of MHC-antigen expression in the contact areas between mother and offspring (reviewed by Brent 1997, p. 403), by general immunosuppression of the mother and by immunodeficiency of the offspring.

To overcome problems of infectious disease during the time needed for full maturation of the newborn's immune system, the following system of prevention by adoptive immunization has evolved. Antibodies are soluble, passively transmissible forms of polyvalent immunological maternal memory, which provide essential protection for the offspring during the crucial period during which it develops T-cell competence and the capacity to generate predominantly T-help-dependent antibody responses. Again, coevolution would have rendered the development of cytopathic agents, which could not be controlled efficiently by antibodies during this critical time, unlikely. An impressive example illustrating this point is the fact that a calf is born without serum immunoglobulins

simply because maternal immunoglobulin cannot pass through the complete double-layered placenta (reviewed by Brambell 1970). The calf has to take up, via the gut, colostral maternal immunoglobulins during the first 24 hours after birth. If this does not happen, the calf will remain without protective antibody and usually die of various infections during the next few weeks, because its own immune system is not yet mature enough to mount effective immune responses quickly. Maintenance of such maternal memory antibody responses depends on both B-cell and T-helper-cell memory, because protective antibody levels cannot be expected to be built up during the 270 days of a human pregnancy or the 20 days of a mouse pregnancy to cover all relevant infectious agents necessary to protect the offspring. In addition, viral and some bacterial infections during pregnancy cause abortion and thus infections after puberty are evolutionarily disadvantageous. Therefore, B- and T-cell memory is needed to accumulate immunological experience before pregnancy. Hormonal regulation may well also contribute to B-cell memory responses and plasma cell survival to maintain protective antibody levels in the mother. This would explain the higher incidence of autoantibody-mediated autoimmune disease in females.

3. WHAT KIND OF IMMUNOLOGICAL MEMORY IS BIOLOGICALLY RELEVANT?

Immune responses and protection against cytopathic virus infections are key to species survival. Without exception, protection against these types of agents is mediated via protective antibodies. Non-cytopathic viruses are usually transmitted before or at the time of birth when offspring are immuno-incompetent and without apparent overall disadvantage for the survival of the species. Examples are hepatitis B virus infections in humans or lymphocytic choriomeningitis virus, mammary tumour virus or leukaemia viruses in mice. For non-cytopathic infections, protective immunity, including neutralizing antibodies or cytotoxic T cells, is not really necessary for survival. Nevertheless, even in these cases, the presence of high titres of neutralizing antibodies may reduce or prevent transmission of infection from mothers to offspring. But overall immunity is not essential for survival of offspring and the host species. In fact, vertical transmission of non-cytopathic agents is most efficient during pregnancy or around birth, because of absence of immune defence by the offspring. Taking these basic considerations into account, it becomes evident that protection against cytopathic agents must be an important key to understanding immunological memory. The following example may illustrate the respective roles of memory helper or cytotoxic T cells versus that of B cells to protect against a lytic virus infection. The lytic vesicular stomatitis virus strains, Indiana or New Jersey, or similarly the influenza A viruses, induce cross-reactive helper and cytotoxic T-cell responses (Gerhard *et al.* 1997; Liang *et al.* 1994; Gupta *et al.* 1986). Nevertheless, infection with one serotype does not protect against infection with the other serotype (or a drift or shift mutant influenza virus). The reason has been elucidated in several experiments. Since only neutralizing antibodies can protect against these viruses, it is the B-cell frequency and kinetics that limit the kinetics of the response and not the frequency of T help or of cytotoxic T lymphocytes (CTLs) (Bachmann & Zinkernagel 1997).

4. WHAT IS THE ROLE OF CYTOTOXIC T-CELL MEMORY?

Cytotoxic T cells have the key function of controlling non-cytopathic virus infection after acute infections. Although protective during this period, they may also be detrimental because they cause immunopathological destruction of otherwise non-lytically infected host cells. This inherent problem makes clear that cytotoxic T-cell responses active against many infected target cells cause disease and therefore must be avoided. A drastic example may illustrate this: if a primed mouse with a reasonably high precursor frequency of virus-specific CTLs is exposed to a high dose of relevant peptide that is bound by many host cells, including cells of the immune system, this challenge dose may cause lethal graft-versus-host-like immunopathology (Oehen *et al.* 1991; Aichele *et al.* 1997).

In contrast to serum antibodies, primed CTL responses cannot be transmitted to offspring because of the usual transplantation antigen difference between mother and offspring, potentially causing a graft-versus-host reaction. In addition, the specificity of T cells from the mother may not fit the paternal MHC peptide configuration of the recipient offspring and thus be useless. Therefore, primed CTL may function primarily to prevent virus spread again within the same host, and limit (or prevent) immunopathological disease.

An example illustrating this point is the spectrum of virus–host relationships found after HBV or HIV infections in humans. If virus is controlled at low levels, chronic disease develops only late or not at all. If, however, virus has spread or there is a widespread recrudescence, a severe autoaggressive disease (aggressive form of HBV hepatitis) may develop. A similar balance exists in leprosy or tuberculosis infections. In all these examples nobody would argue against the obvious fact that low-level infection maintains protective immunity. Mackaness coined the term 'infection immunity' to describe this important coevolutionary equilibrium (Mackaness 1964, 1971).

5. WHAT MAINTAINS ANTIBODY MEMORY?

As stated, protection against evolutionarily important lytic viral infections, including the classical childhood infections, is mediated by neutralizing antibodies. Experience shows that such antibody titres tend to drop with time. I have described the function of maternal antibodies to protect offspring during the physiological period of immunodeficiency caused by the delay in T-cell maturation in offspring. In addition to the role of antibodies attenuating some infections during the early life period of the offspring, they may also help to build up a good immune complex depot on its follicular dendritic cells. Such immune complexes have been shown to be involved in the maintenance of antibody memory (Nossal *et al.* 1965; Tew *et al.* 1990). Alternatively, periodical reinfection as for polio, herpes, influenza, parainfluenza, many diarrhoeal viruses, etc., or persistence of the infectious

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agents, for example, HBV, HIV, the various herpes viruses, etc., is an often-used scenario for natural boosters of immunity.

Some viruses do not reinfect or do not persist as intact virus in the host. They may, however, persist in the host as crippled virus forms. For example, measles virus persists not only in subacute sclerosing panencephalitis patients but also in many (if not most) hosts once infected (Katayama *et al*. 1995; Baczko *et al*. 1984). This explains why in the classical epidemiological studies on the Faeroes or on the Pacific Islands, protective memory was maintained in previously infected survivors but not in those born on the island after the last epidemic (Mims 1987).

Additional mechanisms probably contribute to antibody memory. Plasma cells may be long lived and thereby contribute to long-lived high antibody levels (Slifka *et al*. 1995).

6. CONCLUSION

Although immunological memory has been considered a very special characteristic of the immune system and has been compared to human memory, this notion may turn out to be more idea than fact. Protective immunological memory reflects a rather low-level response that is essentially driven and maintained by persisting or repetitively introduced antigens. This process protects the host against direct or indirect (immunopathologically mediated) damage by infectious agents, via T cells and antibodies. From an evolutionary point of view—because of its selective advantage—it protects the offspring during the physiological phase of immunodeficiency, which is a consequence of MHC-restricted T-cell recognition driving MHC polymorphism.

REFERENCES

Ahmed, R. 1992 Immunological memory against viruses. *Semin. Immunol.* **4**, 105–109.

Aichele, P., Brduscha-Riem, K., Oehen, S., Odermatt, B., Zinkernagel, R. M., Hengartner, H. & Pircher, H. 1997 Peptide antigen treatment of naive and virus-immune mice: antigen-specific tolerance versus immunopathology. *Immunity* **6**, 519–529.

Bachmann, M. F. & Zinkernagel, R. M. 1997 Neutralizing antiviral B cell responses. *A. Rev. Immunol.* **15**, 235–270.

Baczko, K., Carter, M. J., Billeter, M. R. & Meulen, V. 1984 Measles virus gene expression in subacute sclerosing panencephalitis. *Virus Res.* **1**, 585–595.

Brambell, R. W. R. 1970 *The transmission of immunity from mother to young*. Amsterdam: North-Holland Publishing Co.

Brent, L. 1997 *A history of transplantation immunology*. San Diego, CA: Academic Press.

Gerhard, W., Mozdzanowska, K., Furchner, M., Washko, G. & Maiese, K. 1997 Role of the B-cell response in recovery of mice from primary influenza virus infection. *Immunol. Rev.* **159**, 95–103.

Gray, D. 1993 Immunological memory. *A. Rev. Immunol.* **11**, 49–77.

Gray, D. & Matzinger, P. 1991 T cell memory is short-lived in the absence of antigen. *J. Exp. Med.* **174**, 969–974.

Gray, D. & Skarvall, H. 1988 B cell memory is short-lived in the absence of antigen. *Nature* **336**, 70–73.

Gupta, S. C., Hengartner, H. & Zinkernagel, R. M. 1986 Primary antibody responses to a well-defined and unique hapten are not enhanced by preimmunization with carrier: analysis in a viral model. *Proc. Natl Acad. Sci. USA* **83**, 2604–2608.

Katayama, Y., Hotta, H., Nishimura, A., Tatsuno, Y. & Homma, M. 1995 Detection of measles virus nucleoprotein mRNA in autopsied brain tissues. *J. Gen. Virol.* **76**, 3201–3204.

Kündig, T. M., Bachmann, M. F., Ohashi, P. S., Pircher, H., Hengartner, H. & Zinkernagel, R. M. 1996 On T cell memory: arguments for antigen dependence. *Immunol. Rev.* **150**, 63–90.

Liang, S., Mozdzanowska, K., Palladino, G. & Gerhard, W. 1994 Heterosubtypic immunity to influenza type A virus in mice. Effector mechanisms and their longevity. *J. Immunol.* **152**, 1653–1661.

Mackaness, G. B. 1969 The influence of immunologically committed lymphoid cells on macrophage activity *in vivo*. *J. Exp. Med.* **129**, 973–992.

Mackaness G. B. 1971 Resistance to intracellular infection. *J. Infect. Dis.* **123**, 439–445.

Mims, C. A. 1987 *Pathogenesis of infectious disease*. London: Academic Press.

Nossal, G. J. V., Austin, C. M. & Ada, G. L. 1965 Antigens in immunity. VII. Analysis of immunological memory. *Immunology* **9**, 333–348.

Oehen, S., Hengartner, H. & Zinkernagel, R. M. 1991 Vaccination for disease. *Science* **251**, 195–198.

Slifka, M. K., Matloubian, M. & Ahmed, R. 1995 Bone marrow is a major site of long-term antibody production after acute viral infection. *J. Virol.* **69**, 1895–1902.

Tew, J. G., Kosco, M. H., Burton, G. F. & Szakal, A. K. 1990 Follicular dendritic cells as accessory cells. *Immunol. Rev.* **117**, 185–211.

Zinkernagel, R. M. 1990 Antiviral T-cell memory? *Curr. Topics Microbiol. Immunol.* **159**, 65–77.

Zinkernagel, R. M. 1996 Immunology taught by viruses. *Science* **271**, 173–178.

Zinkernagel, R. M., Bachmann, M. F., Kündig, T. M., Oehen, S., Pircher, H. & Hengartner, H. 1996 On immunological memory. *A. Rev. Immunol.* **14**, 333–367.

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