

Immune Response Genes

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The discovery of a set of genes controlling the ability of the individual to mount an immune response to certain antigens (23) came as a major surprise to most immunologists. Nonetheless, it had been noticed for many years that some animals in outbred populations were good and other were poor producers of antibody to selected antigens. An example is the production of antibody to diphtheria toxin by guinea pigs which was found to show great individual variation (36). Breeding of good antitoxin producers with good antitoxin producers yielded progressively better antitoxin producers with each successive generation, and breeding of poor with poor antitoxin producers for several generations yielded offspring which hardly produced any antitoxin at all.

The immune response (Ir) genes were not clearly defined, however, until synthetic polypeptide antigens of relatively simple structure (18) became available, and used for immunization of guinea pigs. One such antigen is the dinitrophenyl conjugate of the homopolymer of L-lysine (DNP-PLL). Among outbred Hartley guinea pigs immunized with DNP-PLL some animals developed delayed hypersensitivity to the antigen and produced antibodies against DNP, but other animals did not respond at all (23). Breeding experiments demonstrated that the responder phenotype was inherited as a simple dominant Mendelian trait. The responsible Ir gene was named the "Poly-L-lysine gene".

Further work with inbred strains of mice, also employing synthetic polypeptide antigens, revealed the existence of several Ir genes in

that species and made way for the startling discovery that the Ir genes were located within the major histocompatibility complex (MHC) – that in fact the Ir genes are histocompatibility genes (26). The same genomic location of Ir genes has been demonstrated in the guinea pig (11), rat (16), and rhesus monkey (9), illustrating the generality of the phenomenon.

It is now clear that the Ir genes control immune responses to the large group of "thymus-dependent" antigens, which are protein or polypeptide antigens, and which comprise a majority of naturally occurring antigens. The types of immune responses under Ir gene control include delayed hypersensitivity and proliferative responses *in vitro* which are directly mediated by T cells, and the production of IgG antibodies by B cells which is dependent upon helper T cells.

During the past two decades since the discovery of the Ir genes a number of observations have been made which indicate that the Ir genes control not only responsiveness to antigens but a number of additional traits. The purpose of this paper is to review some of the several functions controlled by Ir genes, the nature of the gene products, and the concepts which have been put forward to explain their function. The recent literature abounds with valuable reviews describing and analyzing these. References to some of these will be made in order that the reader may consult the details himself.

Location of Ir genes in the genome

In all species studied so far the Ir genes have been located to the MHC. The most thoroughly

studied MHC is the H-2 region of the mouse (19), which is traditionally defined as the segment on chromosome 17 between the K and D regions. The Ir genes are located within the I region (Fig. 1) in which five subregions have been defined. In two of these, the A and E subregions, Ir genes have been unequivocally mapped. The A subregion contains three known loci, A_α , A_β , and E_β . The E subregion contains a single locus, E_α . A question of major importance for the issue of the function of the Ir genes remains unanswered. Are we dealing with only these four loci (20), or do there exist additional heretofore unidentified loci (8, 25, 30)?

A unique feature of the MHC genes, including the Ir genes, is their extreme polymorphism in all of the species that have been studied. Serological H-2 typing of inbred laboratory mice has revealed the existence of 11 alleles at the A_β locus alone (21). It has been estimated that the global number of A_β alleles in wild mice may be tenfold higher. The polymorphism at some of the other H-2 loci is of a comparable magnitude. This degree of genetic polymorphism appears to be unprecedented, and its biological significance is believed to reflect the function of the genes. Selective pressures represented by life-threatening parasites may select against those Ir genes which fail to endow the individual with the capacity to make appropriate immune responses towards the particular parasite and for those which do. In a different geographic region the selective pressures may be represented by other parasites which may select against other Ir genes.

The human MHC, the HLA-region, is situated on chromosome 6. Four regions have been

identified, HLA-A, -B, -C, and -D. Of these the HLA-D region corresponds to the I-region of the mouse and other species, and it is here we should expect to find the human Ir genes.

Products of MHC genes

The gene products are transmembraneous cell surface glycoproteins (51) commonly referred to as Class I and Class II MHC molecules. Class I molecules are expressed by all somatic cells. They are composed of two types of polypeptide chains (Fig. 1). A light invariant chain consisting of beta-2-micro-globulin, and a heavy chain of 45,000 mol.wt. which in the mouse is coded from the K or the D region. The K and D molecules of the mouse constitute the classical transplantation antigens, which are easily detected by serological methods, and which correspond to the HLA-A, -B, and -C molecules in man.

The Class II molecules, the Ia molecules, are expressed only by cells of the immune system. They can be detected on B cells, a proportion of macrophages and macrophage-like cells, and on activated but not resting T cells. Class II molecules (Fig. 2) are composed of two chains: a heavy alpha chain of 33,000 mol.wt. and a light beta chain of 28,000 mol.wt. The two chains are non-covalently attached to one another, the A_α with the A_β and the E_α with the E_β . The complete molecule is formed by post-translational association of the chains. This means that, whereas a homozygote mouse expresses a single A molecule, a heterozygote expresses four since the alpha chain derived from either parent can form an A molecule with the beta chain derived from either parent, as illu-

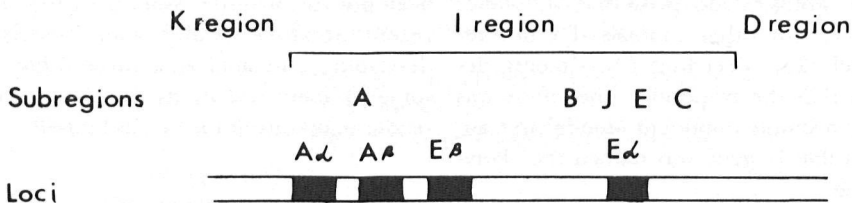


Fig. 1. The mouse H-2 complex. The I region is flanked by the K and D regions. Only loci of the I region are shown. Omitted from the map is the S region (located between I and D) in which genes coding for complement factors are located. The map is not drawn to scale. Modified from Svejgaard et al. (45) with the permission of S. Karger AG, Basel.

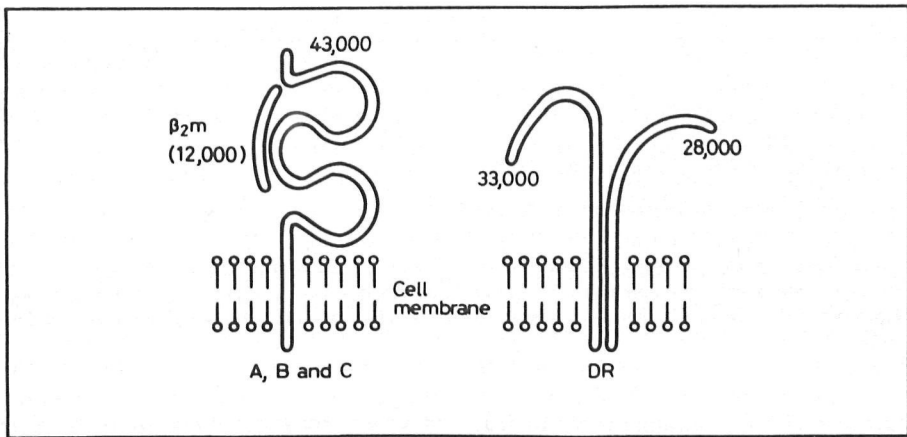


Fig. 2. Models of the Class I and Class II MHC molecules showing their relations to the cell surface. Within each molecule, the two chains are non-covalently bound together. The figures indicate the molecular weights of the chains. β_2m = beta2-microglobulin. Modified from Svejgaard et al. (45) with the permission of S. Karger AG, Basel.

strated in Fig. 4. Partial amino acid sequences of human and murine Class II molecules have been available for some years (51). As expected, murine and human molecules display amino acid sequence homologies. Very recently the amino acid sequence of a large part of the beta-chain of a human HLA-D molecule was determined from the nucleotide sequence of cloned cDNA (22). A comparison of the amino acid sequence in some regions of this Class II molecule with already known sequences in other molecules revealed interesting sequence homologies with HLA-A, -B, -C molecules, and beta-2-microglobulin, and with immunoglobulin chains. It therefore appears that the Ir genes and the immunoglobulin genes may have a common ancestral gene. This is compatible with the notion that the products of Ir genes may be molecules with a recognition function.

Traits controlled by Ir genes

A single Ir gene appears to be pleiomorphic, i.e. it controls several traits (20). In addition to Ia phenotype the Ir gene controls responsiveness to selected antigens and the generation of suppressor T cells (3), collaboration of macrophages and T cells (50), collaboration of T and B cells (50), rejection of allografts and graft-versus host reactions, responsiveness to allo-

genic cells in mixed leukocyte cultures (50), and in man, susceptibility to certain diseases (44, 45, 46). Some of these traits will be reviewed below.

Responsiveness to antigens

As described in the Introduction immunization of outbred Hartley guinea pigs with DNP-PLL elicited delayed hypersensitivity towards DNP-PLL and production of anti-DNP antibodies in some animals, but no response at all in others. It was later discovered that guinea pigs of the inbred NIH strain 2 were all responders to DNP-PLL and that guinea pigs of the inbred NIH strain 13 were all non-responders. These strains of guinea pig are of similar genetic background but differ at the MHC. Experiments with F1-crosses and F2-crosses revealed that the "poly-L-lysine gene" segregated together with the strain 2 MHC. Responsiveness of guinea pig to another synthetic antigen, GT, which is the random copolymer of L-glutamic acid and L-tyrosine is regulated by a different Ir gene linked to the strain 13 MHC (5).

In mice immune responsiveness to a large number of synthetic antigens including linear and branched polypeptides have been shown to be under genetic control. As in guinea pigs the responsible genes are located within the MHC

Table 1

														Immunogenicity for guinea pigs:	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	strain 2	strain 13
PCA-Gly-Val-Asn-Asp-Asn-Glu-Glu-Gly-Phe-Phe-Ser-Ala-Arg-OH														+++	0
PCA-Gly-Val-Asn-Asp-Asn-Glu-Glu-Gly-Phe-Phe-Ser-Ala-OH														0	+++

The 14-residue peptide Hfb is immunogenic in strain 2 but not in strain 13 guinea pigs. The 13-residue peptide produced by removal of the carboxy-terminal Arg is immunogenic in strain 13 but not in strain 2 guinea pigs. Immunogenicity was assessed by assay for proliferation *in vitro* of T cells from animals primed to the peptides *in vivo*. Based on the data of Thomas and co-workers (47).

and behave as simple dominant Mendelian genes. An interesting exception to this rule is the responsiveness to the synthetic antigen GLØ, which is the terpolymer of L-glutamic acid, L-lysine, and L-phenylalanine. Some strains of mice are responders to GLØ. Other strains such as B10.Br (H-2^k) and B10 (H-2^b) are non-responders. Unexpectedly F1-hybrids (B10.Br. × B10) were found to be responders to GLØ. This phenomenon (10), named gene complementation, can be explained as follows. Responsiveness to GLØ requires the possession of an I_a molecule formed by association of the E_α chain from the H-2^k haplotype and the E_β chain from the H-2^b haplotype. This explanation is strongly supported by the finding that inbred recombinant mouse strains B10A.3R and B10A.5R are responders to GLØ. These strains have a recombination in the I region with an E_α subregion derived from H-2^k and an E_β subregion derived from H-2^b.

Ir gene control of responsiveness to some natural protein antigens has also been established. These include insulin (1) myoglobin (4), cytochrome C (7, 42), and some other molecules of limited size. An advantage from the use of these antigens is the availability of different issues of the same protein which may differ from one species to another by a few amino acids at defined sites in the molecule. Small naturally occurring peptide antigens can also be manipulated with profound effects on their quality as antigen. A particularly striking example is the use of human fibrinopeptide B (HfB), as an antigen in guinea pigs (47, 48). Table 1 shows the amino acid sequence of the

molecule and the pattern of responsiveness to different issues of HfB of two strains of guinea pigs which differ in the I region of the MHC. While strain 2 guinea pigs are responders to native HfB and strain 13 are non-responders precisely the opposite was the case for responsiveness to des-Arg HfB. This and other examples (49) emphasize the extremely fine specificity of the Ir gene control.

Collaboration between macrophages and T cells

A convenient method for measuring immune responses to protein antigens is the assay for antigen-specific proliferation of T cells *in vitro*. Primed T cells "purified" from lymph nodes or peritoneal exudates are mixed with irradiated syngeneic spleen or peritoneal exudate cells and cultured for 4 days in medium containing the antigen. Tritiated thymidine is added 20 h before the cultures are terminated and the uptake of tritium by the T cells is measured. The amount of radioactivity is a measure of the intensity of the response. This method carries the advantage that the contributions of different types of cells can be evaluated by the use of defined populations of cells. It was initially demonstrated that proliferation of T cells in response to natural protein antigens required the presence of macrophages or macrophage-like cells in the culture (52), hence the use of irradiated peritoneal exudate cells which are rich in macrophages. Furthermore, it became clear that the antigen to which the T lymphocytes had been primed was not required in soluble form in the culture medium. It was

sufficient that the macrophages had been exposed to (pulsed with) the antigen by brief culture prior to their co-culture (34) with the primed T cells. These findings formed the basis of the now generally accepted concept that macrophages "present" antigens to T cells.

The antigen-presenting function is displayed only by that subpopulation of macrophages and macrophage-like cells, which expresses Ia molecules. Elimination of the Ia-positive members from a population of macrophages by pre-treatment with anti-Ia sera + complement abrogates their capacity for antigen presentation, even though only 20% of the cells may be destroyed by such treatment. Furthermore, in assays of antigen-specific T cell proliferation the addition of alloantisera and of some monoclonal sera directed against the Ia molecules of the antigen-presenting macrophages also blocks or severely decreases the response of the primed T cells (39). It is therefore evident that Ia molecules of macrophages play a crucial role in the presentation of antigen to T cells.

This role was further defined in a series of experiments undertaken by Rosenthal & Shevach (35, 40). They demonstrated that guinea pig T cells primed to antigen *in vivo* would give a specific proliferative response *in vitro* only when stimulated with antigen-pulsed macrophages of the same I-region type, i.e. possessing Ia molecules of the same type as the T cells themselves. This phenomenon has been shown to be a general one in numerous experiments with cells from guinea pigs and mice (38) and has been termed the "MHC-restriction" of macrophage-T cell collaboration. The discovery of MHC-restriction led to the concept that T cells recognize not only the foreign antigen, but also a part of an Ia molecule on the surface of the presenting cell. Most present hypotheses envisage this as a complex antigenic determinant formed by association of the two (Fig. 3), and postulate that the T cell recognizes the complex with a single receptor as shown in alternative (d) of Fig. 3. So far, such complexes have not been identified by chemical methods,

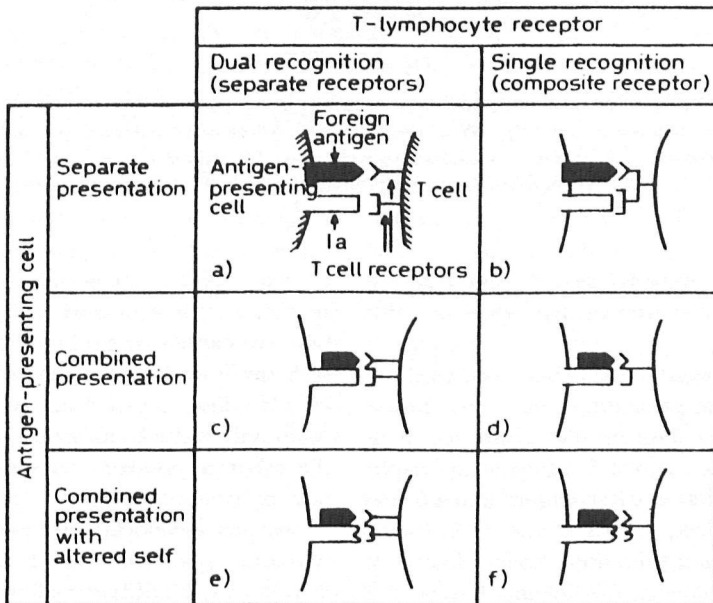


Fig. 3. Models of the molecular interactions involved in the collaboration between macrophage and T cell during activation of the T cell by antigen. Most present hypotheses postulate recognition of a complex determinant via a single T cell receptor as in alternatives d) and f). In the latter the Ia molecule is altered by its interaction with the foreign antigen. Modified from Svejgaard et al. (45) with the permission of S. Karger AG, Basel.

HYBRID I-A ANTIGENS

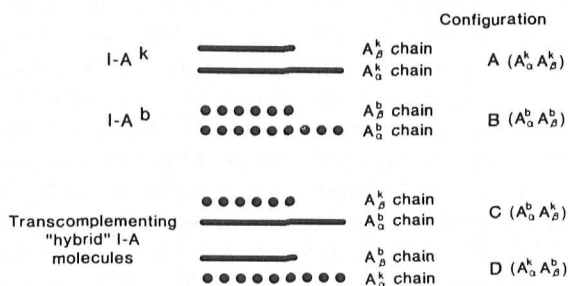
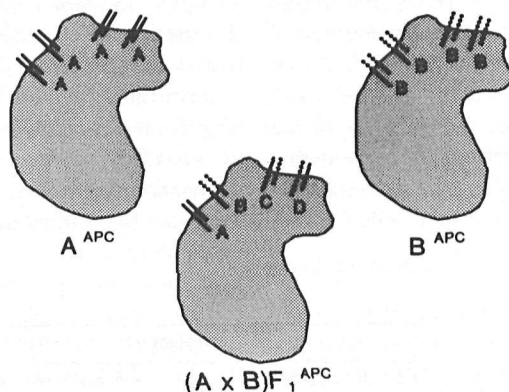
F₁ ANTIGEN PRESENTING DETERMINANTS

Fig. 4. Schematic drawing of hybrid Ia molecules. Mice of haplotype k possess a single A molecule (A^k_α A^k_β) and mice of haplotype b a single A molecule (A^b_α A^b_β). These are formed by association of one chain and one chain. In the (k × b) F₁-hybrid four A molecules are formed by association of each parental α chain with each parental β chain. Modified from Fathman & Kimoto (14) with the permission of Munksgaard International Publishers Ltd., Copenhagen.

and functional experiments designed to demonstrate their existence are open to other interpretations.

In the discussion above it has been assumed that the antigen-presenting cells were homozygous and thus possess the single set of Ia molecules defined by the I region of the haplotype. The situation in heterozygous animals may be more complex. In an (A × B)F₁-hybrid animal the antigen-presenting macrophages express Ia molecules of both A and B type and would thus be expected to present antigens in the "context" of both types of Ia. That this is indeed the case was shown by Paul and co-workers (31), who demonstrated the existence

of two independent populations of ovalbumin-specific T cells in primed F₁-hybrid guinea pigs. One responded by proliferation when cultured with ovalbumin-pulsed macrophages of parent A, but failed to proliferate when cultured with ovalbumin-pulsed macrophages of parent B; the other responded only to ovalbumin-pulsed macrophages of parent B.

Recently developed technology for the isolation and expansion of clones of antigen-specific T cells (14, 32, 43) has allowed a further dissection of the restricted specificity of T cells. Such T cell clones can be assayed for proliferation in the same assay as the one used for heterogeneous populations of T cells. With this

technique Fathman and co-workers were able to isolate from heterozygous mice primed *in vivo* to GAT (the random polymer of L-glutamic acid, L-alanine and L-tyrosine) four distinct clones of T cells all specific for the antigen but each restricted by a different set of Ia molecules (Fig. 4).

What is the restriction specificity of the T cells from a (responder $\times$ non-responder) F1-hybrid primed to an antigen to which responsiveness is under Ir gene control? This was studied in (2×13) F1-hybrid guinea pigs using the antigen DNP-GL. (The DNP conjugate of the random copolymer of L-glutamic acid and L-lysine) to which responsiveness is controlled by an Ir gene possessed only by strain 2 guinea pigs (35, 40). Unexpectedly, the DNP-GL primed T cells were capable of proliferating in response to the antigen only when it was presented by pulsed macrophages of strain 2 (or F1) animals. Thus, macrophages of the non-responder strain 13 were incapable of presenting the antigen. This outcome, which has since been confirmed in mice with other antigens under Ir gene control, was unexpected and pointed to the highly radical solution that Ir gene control was maintained by the antigen-presenting cell and not by the T cell. This is discussed further below.

Although as described above, anti-Ia sera are very efficient in blocking the presentation of antigens by macrophages in assays of T cell proliferation, attempts to likewise block antigen presentation by the addition of antisera directed against the foreign antigen itself notably fails to block presentation (12, 13, 24). Furthermore, trypsin treatment of antigen-pulsed macrophages before their co-culture with primed T cells fails to destroy their capacity for presenting the antigen. This suggests that the foreign antigen may be kept in an antibody and trypsin-inaccessible site in the macrophage (13).

The process of antigen-presentation thus appears to involve several steps, the first of which is an uptake of the antigen by the presenting cell. Subsequently a complex is formed of antigen and the Ia molecules of the cell. The formation of the complex may be preceded or succeeded by partial catabolism of the foreign antigen (56). Recognition of the

complex by T cells takes place during a physical interaction between specific T cell and presenting cell (28, 53, 54, 55) during which the T cell is assumed to receive at least two signals necessary for its activation. One is through its antigen specific receptor; the other is through interleukin 1, a non-specific factor elaborated by the presenting cell (15, 29, 41).

Hypotheses to explain the function of Ir genes

The hypothesis put forward by Rosenthal (33) and by Benacerraf (2) postulates that the Ir genes are functionally expressed in antigen-presenting cells and involved in the presentation of foreign antigens to T cells. In this view the products of Ir genes, the Ia molecules, interact selectively with certain amino acid sequences on protein antigens and thereby dictate which determinants on the antigen will be presented to T cells. The size of the binding site on the Ia molecule is postulated to encompass three or four amino acids (2). A given Ia molecule is envisaged to be capable of reacting with similar sites on different protein antigens. Since the contiguous chain of the antigen becomes a part of the antigenic determinant, one Ia molecule should be capable of creating a large number of different determinants with different protein antigens. In this hypothesis an individual possessing Ia molecules capable of interacting with a given protein antigen will be a responder to the antigen, and will upon priming produce T cells specific for the selected determinants. An individual possessing no such Ia molecules will be a non-responder to the antigen.

There is no definite chemical evidence of association between Ia molecules and foreign antigen, which "determinant selection" hypotheses postulate. Some functional experiments (27) have demonstrated that T cells activated *in vitro* with the antigen GAT did express on their surface that particular Ia molecule which is known to be involved in the presentation of GAT. If the T cells had instead been activated with the antigen GLØ they did express a different Ia molecule, known to be involved in the presentation of GLØ. This finding can be inter-

puted to mean that T cells bind a complex of Ia and foreign antigen derived from antigen-presenting cells during their activation, although it was not excluded that the Ia molecules were instead synthesized by the T cells themselves. Another type of indirect evidence for an association of Ia molecules and foreign antigens comes from this author's laboratory (Werdelin, O. Submitted for publication). I have shown that the two antigens, DNP-PLL and GL, to which responsiveness is assumed to be regulated by the same single Ir gene, compete for being presented by antigen-presenting cells. A likely interpretation of the competition would be that the two antigens compete for interaction with the same Ia molecule of the antigen presenting cell.

The "determinant selection hypothesis" is unique in that it attributes to the products of Ir genes the ability to recognize, albeit with an ill-defined and archaic specificity, sites on foreign antigens defined by a few amino acids. For the presentation of the large world of complicated protein antigens it would appear that several distinct gene products were required, and that accordingly there must be Ir gene loci not yet discovered. As pointed out by McDevitt (25) the number of loci required for the Ia molecules to constitute a true antigen recognition system may still be quite small, since a large number of different Ia molecules can be constructed from a limited number of genes through combinatorial associations as described above and through regulatory polymorphisms.

The "determinant selection hypothesis" has recently been challenged by a series of experiments performed by Ishii et al. (17), which indicate that antigen-presenting cells of strains of mice which are non-responders to the antigen GA (the random copolymer of L-glutamic acid and L-alanine) can after all present GA to T cells. Ishii et al. primed T cells *in vitro* by culturing them with antigen-presenting cells in the presence of GA. Since the experiments involved mixing of T cells with histoincompatible antigen-presenting cells the alloreactive T cells had to be eliminated. This was done by pre-culturing the T cells with the relevant anti-

gen-presenting cells in the absence of GA and then eliminating the alloreactive cells by feeding the cultures bromooxyuridine and ultraviolet light. The surviving T cells were then primed to GA by culture with fresh antigen-presenting cells and GA, and could subsequently be assayed for a proliferative response to GA in the context of antigen-presenting cells of different origins. In the crucial experiment it was shown that T cells derived from one non-responder strain could be primed to give a specific response to GA in the context of antigen-presenting cells of a different non-responder genotype. In fact, the only cell combination in which priming could not be achieved was the one in which T cells and presenting cells derived from the same non-responder strain. Another recent report (6) describes the production of T cell clones or cell lines of guinea pigs capable of giving proliferative response to the antigen GL presented by cells of GL non-responder genotype. These very recent findings strongly contradict the postulate described above that non-responsiveness to an antigen is due to a failure of its presentation. Instead they argue that the defect of the non-responder may be a "hole" in the T cell repertoire with a selective lack of clones reactive with the foreign antigen in the context of self-Ia. It has been suggested that such "holes" are the result of a deletion or suppression of clones of T cells directed against determinants which closely "mimick" self antigens (37).

Prospects

The pleiomorphism of the Ir genes has been alluded to above. At present it is hardly possible to put forward a complete concept bringing together all of the apparently unrelated traits which seem to be controlled by the individual Ir gene. It would appear a sound working hypothesis that all of these traits are artificial derivatives of one basic function of the gene product. In this review I have deliberately concentrated upon a few which I believe to be basic. Once these are thoroughly understood we may understand the other. The rewards should be considerable: they include a keener understanding

of the workings of the immune system and perhaps insight into the etiology of a dozen human diseases.

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REFERENCES

- Barcinsky, M. A. & Rosenthal, A. S.: Immune response gene control of determinant selection. I. Intramolecular mapping of the immunogenic sites on insulin recognized by guinea pig T and B cells. *J. Exp. Med.* **145**, 726-742, 1977.
- Benacerraf, B.: A hypothesis to relate the specificity of T lymphocytes and the activity of I region specific Ir genes in macrophages and B lymphocytes. *J. Immunol.* **120**, 1809-1812, 1978.
- Benacerraf, B. & Germain, R. N.: The immune response genes of the major histocompatibility complex. *Immunol. Rev.* **38**, 70-119, 1978.
- Berzofsky, J. A. & Richman, L. K.: Genetic control of the immune response to myoglobins. IV. Inhibition of determinant-specific Ir gene-controlled antigen presentation and induction of suppression by pretreatment of presentigen cells with anti-Ia antibodies. *J. Immunol.* **126**, 1898-1904, 1981.
- Blueslein, H. G., Green, I. & Benacerraf, B.: Specific immune response genes of the guinea pig. I. Dominant genetic control of immune responsiveness to copolymers of L-glutamic acid and L-alanine, and L-glutamic acid and L-glutamic acid and L-tyrosine. *J. Exp. Med.* **134**, 458-470, 1971.
- Clark, R. B. & Shevach, E. M.: Generation of T cell colonies from responder strain 2 guinea pigs which recognize the copolymer L-glutamic acid, L-lysine in association with nonresponder strain 13 antigens. *J. Exp. Med.* **155**, 635-640, 1982.
- Corradin, G. & Chiller, J. M.: Lymphocyte specificity to protein antigens. II. Fine specificity of T-cell activation with cytochrome C and derived peptides as antigenic probes. *J. Exp. Med.* **149**, 436-447, 1979.
- Delovitch, T. L. & Barber, B. H.: Evidence for two homologous, but nonidentical Ia molecules determined by the I-EC subregion. *J. Exp. Med.* **150**, 100-107, 1979.
- Dorf, M. E., Balner, H. & Benacerraf, B.: Mapping of the immune response genes in the major histocompatibility complex of the rhesus monkey. *J. Exp. Med.* **142**, 673-693, 1975.
- Dorf, M. E. & Benacerraf, B.: Complementation of H-2-linked Ir genes in the mouse. *Proc. Natl. Sci. USA* **72**, 3671-3675, 1975.
- Ellman, L., Green, I., Martin, W. I. & Benacerraf, B.: Linkage between the poly-L-lysine gene and the locus controlling the major histocompatibility antigens in strain 2 guinea pigs. *Proc. Natl. Acad. Sci. USA* **66**, 322-328, 1970.
- Ellner, J. J. & Rosenthal, A. S.: Quantitative and immunologic aspects of the handling of 2,4-dinitrophenyl guinea pig albumin by macrophages. *J. Immunol.* **114**, 1563-1569, 1975.
- Ellner, J. J., Lipsky, P. E. & Rosenthal, A. S.: Antigen handling by guinea pig macrophages: Further evidence for the sequestration of antigen relevant for activation of primed T lymphocytes. *J. Immunol.* **118**, 2053-2057, 1977.
- Fathman, C. G. & Kimoto, M.: Studies utilizing murine T cell clones: Ir genes, Ia antigens and MLR stimulating determinants. *Immunol. Rev.* **54**, 57-79, 1981.
- Gery, I. & Waksman, B. H.: Potentiation of the T-lymphocyte response to mitogens. II. The cellular source of potentiating mediator(s). *J. Exp. Med.* **136**, 143-155, 1972.
- Günther, R., Rüde, E. & Stark, O.: Antibody response in rats to the synthetic polypeptide (T,G)-A-L genetically linked to the major histocompatibility system. *Eur. J. Immunol.* **2**, 151-155, 1972.
- Ishii, N., Nagy, Z. A. & Klein, J.: Absence of Ir gene control of T cells recognizing foreign antigen in the context of allogenic MHC molecules. *Nature* **295**, 531-533, 1982.
- Katchalsky, E. & Sela, M.: Synthesis and chemical properties of poly-amino acids. *Adv. Protein Chem.* **13**, 243-, 1958.
- Klein, J.: Biology of the mouse histocompatibility complex. Springer Verlag, Berlin, 1975.
- Klein, J., Juretic, A., Baxevanis, C. N. & Nagy, Z. A.: The traditional and a new version of the mouse H-2 complex. *Nature* **291**, 455-460, 1981.
- Klein, J. & Figueroa, F.: Polymorphism of the mouse H-2 loci. *Immunol. Rev.* **60**, 23-57, 1981.
- Larhammar, D., Wiman, K., Schenning, L., Claesson, L., Gustafsson, K., Peterson, P. A. & Rask, L.: Evolutionary relationship between HLA-DR antigen β -chains, HLA-A, B, C antigen subunits and immunoglobulin chains. *Scand. J. Immunol.* **14**, 617-622, 1981.
- Levine, B. B., Ojeda, A. & Benacerraf, B.: Studies on artificial antigens. III. The genetic control of the immune response to hapten-poly-L-lysine conjugates in guinea pigs. *J. Exp. Med.* **118**, 953-957, 1963.
- Loblay, R. H., Shroer, J. & Rosenthal, A. S.: Attempts of determinant-specific antibody blockade of macrophage presentation. In Uranue, E. R. & Rosenthal, A. S. (eds.): Macrophage regulation of immunity, p. 87. Academic Press, New York, 1979.
- McDevitt, H. O.: The role of H-2 I region genes in regulation of the immune response. In Fougereau, M. &

- Dausset, J. (eds.): Progr. Immunol. IV, p. 503. Academic Press, New York, 1980.
26. McDevitt, H. O. & Chinitz, A.: Genetic control of antibody response: Relationship between immune response and histocompatibility (H-2) type. *Science* **163**, 1207–1208, 1969.
 27. Nepom, J. T., Benacerraf, B. & Germain, R. N.: Acquisition of syngeneic I-A determinants by T cells proliferating in response to poly (Glu⁶⁰ Ala³⁰ Tyr¹⁰). *J. Immunol.* **127**, 888–892, 1981.
 28. Nielsen, M. H., Jensen, H., Brændstrup, O. & Werdelin, O.: Macrophage-lymphocyte clusters in the immune response to soluble protein antigen in vitro. II. Ultrastructure of clusters formed during the early response. *J. Exp. Med.* **140**, 1260–1272, 1974.
 29. Oppenheim, J. J., Northoff, H., Greenhill, A., Mathieson, B. J., Smith, K. & Gillis, S.: In DeWeck, A., Kristensen, F. & Landy, M. (eds.): Characterization of lymphokines, p. 399. Academic Press, New York, 1980.
 30. Ozato, K. & Sachs, D. H.: Detection of at least two distinct mouse I-E antigen molecules by the use of a monoclonal antibody. *J. Immunol.* **128**, 807–811, 1982.
 31. Paul, W. E., Shevach, E. M., Pickeral, S., Thomas, D. W. & Rosenthal, A. S.: Independent populations of primed F1 guinea pig T lymphocytes respond to antigen-pulsed parental peritoneal exudate cells. *J. Exp. Med.* **145**, 618–630, 1977.
 32. Paul, W. E., Sredni, B. & Schwartz, R. H.: Long-term growth and cloning of non-transformed lymphocytes. *Nature* **294**, 697–699, 1981.
 33. Rosenthal, A. S.: Determinant selection and macrophage function in genetic control of the immune response. *Immunol. Rev.* **40**, 136–152, 1978.
 34. Rosenstreich, D. L. & Rosenthal, A. S.: Peritoneal exudate lymphocyte. II. In vitro lymphocyte proliferation induced by brief exposure to antigen. *J. Immunol.* **110**, 934–942, 1973.
 35. Rosenthal, A. S. & Shevach, E. M.: Function of macrophages in antigen recognition by guinea pig T lymphocytes. I. Requirement for histocompatible macrophages and lymphocytes. *J. Exp. Med.* **139**, 1194–1212, 1973.
 36. Scheibel, I. F.: Hereditary differences in the capacity of guinea pigs for the production of diphtheria antitoxin. *Acta Pathol. Microbiol. Scand.* **20**, 464–484, 1943.
 37. Schwartz, R. H.: The nature of immune response gene defect. *Nature* **295**, 455–456, 1982.
 38. Schwartz, R. H., Yano, A. & Paul, W. E.: Interaction between antigen-presenting cells and primed T lymphocytes: An assessment of Ir gene expression in the antigen-presenting cell. *Immunol. Rev.* **40**, 153–180, 1978.
 39. Shevach, E. M., Paul, W. E. & Green, I.: Histocompatibility linked immune response gene function in guinea pigs. Specific inhibition of antigen-induced lymphocyte proliferation by alloantisera. *J. Exp. Med.* **136**, 1207–1221, 1972.
 40. Shevach, E. M. & Rosenthal, A. S.: Function of macrophages in antigen recognition by guinea pig T lymphocytes. II. Role of the macrophage in the regulation of genetic control of the immune response. *J. Exp. Med.* **138**, 1213–1229, 1973.
 41. Smith, K. A. & Ruscetti, F. W.: T-cell growth factor and the culture of cloned functional T cells. *Adv. Immunol.* **31**, 137–175, 1981.
 42. Solinger, A. N., Ultee, M. E., Margoliash, E. & Schwartz, R. H.: T lymphocyte response to cytochrome C. I. Demonstration and identification of a topographic antigenic determinant on pigeon cytochrome C whose immune recognition requires two complementing major histocompatibility complex-linked immune response genes. *J. Exp. Med.* **150**, 830–848, 1979.
 43. Sredni, B. & Schwartz, R. H.: Antigen-specific, proliferating T lymphocyte clone. Methodology, specificity, MHC restriction and alloreactivity. *Immunol. Rev.* **54**, 187–223, 1981.
 44. Svejgaard, A.: HLA and autoimmune diseases. *Allergy* **34**, 27–281, 1979.
 45. Svejgaard, A., Hauge, M., Jersild, C., Platz, P., Ryder, L. P., Staub Nielsen, L. & Thomsen, M.: The HLA system. An introductory survey. In Beckman, L. & Hauge, M. (eds.): Monographs in human genetics, vol. 7, 2nd revised edn. S. Karger, Basel, 1979.
 46. Svejgaard, A., Morling, N., Platz, P., Ryder, L. P. & Thomsen, M.: HLA and disease. In Fourereau, M. & Dausset, J. (eds.): Progr. Immunol. IV, p. 530. Academic Press, New York, 1980.
 47. Thomas, D. W., Meltz, S. K. & Wilmer, G. D.: Nature of T lymphocyte recognition of macrophage associated antigens. I. Response of guinea pig T cells to human fibrinopeptide B. *J. Immunol.* **123**, 759–764, 1979.
 48. Thomas, D. W., Hsieh, K. H., Schauster, J. L. & Wilner, G. D.: Nature of the T lymphocyte recognition of macrophage-associated antigens. The contribution of individual peptide residues of human fibrinopeptide B to T lymphocyte responses. *J. Exp. Med.* **152**, 620–632, 1980.
 49. Thomas, D. W., Hsieh, K. H., Schauster, J. L. & Wilner, G. D.: Fine specificity of genetic regulation of guinea pig T lymphocyte responses to angiotensin II and related peptides. *J. Exp. Med.* **153**, 583–594, 1981.
 50. Unanue, E. R.: The regulatory role of macrophages in antigenic stimulation. Part two: Symbiotic relationship between lymphocytes and macrophages. *Adv. Immunol.* **31**, 1–136, 1981.
 51. Vitetta, E. S. & Capra, J. D.: The protein products of the murine 17th chromosome: Genetics and structure. *Adv. Immunol.* **26**, 147–193, 1978.
 52. Waldron, J. A., Horn, R. G. & Rosenthal, A. S.: Antigen-induced proliferation in vitro: Obligatory role of macrophages in the recognition of antigen by immune T lymphocytes. *J. Immunol.* **131**, 58–64, 1973.
 53. Werdelin, O., Brændstrup, O. & Pedersen, E.: Macrophage-lymphocyte clusters in the immune response to soluble protein antigen in vitro. I. Roles of lymphocytes and macrophages in cluster formation. *J. Exp. Med.* **140**, 1245–1259, 1974.
 54. Werdelin, O., Brændstrup, O. & Shevach, E. M.: Specific absorption of T lymphocytes committed to soluble protein antigens by incubation of antigen-pulsed macrophage monolayers. *J. Immunol.* **123**, 1755–1762, 1979.
 55. Werdelin, O. & Shevach, E. M.: Role of nominal antigen and Ia antigen in the binding of antigen-specific T

- lymphocytes to macrophages. *J. Immunol.* 123, 2779–2784, 1979.
56. Ziegler, K. & Unanue, E. R.: Identification of a macrophage antigen-processing event required for I-region restricted antigen presentation to T lymphocytes. *J. Immunol.* 127, 1896–1875, 1981.

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