T LYMPHOCYTES TODAY

Edited by J. R. Inglis

Elsevier

T Lymphocytes Today

Edited by J. R. Inglis

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1983

ELSEVIER SCIENCE PUBLISHERS
Amsterdam – New York – Oxford

ISBN: 0 444 80525 9

Published by
Elsevier Science Publishers BV
PO Box 1527
1000 BM Amsterdam
The Netherlands

Sole distributors worldwide except for USA and Canada
Elsevier Publications (Cambridge)
68 Hills Road
Cambridge CB2 1LA
United Kingdom

Sole distributors for the USA and Canada
Elsevier Science Publishing Company Inc.
52 Vanderbilt Avenue
New York, NY 10017, USA

Cover design by Kate Wright

Printed in the United Kingdom

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Preface

This volume contains a selection of the articles on the biology of T lymphocytes that have been commissioned for publication in the monthly journal *Immunology Today*. Three were written in 1980 and the remaining twenty-eight in 1981, 1982 and 1983. Postscripts have been added to five of the seven 1981 articles, updating them to March 1983.

The articles are grouped in five sections each addressing a major aspect of T-cell biology: antigen receptors; development; interactions with other immunologically involved cells; cell- and tissue-damaging responses; and disorders of function. Because this classification scheme has been imposed on articles written for the journal it is not a rigid one, and there are instances in which papers in one section are relevant to another.

The scheme and its imperfections were also imposed on the four distinguished students of the T cell who nevertheless each kindly consented to provide an introduction to a section. This was not a straightforward task and all have performed it with admirable results. To each of them, Charles Janeway, Richard Miller, Fritz Bach and Elizabeth Simpson, I am sincerely grateful.

T-cell biology is unfolding at a formidable pace and its developments continue to be charted in contributions to *Immunology Today*. But a selection of articles such as this has to stop somewhere and the end of the first quarter of 1983 does not seem inappropriate. The techniques of molecular genetics are now beginning to illuminate just how the processes of gene transcription and translation combine to give the T cell (more accurately each functional class of T cell) its uniqueness. The recent isolation and cloning of the gene for interleukin 2 is one example of the first fruits of a new era of attempts to understand T cells at the DNA level. It remains to be seen what impact these will have on the concepts that matured on the strength of the classic techniques of cellular immunology. What is certain is that the next few years promise to be as exciting for T-cell biology as the last few have been. These recent strides in understanding and the challenges, theories and paradoxes they have revealed are recorded here by writers who are closely involved with the events concerned. It is a pleasure to be able to record my thanks to these contributors for generously agreeing to communicate their enthusiasms in a style which appeals to as wide an audience as possible. I am also grateful to Nina Muir for her invaluable assistance in compiling this volume.

John R. Inglis

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Genes and receptors

Introduction

C. A. Janeway, Jr

One of the most fascinating and important problems in modern immunobiology is the nature of the T-cell receptor, the molecule or molecular complex used by T cells for specific recognition of antigen. We know very little, even now, about the molecular composition of this structure or the genes which encode it. The articles in this section represent a spectrum of views of this problem caught at a particular moment in time. In introducing this very heterogeneous collection of articles, I will attempt to state the problem, to outline the major observations about T-cell behavior that need to be accommodated by any theory of T-cell receptors, to link each of the papers here into these central questions, and finally to give my own current view of a reasonable minimal hypothesis.

The first and most obvious thing to clarify is the beast under study, and this is almost certainly the source of a good deal of the problems immunologists have in agreeing with one another about T-cell receptors. We call a collection of functionally diverse but morphologically similar cells 'T cells' because they look like lymphocytes, behave in an antigen-specific fashion, and do not express surface Ig, the hallmark of the other major lymphocyte subdivision, the B cells. T cells also share cell-surface antigenic determinants, Thy-1 in the mouse or T3 in man. Finally, their functional activity cannot be directly elicited in athymic mice or human beings, suggesting that a sojourn in the thymus is essential to their function. However, these shared characteristics apart, T cells are highly heterogeneous. Some even appear to mature quite well in the absence of a thymus (see Hunig, p. 42). Some T cells bind directly to antigen, while others bind antigen only when presented on the surface of cells identical at the major histocompatibility complex (MHC). Some T cells appear to require cell contact to mediate their effects, while others secrete long-range antigen-specific or non-specific mediators. Finally, T-cell function often involves complex cell interactions, making analysis of specificity by functional assay difficult, since it is not clear which cell one is influencing with a particular reagent. Indeed, it might be useful at some future time, when T-cell function is better understood, to rename T-cell subpopulations so as not to confuse them with one another.

Most of the papers in this section focus on the most easily analysed T-cell sets, helper and cytolytic T cells. What has aroused the greatest interest in these T cells is their property of recognizing antigen in the context of self-MHC molecules. To explain this apparent dual specificity, a great many different models for the T-cell receptor have been proposed. Two additional questions enter the problem at this stage. One is to account for the very high frequency of T cells reactive to non-self-MHC determinants. This is generally taken nowadays to reflect a cross-reactive recognition by T cells which are also specific for some foreign antigen, conventionally designated X, seen in the context of self MHC. How different theories of T-cell receptor structure accommodate the recognition of non-self MHC is one of their distinguishing characteristics. The second problem is the association, or lack of it, of X with self-MHC molecules. Some prefer to assume that this association does not occur, or has no specificity; indeed, some authors (see Parish *et al.*, p. 7) prefer to think that MHC proteins are not involved in this process at all.

Interestingly, in the ten years since it was observed that helper T cells and cytotoxic T cells recognize antigen in the context of self-MHC molecules, little advance has been made in the theoretical formulation of T-cell receptor specificity. Basically, there are two schools of thought, with many variants. One school argues that the

receptor has two combining sites, one specific for self-MHC molecules and one specific for X: the other school proposes that a single combining site recognizes a neoantigenic determinant generated by the physical interaction of X with self MHC. A variety of different models to account for alloreactivity have been engrafted on to one or other paradigm, after it was observed that alloreactivity was generally a property of T cells which react with self-MHC plus X. Several of the articles in this section deal with this question in a variety of modes, and other articles in this book also deal with similar arguments, most notably in the section on the role of the thymus in determining the T-cell repertoire. For the present section, however, the problem is not how the repertoire is molded, but rather the raw material, genes and proteins, that comprise the recognition molecules which allow us to speak of a T-cell repertoire at all.

To turn to these molecules, and the genes which encode them, one can immediately say that at the present time, little is agreed upon by most workers in the field, and much that appeared convincing when first published has been revealed either to be difficult to reproduce or misleading in its implications. Why is this so? There are perhaps three major reasons. The first concerns the heterogeneity of T cells themselves: such studies as have been performed have almost exclusively involved mixed populations of cells, often poorly characterized and certainly heterogeneous as to specificity and function. Second, most classes of T cells produce little or no antigen-binding material, thus making isolation of receptors with antigen, the obvious approach, difficult or even theoretically impossible. Third, many of us working in the field have been guided by the seemingly reasonable (and often apparently verifiable) assumption that Nature, having devised in the immunoglobulins a complex, elaborate and highly functional antigen-recognition system, would be unlikely to devise a second, similar but distinct genetic system. This minimal hypothesis, or argument from parsimony, is championed by Marchalonis (p. 11) and vigorously refuted by Miller and his colleagues (p. 23) and by Jensenius and Williams[1]. A middle ground is taken by Williamson (p. 18), who has proposed an Ig-like, and possibly even Igh-linked, system of genes that undergo novel rearrangements. However, one may readily ask whether we need the argument of parsimony. We now know that the genome is almost profligate in its waste; perhaps more than 90% of murine genome consists of what Susumu Ohno terms 'junk DNA'. We also know that gene duplication and divergent evolution are facts of life for the eukaryotic genome. Indeed, one might go so far as to propose that far from using the same V_H genes employed in forming conventional Ig molecules, several different families of T-cell receptor genes, each specialized to carry out unique functions, may have evolved by divergent evolution. Nor need the divergence be so great; the strong arguments against the use of conventional Ig V genes is the failure to observe hybridization of Ig V probes with rearranged DNA or mRNA (summarized by Miller *et al.*, p. 23) in functionally specific T cells. However, the closely related Igh-C genes, or V_H and V_L genes, do not cross-hybridize under these same conditions. Thus, related but non-hybridizing genetic elements could be used by T cells to form their receptors.

One other reason why the argument of parsimony, or the minimal hypothesis, has had so many adherents is the repeated observation that T cells and B cells share idiotypic determinants, and that expression of these determinants in T and B cells is tightly linked to Igh in genetic studies. There are two possible flaws in such experiments. The first lies in the cells analysed; in most cases, these were not well characterized, and this is particularly true in terms of self-MHC recognition. The second lies in a combination of the reagents used and the apparently extraordinary sensitivity of T cells to activation by 'anti-idiotypic' antibodies. Thus, reagents might be contaminated by trace amounts of material reactive exclusively with T cells that could contribute all of the biological activity to an antiserum, but little to its specificity

for Ig idiotypes. Studies with monoclonal reagents may well clarify this situation. A case in point is described by Reinherz *et al.* (p. 26) who have succeeded in isolating a molecule from a cloned T-cell line using a monoclonal clone-specific antibody raised against a human cytolytic T-cell line. This molecule has a structure that is distinct from that described by several authors using anti-idiotypic reagents that cross-react with serum antibodies of the same specificity. The molecule detected by Reinherz *et al.* and subsequently in several laboratories, including my own (Kaye *et al.*, unpublished observations), is a disulfide-linked dimer of approximate mol. wt 80 000 – 90 000 which on reduction runs as two bands at mol. wt 40 000 – 50 000. Little else is known of this molecule at the present time, but all the evidence points to a role in specific antigen recognition by T cells that are MHC-specific or MHC-restricted (or both). This is in contrast to the structure of mol. wt 70 000 previously detected in numerous studies summarized most completely in the article of Marchalonis. Who is right? I certainly do not want to insert myself into this sticky matter. However, without wanting to appear to be a mugwump*, our own data suggest that both structures may be correct, but that the class of T cells studied is different in the two cases. This is based on the isolation of antigen-specific T-cell molecules of both types from different T-cell subsets with different reagents, and the associated finding that reagents specific for putative T-cell isotypes distinguish between the two types of cells and molecules. Thus, the growing momentum in favor of the view that the molecule isolated by Reinherz *et al.* and in several other laboratories is the T-cell receptor is almost certainly premature, and will make up only a part of the picture.

None of this tells us anything about the genes that encode the T-cell receptor, but we all feel confident that with monoclonal T cells making antigen-binding molecules detectable by monoclonal antibodies in hand, we should soon know everything about T-cell receptors, except how they perform their unique dual recognition functions. I share in this optimism, tempered as it is by the knowledge that several studies have appeared showing *in-vitro* translation of putative T-cell receptor mRNA, but have not yet given us the genes. It is undoubtedly from molecular genetics approaches that many great strides in our understanding will soon come. However, molecular genetics by itself will not soon tell us how the molecules are assembled to give rise to the functional attributes described above for T-cell receptors. For this understanding, protein chemistry and cell biology will have to combine with molecular genetics to give answers.

What will these answers look like? I am not prepared to predict anything about T-cell receptor genes at present, nor have I been asked to. However, certain attributes of T-cell behavior have suggested the following picture of the assembled nature of the T-cell receptor, which I would like to summarize in closing this introduction. It has long been assumed that MHC-restriction, and particularly the influence of the thymus on self-MHC recognition, requires that the T-cell receptor site for self-MHC determinants recognizes the polymorphic parts of the self-MHC molecule, indeed the T-cell equivalent of B-cell defined 'private' specificities. However, I would favor an alternative, albeit radical, possibility as at least worthy of consideration. That is, that the T-cell receptor site contacting the self-MHC molecule in fact binds to a non-polymorphic portion of the molecule. In this model, all the polymorphic residues on the MHC molecule would be clustered in what is essentially one topographic region of the MHC molecule, much like the antigen-binding cleft of an antibody. This polymorphic region would be involved in specific interactions with antigenic fragments; these interactions, while of low affinity, would be of a high degree of stereospecificity, and would be stabilized by occurring on a cell surface. At any one time, very few such antigen–MHC complexes would exist on a given cell, but

**A mugwump is a politician who sits on the fence: his mug is on one side, and his wump on the other.*

due to the extraordinary sensitivity of the T-cell receptor for interaction with such a complex, that number would be sufficient to trigger the T cell. The site on the T cell specific for the foreign antigen X would, as has been previously suggested by many others, also react to genetic variations in MHC molecules, and would account for alloreactivity. Thus, the T-cell receptor in such a model would consist of two sites, one rather boring one that does not discriminate between MHC molecules of a given class (for example I-A and I-E, or K and D) although perhaps being MHC class-specific (Ia vs K/D) but which serves to align the second site, which is specific for the highly precise interaction of antigen with self-MHC molecules. In this model, specificity would derive both from the nature of the T-cell receptor and from the nature of the interaction of antigen with self-MHC molecules, itself a highly precise phenomenon. What is perhaps novel about this model (and it is hard, with so many models in existence, to be really novel in this area, or to be sure when one is not copying someone else's earlier ideas), is that thymic selection would have to act on the antigen-specific site rather than the self-MHC-specific site, since the latter would not discriminate self from non-self. While some studies would argue that the thymus does not influence self-recognition in a specific fashion at all, the bulk of the data suggest that the thymus does so influence the repertoire (see the section of this book on 'Ontogeny and education', p. 31). Another possibly novel aspect of such a model is that it would predict a constant molecular form for the anti-self-MHC receptor site. And finally, it would predict that T cells might appear to react in a non-MHC-restricted fashion and still be recognizing MHC determinants via its anti-self receptor alone, as perhaps occurs during activation with certain mitogens or antibodies such as anti-T3 or rabbit anti-mouse brain. This last proposal can at least be tested, and is consistent with observations of inhibition of these responses by monoclonal anti-Ia antibodies.

The next two or three years should see rapid progress, including the determination of the genes involved in receptor formation in those classes of T cells which have been isolated and cloned, the characterization of their protein products and, we may hope, the production of reagents that will definitively distinguish between what are now termed T-cell subsets. Let us hope that this exciting time will be illuminated by facts, and will sweep the models of the T-cell receptors propounded by so many of us, even at this late date, into the same historical closet as the Piltdown man – interesting examples of how easy it is to be misled by seemingly plausible data into the wildest of speculative ideas.

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Glycosyltransferases and T-cell recognition

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Recent studies suggest that the MHC locus controls families of carbohydrate, as well as protein, histocompatibility antigens. In this article Christopher Parish and his colleagues discuss the molecular and genetic implications of these findings and present the hypothesis that the glycosyltransferase enzymes which construct the carbohydrate histocompatibility antigens may be involved in T-cell recognition.

There is now ample evidence that the major histocompatibility complex (*MHC*) of man and several other species plays a key role in the induction and regulation of immune responses[1]. In this context a crucial finding is that lymphocytes must recognize antigen in association with self-MHC structures for activation. In the case of cytotoxic T lymphocytes, these self structures represent the major transplantation antigens of the species[2] (controlled by the *K* and *D*-regions in the mouse), whereas helper[3] and delayed-type hypersensitivity[4] T cells usually recognize antigen in association with products of immune response (*I*-region) genes[5]. Currently there is much debate amongst immunologists as to how this recognition occurs. Some believe that *MHC*-restricted recognition is mediated by two different classes of receptors on the lymphocyte surface, namely a receptor for the foreign antigen (termed the 'anti-X' receptor) and a receptor for self-MHC antigens (termed the 'anti-self' receptor)[2]. Several detailed theories have been proposed to explain the generation and regulation of these anti-X and anti-self receptors[2,6]. The alternative view is that T cells express a single receptor that recognizes a structure resulting from the interaction between antigen and MHC molecules[2,6]. However, we have recently demonstrated that there are carbohydrate MHC antigens as well as protein MHC antigens and we believe that this finding necessitates a re-evaluation of the mechanisms of T-cell recognition.

Carbohydrate and protein MHC antigens

Extensive serological studies have revealed that the *MHC* controls several polymorphic families of alloantigens[1]. In the case of the mouse, the *K* and *D*-regions control the H-2K and H-2D antigens[7] and the *I*-region controls the *I*-region-associated (Ia) antigens[7,8]. There is mounting evidence that at least some of these antigens represent the self-MHC structures recognized by T lymphocytes. Chemical analyses have clearly demonstrated that some H-2K, H-2D and Ia antigenic specificities are protein in nature[9–11]. However, studies in our laboratory with monclonal antibodies indicate that there are carbohydrate, as well as protein, H-2 and Ia antigens[12,13]. Additional evidence in favour of carbohydrate H–2 antigens is the recent finding that the binding of autologous erythrocytes by murine thymocytes involves the recognition of carbohydrate-defined H-2L antigens on erythrocytes by a *H-2L*-region controlled protein receptor on thymocytes[14,15].

Glycosyltransferases and the MHC

The demonstration of *both* protein and carbohydrate defined antigens controlled by the *K*, *D/L* and *I* regions of the murine *MHC* has important theoretical implications. The most obvious is that these three regions code for families of glycosyltransferase enzymes that construct the carbohydrate antigens. The manner in which glycosyltransferases catalyse the transfer of a monosaccharide residue from a sugar nucleotide (sugar donor) to the non-reducing terminus of a specific sugar acceptor is depicted in Fig. 1. It should be emphasized that the attachment of each sugar in a carbohydrate chain requires a separate glycosyltransferase that has specificity for both the sugar acceptor and the sugar donor. Whether the protein H-2K, H-2D and Ia antigens actually represent the glycosyltransferases that construct the carbohydrate MHC antigens is an intriguing question which requires investigation. On the other hand, a more

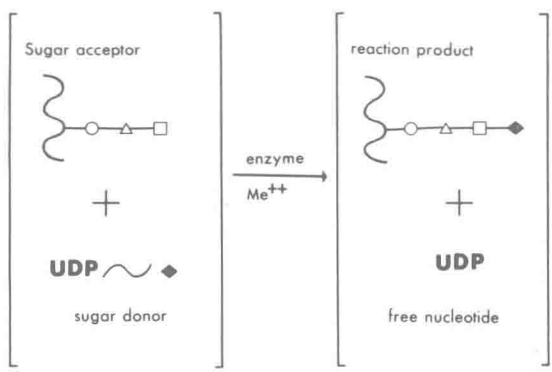

Fig. 1. Glycosyltransferase reaction
Various monosaccharides are represented by circles, triangles, squares and diamonds. A trisaccharide sugar acceptor is depicted, linked at its reducing end to a protein or lipid moiety represented by the wavy line. The enzyme, usually in the presence of divalent metal cations, catalyzes the transfer of a monosaccharide from its uridine diphosphate donor to the nonreducing terminus of the sugar acceptor. The reaction product is a tetrasaccharide, represented here with a terminal 'diamond' moiety, and the free nucleotide. (Reproduced from Shur, B. D. and Roth, S. (1975) *Biochem. Biophys. Acta* 415, 473–512, with permission).

complex possibility is that the glycosyltransferases are coded for by genes located outside the *MHC* and the *K*, *D* and *I*-regions produce regulators of these enzymes.

T-cell recognition by MHC-controlled glycosyltransferases

From the data summarised above, an inescapable conclusion is that the *MHC* determines the specificity of several families of glycosyltransferases. This raises the possibility that *MHC*-controlled glycosyltransferases may mediate communication between lymphoid cells in a manner originally proposed by Roseman[16]. By this model glycosyltransferases on the surface of one cell interact with their carbohydrate substrate (an incompletely glycosylated structure) on another cell. Such a model can be readily adapted and expanded to accommodate *MHC*-restricted recognition.

The model is presented schematically in Fig. 2. It is proposed that activation of T lymphocytes involves two distinct classes of receptors. The first is an antigen-specific receptor (anti-X receptor) that probably expresses V_H-gene amino-acid sequences, is clonally expressed and has a diversity of combining sites similar to that of serum immunoglobulins. The existence of such a T-cell receptor has been proposed frequently in the past[2,6]. The second receptor is a *MHC*-controlled glycosyltransferase that functions as an anti-self receptor by recognizing its substrate, an incompletely glycosylated carbohydrate MHC antigen, on target cells. In the absence of the appropriate foreign antigen (Fig. 2, part 1) this glycosyltransferase can bind its substrate, catalyse the transfer of a monosaccharide from a sugar nucleotide and then dissociate from its modified substrate. On the other hand, when foreign antigen is present a completely different chain of events occurs (Fig. 2, part 2). Once the anti-X receptor binds antigen it interacts with and modifies the glycosyltransferase (anti-self receptor) in such a way that it can bind but cannot glycosylate its carbohydrate substrate. Lymphocyte activation is initiated when this form of self-recognition occurs.

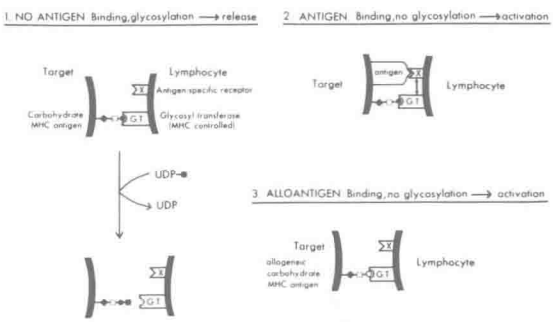

Fig. 2. Model for recognition of antigens and alloantigens by T lymphocytes.

The lymphocytes are depicted as expressing two receptors, an antigen-specific (X) receptor and an anti-self glycosyltransferase (G.T.). The different monosaccharides that constitute the carbohydrate MHC antigen on the target cell are represented by diamonds, squares and circles. The sugar nucleotide donor recognized by the glycosyltransferase is represented as UDP – ■. The figure depicts the interaction of lymphocytes with target cells under three different circumstances: (1) in the absence of antigen, (2) in the presence of antigen or (3) in the presence of alloantigen. The double-headed arrow in part (2) signifies interaction between X and G.T. For details of the model see text.

With alloantigens a third form of interaction with target cells occurs (Fig. 2, part 3). In this case it is postulated that some allogeneic carbohydrate *MHC* antigens sufficiently resemble the substrate of the anti-self glycosyltransferase to allow binding but not glycosylation. Under these circumstances lymphocyte activation would occur without involvement of the anti-X receptor.

Thymic processing, mutant mice and the T-cell receptor

Some important features of the model we propose are listed in the box on p. 100.

Any model of T-cell recognition must incorporate the recent observation that MHC structures both inside and outside the thymus can determine the specificity of *MHC*-restricted recognition[2,6]. If the anti-self receptors are glycosyltransferases it can be postulated that selection occurs for those transferases that can *both* bind and glycosylate the carbohydrate MHC antigens of the host. Any cells carrying transferases that either fail to bind, or bind but cannot glycosylate these carbohydrate antigens would be eliminated. Recent reports which suggest that, in irradiation chimeras, the MHC antigens of the recipient can profoundly influence the MHC antigens expressed on donor cells[22,23] support this proposal.

It should be noted that the selection process discussed above is a critical feature of the model presented in Fig. 2, particularly in outbred populations, where the glycosyltransferases contributed by one parent could react, in an allogeneic manner, with the carbohydrate MHC antigens of the other parent (see Fig. 2, part 3). Thus, possibly the major function of 'thymic processing' is the elimination of autoreactivity.

Models of T-cell recognition must also explain the important observation that *H-2* mutant strains of mice, although expressing only slightly modified protein H-2 molecules, usually can only recognize antigens in association with mutant and not wild-type H-2 antigens[24]. In explaining this apparent paradox it must be remembered that *H-2* mutant mice are detected by their ability to reject wild-type skin grafts. Thus, according to our model, mutant mice must express a mutant glycosyltransferase that can bind but cannot glycosylate wild-type carbohydrate MHC antigens (Fig. 2, part 3). Furthermore, a modification in the substrate specificity of a single glycosyltransferase could result in substantially changed carbohydrate MHC antigens and, consequently, the selection of different glycosyltransferases as anti-self receptors. In support of this explanation is our finding that *H-2*

Some important features of the model

- Lymphocyte activation is induced *only* when the anti-self receptor (glycosyltransferase) binds but cannot glycosylate its carbohydrate substrate.
- The model applies to the induction of *MHC*-restricted immune responses as well as to the delivery of effector cell function, such as the *MHC*-restricted recognition of target cells by cytotoxic T cells[2]. Similarly, the model applies to *MHC*-restricted recognition by all classes of T lymphocytes, whether *K, D* and/or *I*-region-controlled self structures are involved[2–6].
- The model can also accomodate *I*-region-restricted interactions between antigen-specific factors and lymphoid cells[17]. In this instance the helper or suppressor factors would carry carbohydrate Ia antigens and the interacting lymphocyte would be activated by a complex of factor and antigen as depicted in Fig. 2, part 2. The demonstration of carbohydrate Ia antigens on helper[18] and suppressor[19] factors supports this contention.
- The model proposes that lymphocyte activation by foreign antigens requires two receptors (Fig. 2, part 2) whereas activation by alloantigens involves only a single receptor, the anti-self glycosyltransferase (Fig. 2, part 3). It seems probable, however, that some antigens and, particularly, viral and bacterial infections, may modify the carbohydrate MHC antigens in such a way that they cannot be glycosylated and thus can stimulate lymphocytes like alloantigens, i.e. only a single receptor is involved. Thus, according to the manner in which an antigen interacts with self-MHC structures *either* single or dual receptor recognition could be involved.
- Fig. 1. depicts only one glycosyltransferase as the anti-self receptor. This is an oversimplification, as a different glycosyltransferase is required to attach each sugar of the carbohydrate MHC antigens (see Fig. 1). Potentially any one of these transferases could act as an anti-self receptor. However, the most likely anti-self receptors are those transferases which catalyse the attachment of the terminal and penultimate sugars of the complete MHC structure, i.e. possibly 10–20 transferases for each region of the *MHC*. Furthermore, the substrate specificity of these glycosyltransferases could be further diversified by their interaction with specifier proteins, as has been shown in the interaction of α-lactalbumin with certain galactosyltransferases[20].
- The model readily explains the high proportion of lymphoid cells that react to alloantigens compared with foreign antigens since every anti-self receptor has potential alloreactivity[21]. Furthermore, the system can withstand a high degree of genetic polymorphism and still maintain self recognition.
- Earlier models of T-cell recognition that propose an anti-self receptor face the problem of autoreactivity[2–6]. Our model overcomes this problem by proposing that the anti-self receptor is a glycosyltransferase. Thus, if the anti-self receptor binds self MHC antigens it rapidly dissociates from its substrate via glycosylation (Fig. 2, see part 1).
- The model implies the continual expression of incompletely glycosylated carbohydrate *MHC* antigens on target/stimulator cells.

mutant mice *simultaneously* express modified protein and carbohydrate H-2 antigens[15].

The model depicted in Fig. 2 proposes that *MHC*-controlled glycosyltransferases recognize allogeneic histocompatibility antigens. In contrast, studies with anti-idiotypic sera suggest that the receptors on alloreactive T cells share V_H idiotypes with antibodies specific for the same alloantigenic determinant[25]. However, it seems quite conceivable that the anti-idiotypic sera used in these studies would also react with the combining sites of the alloreactive glycosyltransferases. In fact, anti-idiotypic sera raised against anti-retinol-binding protein (RBP) antibodies react with the RBP binding site on prealbumin[26].

General implications

The model we propose here has been discussed in the context of *MHC*-restricted recognition by T lymphocytes. It seems highly likely, however, that the glycosyltransferases proposed as anti-self receptors have evolved from a more primitive recognition system, possibly used for self-non-self discrimination in invertebrates[27,28]. Similarly, other *MHC*-linked loci, such as the *T/t* locus in the mouse[29], may code for different families of glycosyltransferases involved in a related form of cell-cell communication.

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Addendum – February 1983

Since the publication of this article in June 1981, additional evidence has appeared suggesting that MHC-controlled carbohydrate structures and/or carbohydrate recognition may play a key role in immune responses. Recent studies in this laboratory have indicated that certain monosaccharides can selectively inhibit T–B collaboration, an effect that is mouse-strain dependent and maps to the *I*-region of the murine MHC[+] (Ref. 1). Furthermore, it appears that the monosaccharides inhibit the interaction of a T-cell-derived helper factor with B cells, the helper factor being an *I*-region-controlled lectin that recognizes carbohydrate structures on B cells[2].

Further support for MHC-controlled carbohydrate recognition comes from the work of Stewart *et al.*[3], who reported that mouse peritoneal macrophages bind bacteria via a cell-surface lectin whose activity is blocked by anti-Ia antibodies. Such findings can be used as support for our hypothesis that the MHC controls recognition by and communication between cells of the immune system by coding for lectins (glycosyltransferases) and complementary carbohydrate structures.

A central component of our glycosyltransferase model is that T lymphocytes recognize carbohydrate MHC antigens on target/stimulator cells (see Fig. 2). Some recent findings are consistent with this concept. First, it has been shown that inhibition of glycosylation of glycoprotein H-2 and Ia antigens by tunicamycin prevented allogeneic cells acting as stimulators in mixed lymphocyte reactions[4]. Such a result was obtained even though tunicamycin had no effect on the synthesis and insertion of the H-2 and Ia antigen polypeptides into the plasma membrane. Using a similar approach, Black *et al.*[5] have suggested a role for cell-surface oligosaccharides in the *H-2*-restricted cytolysis of virus-infected cells.

Second, the removal of sialic acid from the Ia antigens of B lymphocytes converts these lymphocytes into good antigen-presenting cells, presumably by exposing appropriate carbohydrate structures (C. Cowing and J. M. Chapdelaine, unpublished observations). Furthermore, this finding correlates with the observation that macrophages, that are good antigen presenters, express Ia antigens low in sialic acid[6].

Third, there is increasing evidence for a high degree of heterogeneity in the oligosaccharide portion of glycoprotein Ia antigens[7], suggesting that this portion of the molecule may be antigenic. It should be emphasized, however, that the carbohydrate MHC antigens which we have described previously are glycolipid in nature. The relationship between these glycolipid antigens and the carbohydrate portion of the glycoprotein MHC antigens is unknown, but it is interesting to speculate that similar carbohydrate structures could be lipid- and protein-associated, as has been observed with the blood-group antigens[8].

The nature of the T-cell receptor for antigen is still an unresolved issue. Certainly, recent evidence for MHC-controlled lectins[1–3,9] is consistent with glycosyltransferase involvement. On the other hand, the involvement of V_H gene products in the T-cell receptor is being seriously questioned[10]. A rigorous test of all models of T-cell recognition awaits the unequivocal identification of this receptor.

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