

Chapter 12. The T cell repertoire and MHC restriction

The T cell repertoire is the set of all the V regions expressed by T cells, together with the frequency of each of the V regions. T cell V regions are enormously diverse, but the repertoire is not random; not all protein antigens are recognized by T cells with equal frequency. T cell receptors preferentially recognize certain self-components called MHC (major histocompatibility complex) molecules. MHC molecules are cell surface proteins and are the main self molecules that determine organ transplant compatibility. If two individuals have the same MHC molecules (as do some siblings) one will accept a graft from the other more readily than if this is not the case. A related finding is that the frequency of mouse T cells reactive to the MHC molecules of another mouse strain is significantly higher than the frequency of T cells reactive to other antigens, such as soluble proteins. The same phenomenon is seen in other vertebrates including humans. The fraction of T cells that recognize particular non-self MHC molecules is typically one to five percent.

Classes of T cells

Up to this point we have treated T cells as though, apart from having different specificities, they all have the same properties. In fact the immune system contains three functionally distinct classes of T cells. The three classes of T cells are cytotoxic T cells, helper T cells and suppressor T cells. Their names express their functions.

MHC restriction

About the same time that the first immune network theories were being formulated, it was reported that recognition of cell-associated antigen by T cells involved two aspects, namely firstly, the recognition of the antigen itself, and secondly, the recognition of MHC molecules. This was demonstrated by Alan Rosenthal and Ethan Shevach for T cell proliferation, in which case the macrophages and T cells in the culture had to have the same MHC.¹⁷⁰ Then Rolf Zinkernagel and Peter Doherty of the Australian National University in Canberra found that when they infected mice with a virus, the mice produced cytotoxic T cells (also known as cytotoxic T cells), and these T cells were specific for both the virus and the mouse's MHC molecules. Cytotoxic T cells sensitized against a virus "X" in a host with MHC type "A" were found to be able to kill cells of MHC type A infected with X, but were unable to kill cells of

¹⁷⁰ A. S. Rosenthal and E. M. Shevach (1973) The function of macrophages in antigen recognition by guinea pig T lymphocytes. I. Requirement for histocompatible macrophages and lymphocytes. *J. Exp. Med.* 138, 1194-1212.

MHC type B cells infected with X, and were likewise unable to kill MHC type A cells infected with a different virus.¹⁷¹ Analogous results were soon obtained by other investigators with different viruses, and with systems involving haptens or other foreign cell-surface molecules instead of virus.

These results had a big impact on the field of immunology, and eventually led to Nobel prizes for Zinkernagel and Doherty. Initially however, there was a considerable amount of confusion and controversy about how the findings should be interpreted. The attention of experimentalists was first focused on two complex models that were proposed by Doherty and Zinkernagel¹⁷² and their colleagues¹⁷³. One model was that there are two specific receptors on T cells, one of which recognizes MHC, and the other recognizes the foreign antigen X. The other model they proposed was that T cells have a repertoire of specificities that recognize "altered self", meaning something a little bit different from self. Much ingenuity was devoted to the cause of distinguishing between these two models. There is however a simpler interpretation, namely that the T cell repertoire is biased by clonal selection (positive selection) to recognize self MHC molecules with low affinity. By virtue of the similarity of self MHC and foreign MHC, this results in a high frequency of reactivity to foreign MHC molecules.

The positive selection for clones to have some affinity for MHC takes place especially in the thymus, where there is a lot of cell proliferation and cell death. The positive selection process means that cells of other specificities would be simply eliminated by dilution, that is, a combination of a lack of stimulation and non-specific death.

There must be lower and upper limits for the affinity of the T cell receptor for such positive selection to occur. If a T cell binds with high affinity to MHC on an accessory cell such as a macrophage, it would not be able to release itself by secreting its specific T cell factors, and would presumably be phagocytosed by the accessory cell. This would lead to the deletion of clones with such high affinity for MHC. T cells with a somewhat lower affinity for self MHC can be expected to receive a high level of stimulation, leading to their proliferation and also to the selection of antiidiotypic clones, and to the establishment of the

¹⁷¹ P. C. Doherty and R. M. Zinkernagel (1975) A biological role for the major histocompatibility antigens. *Lancet* i:1406-1409.

¹⁷² R. M. Zinkernagel and P. C. Doherty (1979) MHC-restricted cytotoxic T cells: studies on the biological role of polymorphic major transplantation antigens determining T cell restriction – specificity, function and responsiveness. *Adv. Immunol.* 27, 51-177.

¹⁷³ P.C. Doherty, D. Gotze, G. Trinchieri, and R. M. Zinkernagel (1976) Models for recognition of virally modified cells by immune thymus derived lymphocytes. *Immunogenetics* 3, 517-524

suppressed state of our theory. This means there is room for both deletion and suppression in the context of this theory. At a still lower level of affinity clones would also be positively selected, but without the induction of the suppressed state. Finally clones with a still lower level of affinity would not be positively selected at all. Many experimental findings are compatible with this concept.¹⁷⁴

In order to understand tolerance to other self antigens, namely those not present on phagocytic cells, there has been much speculation about "negative selection," such that an encounter between the antigen and an antigen-specific lymphocyte somehow directly eliminates or inactivates the cell. With the exception of cells that bind to phagocytic cells with high affinity, our network theory contains no lethal or inactivating role for antigen. This makes sense because there is an astronomical number of different antigens (essentially all foreign proteins are antigens, for example), and there is no readily imaginable physical mechanism, by which they could all have the capacity to inactivate or kill cells. (How does a lymphocyte "know" that an antigen is foreign?) Positive selection, on the other hand, is just another name for clonal selection. A model based primarily on positive selection is a conservative construct that makes sense in the context of the first law of immunology, the clonal selection theory.

The reason that the Zinkernagel and Doherty finding had a large impact on immunology was that their finding was an example of multispecificity of the V regions of T cells. This was difficult to accept for immunologists, who were used to the idea of the "exquisite specificity" of antibodies, meaning monospecificity, and by extension, monospecificity of their T cell partners. The "two-receptor" and "altered self" models survived and attracted the attention of immunologists for a long time, which is an indication of the extent to which immunologists were wedded to the idea that a single receptor has a single specificity. The phenomenon of MHC restriction is a paradox within that framework, but the paradox is immediately resolved if we admit the possibility of multispecificity of V regions. MHC restriction is due to T cells being positively selected by self MHC molecules, which for some reason are very potent self-antigens.

MHC genes, molecules and haplotypes

The major histocompatibility complex in mice, the main species for immunogenetic studies, is called H-2. The H stands for histocompatibility and H-2 was the second histocompatibility locus to be discovered. In humans the MHC is called HLA, which stands for human leukocyte antigens.

¹⁷⁴ A. W. Goldrath and M. J. Bevan (1999) Selecting and maintaining a diverse T-cell repertoire. *Nature* 402, 255-262.

There are three classes of MHC genes called MHC class I, MHC class II and MHC class III. In the mouse the two main class I molecules are called H-2K and H-2D, or just K and D for short. There are two MHC class II molecules, A and E, that are each heterodimers, $A_\alpha A_\beta$ and $E_\alpha E_\beta$. MHC class I and MHC class II molecules are highly polymorphic and strongly affect the T cell repertoire. The MHC class III ("S region") encodes at least six genes that are not known to have a comparable level of polymorphism, and do not have the same effect on the T cell repertoire. In the following I therefore focus on MHC class I and MHC class II genes. The main MHC class I and MHC class II genes of the mouse are on chromosome 17 as shown in **Figure 12-1**. An inbred mouse of a given strain is homozygous, and its particular set of MHC genes is called its "MHC haplotype" or "H-2 haplotype". Common mouse strains include the B6 mouse (MHC haplotype b, H-2^b), the CBA mouse (H-2^k) and the Balb/c mouse (H-2^d). A mouse of the H-2^b haplotype expresses the MHC molecules K^b A^b E^b and D^b.

Each MHC class I molecule consists of a polymorphic polypeptide chain encoded by a K or D gene and a nonpolymorphic polypeptide chain called β 2-microglobulin. Each of the MHC class II molecules consist of two polymorphic polypeptides, namely A α and A β (for A) and E α and E β (for E). The order of the MHC class I and MHC class II genes on chromosome 17 of the mouse genome is K A α A β E β E α D, as shown in Figure 12-1. The MHC class I molecules are expressed on most cell types, and are strong self-antigens for the positive selection of T cells that express a cell surface marker called CD8. These include suppressor T cells and cytotoxic T cells. MHC class II molecules are present mainly on B cells and macrophages. MHC class II is a strong self-antigen for the positive selection of T cells that express a cell surface marker called CD4. CD4 also has some complementarity to MHC class II. The CD4 bearing cells are mainly helper T cells.

The high frequency of cells reactive to allogeneic MHC molecules

Allogeneic MHC is MHC of a different haplotype. The positive selection concept automatically explains the fact that T cells have a special relationship to self MHC encoded molecules. But why do a high proportion of T cells recognize a particular *foreign* MHC? The answer is presumably that allogeneic MHC molecules resemble self MHC, and by cross-reactivity a significant fraction of the T cells respond to the foreign MHC.

Figure 12-1. The MHC class I genes and the MHC class II genes of the major histocompatibility complex in the mouse. The MHC class I genes are K and D and the MHC class II genes are A β A α E β and E α . Not shown are the MHC class III genes (between E α and D) and some additional MHC class I genes in the D region, neither of which are known to be involved in the selection of the T cell repertoire. MHC class III genes encode some of the complement proteins.

MHC class I and MHC class II in the mouse

Genes	K	A α	A β	E β	E α	D
Class	I	II	II	II	II	I

MHC class II differences associated with strong proliferative responses

An MHC class II difference between two mouse strains is a sufficient condition for a very strong *in vitro* proliferative response of lymphocytes of one strain in response to stimulation by irradiated cells of the other strain. This is called a mixed leukocyte reaction (MLR). Helper T cells, which are selected by MHC class II, are the cells that proliferate in the MLR. An *in vivo* correlate of the MLR is the graft versus host (GVH) reaction, in which a host is irradiated and allogeneic lymphocytes are injected. The injected helper T cells proliferate vigorously in response to the allogeneic (foreign strain) MHC class II of the host. (The irradiation is necessary in order to prevent a response by the host, which would complicate the process.) An animal's helper T cells can also respond in an MLR to its own lymphocytes from a different organ, for example spleen cells can respond to autologous thymus cells^{175,176}. This is called an autologous mixed leukocyte reaction (AMLR). Macrophages also play an essential role in the MLR.¹⁷⁷

We can account for the MLR, GVH and autologous MLR by assuming that MHC class II and the T cells that recognize MHC class II define a fundamental

¹⁷⁵ G. M. Opelz, M. Kiuchi, M. Takasugi and P. I. Terasaki (1975) Autologous stimulation of human lymphocyte subpopulations. *J. Exp. Med.* 142, 1327-1333.

¹⁷⁶ M. E. Weksler and R. Kozak (1977) Lymphocyte transformation induced by autologous cells. Part 5. Generation of immunologic memory and specificity during the autologous mixed lymphocyte reaction. *J. Exp. Med.* 146, 1833-1838.

¹⁷⁷ M. Minami, D. C. Schreffler and C. Cowing (1980) Characterization of the stimulator cells in the murine primary mixed lymphocyte response. *J. Immunol.*, 124, 1314-1321.

direction in shape space, for which idiotypic regulation is the least rigid. In other words, the helper T cells are not as tightly regulated as other T cells. This concept is developed in more detail in chapter 17. In chapter 15 we will suggest that this is also the reason why many autoimmune diseases are linked to particular MHC class II alleles.

More specifically, an interpretation in the context of our theory is that allogeneic MHC class II causes the stimulation of helper T cells to release specific factors, that are adsorbed onto accessory cell (for example macrophage) surfaces. The "armed" macrophage surface is then highly stimulatory for T cells with anti-anti-MHC class II specificity. In addition, macrophages produce IL-1, which give T cells a second signal for proliferation, so it is not surprising that there is a vigorous reaction.

CD4 has affinity for MHC class II and CD8 has affinity for MHC class I

The plot now thickens. MHC class I molecules have affinity for CD8 molecules, and MHC class II molecules have affinity for CD4 molecules. While most cytotoxic T cells express CD8, cytotoxic T cells specific for MHC class II express CD4, not CD8. A third class of T cells, in addition to helpers and cytotoxic T cells, are suppressor T cells. These cells typically express CD8, and in the mouse they express a cell-surface marker called I-J. I-J was discovered and has been characterized in inbred mouse strains, and while a similar antigenic determinant has been detected on regulatory cells in humans,¹⁷⁸ there has been no immunogenetic mapping of the determinant for humans. The I-J story is an important one for suppression and for immune network theory. The network theory interpretation is that an I-J marker is present on suppressor T cell V regions that recognize helper T cell V regions, with the latter being positively selected due to complementarity to MHC class II. **Error! Bookmark not defined.** But this is getting complicated, and we will first say more about CD4 and CD8. We return to I-J in chapter 13.

Why do suppressor T cells express CD8, and helper T cells express CD4? The symmetrical network theory provides us with a rational basis for the various T cell types having their particular biases.

Firstly we recall the postulate that IL-1 is secreted by A cells and gives T cells a second signal for proliferation (see chapter 10). The repertoire of T cells is then automatically strongly influenced by molecules that are present on the A cell surface. These molecules include MHC class I (present on most cell types), MHC class II (present on A cells and B cells) and adsorbed specific T cell factors. T cells that have specific receptors that bind to molecules on the A cell

¹⁷⁸ T. Lehner, R. Brines, T. Jones and J. Avery (1984) Detection of cross-reacting murine I-J like determinants on a human subset of T8+ antigen binding, presenting and contrasuppressor cells. *Clin. Exp. Immunol.* 58, 410-419.

surface are most likely to receive the IL-1 signal to divide. Now we consider how CD8 cells and CD4 cells differ, and what the consequences are.

On the network connectivity of CD4 T cells and CD8 T cells

- Suppressor T cells express CD8.^{179,180}
- CD8 molecules have affinity for the MHC class I molecules¹⁸¹.
- MHC class I antigens are expressed on almost all tissues¹⁸².
- Hence T cells that recognise MHC class I receive more stimulation than cells of other specificities.
- We can then expect that there are more anti-MHC class I specific T cell factors on the surface of A cells than specific T cell factors of other specificities.
- T cells that are anti-idiotypic for specific T cell factors that are anti-MHC class I will then be positively selected.
- This results in anti-MHC class I T cells having high idiotypic connectivity. This is just what we require for suppressor T cells. In the symmetrical network theory, the suppressed state is a state of high network connectivity, in contrast to the immune state, which is a state of low network connectivity (chapter 10). So it readily follows from the postulates of the symmetrical network theory that CD8 T cells are selected to be anti-class I MHC and are suppressor cells.

An analogous interpretation applies to the fact that MHC class II specific cells tend to be helper cells:

- In the symmetrical network theory, helper cells help to induce the immune state, which is a state of low network connectivity for the antigen-specific cells (chapter 10).
- The CD4 molecule of helper T cells has affinity for MHC class II molecules^{183,184}

¹⁷⁹ H. Cantor and E. A. Boyse (1975) Functional sub-classes of T lymphocytes bearing different Ly antigens. I. The generation of functionally different T-cell subclasses is a differentiative process independent of antigen. *J. Exp. Med.* 141, 1376-1389.

¹⁸⁰ E. L. Reinherz and S. F. Schlossman (1980) Differentiation and function of human T lymphocytes. *Cell*, 19, 821-827.

¹⁸¹ H. R. MacDonald, A. L. Glasebrook, C. Bron, A. Kelso and J.-C. Cerottini (1982) Clonal heterogeneity in the functional requirement for Lyt-2/3 molecules on cytolytic T lymphocytes (CTL): possible implications for the affinity of CTL antigen receptors. *Immunol. Rev.* 68, 89-115.

¹⁸² J. Klein (1975) *Biology of the mouse major histocompatibility-2 complex.* Springer-Verlag. (Berlin) p. 331.

- MHC class II molecules are not expressed on many cell types. They are present primarily only on B cells and A cells¹⁸⁵.
- We conclude that MHC class II specific T cells receive less stimulation than MHC class I specific T cells.
- The surface of the A cell will therefore be dominated by the presence of specific factors from MHC class I specific T cells, rather than from MHC class II specific T cells.
- There will then be relatively little positive selection of T cells that are specific for anti-(MHC class II specific T cell factor).
- This ensures that anti-MHC class II T cells have low idiotypic connectivity. This is just what we require for helper T cells. So it likewise follows from the postulates of the symmetrical network theory that CD4 T cells are both anti-MHC class II and helper cells.

In summary, experimental findings and the ideas of the symmetrical network theory are meshing with each other nicely in this part of immunology.

T cell preferences

Helper T cells	Biased to preferentially recognize MHC class II Express marker molecule CD4 CD4 has affinity for MHC class II
Cytotoxic T cells	Biased to preferentially recognize MHC class I Express marker molecule CD8 CD8 has affinity for MHC class I
Suppressor T cells	Include Ts1, Ts2 and Ts3 suppressor T cells Ts1 cells express CD4, Ts2 and Ts3 express CD8 Anti-I-J antibodies bind to Ts2 V regions

¹⁸³ J. L. Greenstein, J. Kappler, P. Marrack and S. J. Burakoff (1984) The role of L3T4 in recognition of Ia by a cytotoxic H-2D^d-specific T cell hybridoma. *J. Exp. Med.* 159, 1213-1224.

¹⁸⁴ W. E. Biddison, P. E. Rao, M. A. Talle, G. Goldstein and S. Shaw (1984) Possible involvement of the T4 molecule in T-cell recognition of class II HLA antigens. Evidence from studies of CTL-target cell binding. *J. Exp. Med.* 159, 783-797.

¹⁸⁵ D. H. Sachs (1984) The major histocompatibility complex. In *Fundamental immunology*, W. E. Paul, Ed., Raven Press (New York) p. 327.

The polymorphism of MHC molecules and linkage disequilibrium

MHC molecules are among the most polymorphic proteins known.¹⁸⁶ If these proteins are important for the regulation of the system, why do we not have a small number of optimal forms, that have been selected and used uniformly in all strains? An answer may be that it doesn't matter much exactly what the precise structure of the many different MHC molecules look like, except that the complete set of the various MHC molecules in an animal or person are boundary conditions of the T cell repertoires, and certain combinations of boundary conditions work better than others. The influence of MHC genes on the T cell repertoire then provides a rationale for the evolutionary *linkage disequilibrium* between these genes.¹⁸⁷ This means that certain MHC alleles stay together with each other on chromosomes to a greater extent than can be accounted for by chance. According to the boundary condition interpretation, an MHC molecule "A" is more compatible with another MHC molecule "B" than with other MHC molecules "C" or "D" as boundary conditions of the T cell repertoires. Both MHC class II molecules and MHC class I molecules are important network boundary conditions, and there would inevitably be selection during evolution for compatibility of the two classes of boundary conditions, in the sense of the selection of T cell repertoires that are optimally stable. The system involves CD4 T cells that are selected to have affinity for MHC class II and CD8 cells that have affinity for MHC class I. There is furthermore co-selection of CD4 cells and CD8 cells. The co-selection of CD4 and CD8 cells is plausibly influenced by the MHC class II and MHC class I boundary conditions of the CD4 and CD8 cells respectively. Consequently there is plausibly co-selection of certain MHC class I alleles and corresponding MHC class II alleles on an evolutionary time scale, leading to the observed linkage disequilibrium. The evolution of MHC molecules would then be very different from the evolution of enzymes, that are highly optimized to do a particular function, and are much less polymorphic.

The polymorphism of MHC molecules has often been ascribed to a perceived advantage in making a species more robust with respect to epidemics, since the vigor of immune responses to a given pathogen can vary as a function of MHC alleles. Then in an epidemic some individuals of a species with some MHC molecules could survive while many, with different MHC molecules, succumb. This concept does not however seem to provide an explanation for the observed linkage disequilibrium. Furthermore, some combination of MHC

¹⁸⁶ W. F. Bodmer and J. G. Bodmer (1978) Evolution and function of the HLA system. Br. Med. Bull. 34, 309-316.

¹⁸⁷ W. F. Bodmer and J. G. Bodmer (1978) Evolution and function of the HLA system. Br. Med. Bull. 34, 309-316.

molecules would seem to be optimal for dealing with the spectrum of pathogens to which the species has historically been exposed, and one could expect this combination to be the most prevalent. I am not aware of any data that is supportive of that.

MHC restriction and T-B collaboration

Kindred and Schreffler¹⁸⁸ found that B cells and T cells that express different MHC genes are unable to cooperate to produce specific antibodies:

Strain of B Cells	Strain of T cells	Response
<i>a</i>	<i>a</i>	+
<i>a</i>	<i>b</i>	-
<i>b</i>	<i>a</i>	-
<i>b</i>	<i>b</i>	+

This effect was found to involve differences in MHC class II antigens and hence differences in their helper (CD4) T cells. The phenomenon can be interpreted in terms of the fact that B cells express MHC class II antigens, and CD4 expressing T cells are selected to recognize MHC class II. B cells are strongly regulated by both helper T cells and suppressor T cells, so the repertoire of B cells is strongly influenced by the repertoire of T cells. In addition, it is inevitable that, conversely, the V region repertoire of B cells has some influence on the V region repertoire of T cells. The resulting fine structure of the network of V_T - V_B interactions can be thought of as the idiotypic language of the animal. In this context it is not surprising that B cells of a particular MHC class II haplotype interact preferentially with helper T cells that have been selected in the same MHC environment (“speak the same language”) as themselves. One of the results of combining such populations can be an allogeneic response to the MHC of foreign cells, that competes with the response to the antigen (see the sections on antigenic competition, chapters 6 and 10).

Antigen presenting cells

An antigen displayed on the surface of an A cell such as a macrophage, to which it may be adsorbed via specific T cell factors, provides a highly immunogenic array that efficiently cross-links receptors on T cells and B cells. Macrophages and B cells can function as antigen presenting cells, such that very little antigen on their surfaces is needed for evoking an immune response.

¹⁸⁸ B. Kindred and D. Schreffler (1972) H-2 dependence of co-operation between T and B cells in vivo. *J. Immunol.* 109, 940-943.

These cells express MHC class II, the self antigens that positively select the helper T cells. The presence of MHC class II gives the helper cells some affinity for antigen presenting cells even without the antigen. In the presence of antigen, lymphocytes have been seen to aggregate around antigen presenting cells. These lymphocytes are presumably antigen-specific and/or antiidiotypic with respect to the antigen.

Do T cells recognize only antigen fragments in MHC clefts?

A widely accepted dogma is that T cells recognize only peptides in the clefts of MHC molecules. The kind of experiment that leads to this viewpoint consists of the priming of a mouse with a protein antigen, then challenging T cells from the mouse with macrophages together with various peptides derived from the antigen. Under these circumstances, peptides that can be produced by proteolysis of the antigen and which bind to the MHC cleft do indeed cause proliferation of the T cells, and other peptides fail to do so. What has been missing in the dogma is an answer to the question "why"? Should not T cells be able to respond to anything, even if they have been biased to preferentially recognize MHC?

Experiments that have been interpreted in terms of T cells recognizing only antigen in MHC clefts are more simply understood in terms of a process of molecular Darwinism. Following immunization of the mouse with the antigen, some antigenic fragments last longer than others, and hence are available for stimulation of the T cells for a longer time. The ones that last longest are the ones that are protected from proteolytic degradation by being bound within an MHC cleft. If these protected fragments last for the time needed for a significant number of cell divisions, the response subsequently observed in an *in vitro* secondary response can appear to be completely specific for the protected peptides. The survival of the fittest process for peptides results in the observed specificity. Since the T cells are selected to have affinity for MHC to start with (and they are diverse), the presence of the peptides will cause a subset to proliferate, and the ones that are protected from proteolytic degradation for the longest time become the most strongly selected clones. This idea removes the mystery from the preference of T cells for fragments in MHC clefts; we are just seeing an inevitable consequence of natural selection at the molecular level.

The dogma of T cells responding only to fragments of antigens in MHC clefts is often overstated. Some monoclonal antibodies can be used to stimulate unprimed T cells, independently of any apparent role for MHC clefts.^{Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.} This is to be expected in the context of our postulate that the cross-linking of receptors is the essential component for the specific stimulation of lymphocytes, including T cells.

Specific T cell factors may lubricate the system

The immune system is a well lubricated system. We do not have cells spontaneously forming clumps in the blood, for example, even though it may appear we should have the prerequisites for that. T cells are selected to recognize MHC and MHC is expressed on antigen-presenting cells (A cells) that are present in the system, so why aren't T cells and A cells typically immobilized by binding to each other? A speculative answer is that when a T cell encounters a cell to which it binds using the V region of its receptor, it can utilize inhibitory interactions to free itself. It can do this by simply releasing some antigen-specific T cell factor into its environs, which would immediately compete with its own cell-bound receptors in their binding to the other cell, and the T cell then floats away free. Specific T cell factors may thus have the additional function of lubricant.