**Update On T-Cell Recognition Of Viral Antigens With Particular Reference to Cytomegalovirus**

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ملخص

يتمثل جسم الفقاريات في ذاته وسائر دفاع ضد الأمراض وجميع المسببات المرضية مثل البكتيريا والفيروسات والطفيليات وكذلك الخلايا السرطانية. بعض الفيروسات لها القدرة على أن تبقى فترة طويلة داخل الجسم ومن ثم تسبب تغيرات في خلايا الجسم أو أن تحدث التهاباً موضعاً أو أن تحدث مرضًا عاماً في الجسم. في بعض الحالات يعمر جسم المناعة على القضاء على الفيروس. وفي هذا السياق تهدف الدراسة إلى تناول آخر ما توصل إليه العلم في مجال مقاومة الجسم لدخول الفيروس والقضاء عليه أو مقاومته بالاعتماد على أبحاث حديثة أجريت في هذا المجال.

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ABSTRACT:

Vertebrates possess a surveillance mechanism, called the immune system, that protects them from disease-causing (pathogenic) microorganisms such as bacteria, viruses, form parasites and from cancer cells. Some viruses are regularly lethal for particular host species; other regularly establish persistent infections, often for life. At other times the immune response fails to eliminate the virus. This review is an update on the role of the immune response in recovery from viral infection and resistance to reinfection. The features are surveyed of modern immunology as relevant to virology.

Key words: T-cells, Antigen recognition, T-cell receptors, Viral antigens, Infection of immune cells, Cytomegalovirus, Epstein-Barr virus, Influenza virus, Herpes simplex virus, Lymphocytic choriomeningitis, Varicella-Zoster virus.

Introduction

The defence of a host against an invading viral pathogen is complex and probably depends on the interaction of a number of cellular and humoral factors which restrict and clear the infection. The mechanisms involved can be classified as either antigen specific or non-specific because neither demonstrate a requirement for previous exposure nor show evidence of an anamnestic response, such as natural killer (NK) cells activities and interferon production. This review will focus on T-cells which play a major role in the host defence against virus infections, either as helper cells permitting the optimal production of antibody by B- cells, or directly as effector cells permitting the clearance of intracellular viruses, through mechanisms not clearly understood.
T-lymphocytes:

Lymphocytes circulate freely through the blood and lymphatic vessels of the body and are directly responsible for all specific immune responses. The lymphocyte population as a whole is divisible into two classes: the T-lymphocytes (or T-cells), so-called because their maturation requires processing in the thymus and the B-lymphocytes (or B-cells), which are continuously generated in bone marrow and produce antibodies\(^\text{31,45}\).

T-cells are important in several ways: (1) while some T-cells fight infection directly by killing virus-infected cells, most regulate the activity of other effector cells, such as B-cells and macrophages, (2) both effector and regulatory T-cells act mainly at short range, interacting directly with the cells they kill or regulate; B-cells on the other hand, secrete antibodies that can act far away, (3) presumably for this reason, T-cells bind foreign antigen only when it is on the surface of another cell in the body. T-cells kill virus-infected cells, and they help or inhibit the responses of other white blood cells.

These three functions are carried out by different classes of T-cells, called cytotoxic T-cells (T\(_c\), usually are CD8\(^+\)), helper (or inducer) T-cells (T\(_h\), usually are CD4\(^+\)), and suppressor T-cells (T\(_s\), usually are CD8\(^+\)CD4\(^-\)), respectively. T\(_c\) together with B-cells, are the main effector cells of the immune system; T\(_h\) and T\(_s\) are collectively referred to as regulatory T-cells\(^45\).

T-cell antigen recognition:

Antigen recognition by T-cell receptors is now fairly well understood\(^47\). T-cell receptors do not bind antigen directly; rather, they recognize foreign antigens in the form of peptide
fragments bound to a molecule encoded in the major histocompatibility complex (MHC). Furthermore, the great majority of antigens require some form of internal processing before they can be presented to the T-cells in an immunogenic form (Figure-1).

Peptide-binding by MHC molecules occurs primarily intracellularly, and the majority of class I and class II histocompatibility molecules expressed on the cell surface appear to be already occupied by bound peptides. The peptide-binding capacity of purified MHC molecules is very low, and class I molecules bind significantly less peptide (8 - 9 amino acids long) than do class II molecules (13 - 17 amino acids long).

Peptides from endogenously synthesized proteins are transported into the endoplasmic reticulum (ER) after cytoplasmic degradation or are generated from translocated proteins possibly in the intermediate compartment between the ER and the Golgi apparatus or are generated following translocation into the lysosome or late endosome in a process involving a 70 kDa heat shock-family protein. The peptides in the ER can be bound by assembling class I molecules and may compete with invariant chain for binding to assembling class II molecules. The peptides from endogenous proteins generated in the endosomal/lysosomal pathway may have access to the peptide-binding site of class II molecules, exposed after dissociation of the invariant chain in the endosome (Figure -2). Exogenous antigen is internalized via the endocytic pathway and is subject to gradual degradation by the proteases cathepsin B and D in the early endosome, by cathepsin B and D plus lysosomal enzymes in transit in the late endosome, and finally by fully active lysosomal hydrolases in the lysosome. The compartments of the endocytic pathway progressively decrease in pH and consequently increase their proteolytic
activity, as is indicated by the increase in shading of the compartment interiors in Figure-2. Class II molecules with their associated invariants chain are delivered to early endosomes and it is proposed they remain in the endocytic pathway until invariant chain is removed. When the invariant chain is removed, the class II molecule becomes competent to bind peptide, can be released from either the early or late endosome, and can transport peptide to the cell surface. Internalization and recycling of class II molecules provide a second opportunity for empty class II molecules to bind peptide, and these processes may promote peptide exchange, with the possible involvement of a 70 kD peptide binding protein of the heat shock family (Figure-2)\(^{(49)}\).

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**Figure-1.** Antigens are internalized by antigen - presenting cells (APCs) and are then degraded by proteolytic enzymes in the phagolysosomes. Some of the material is only partly degraded and is re-expressed at the cell surface, where it comes to be associated with MHC molecules\(^{(39)}\).
Figure-2. Intracellular trafficking pathways involved in the generation of antigenic peptides (antigen processing) and the binding of peptides by class I and class II histocompatibility molecules (antigen presentation)⁴³.

T<sub>e</sub> cells recognize peptides of protein antigens presented by MHC class I molecules; whereas T<sub>h</sub> cells recognize peptide fragments of foreign proteins bound to self class II molecules of the MHC⁴⁷. The protease involved in the generation of endogenous peptides are unknown. One candidate is the proteasome, a non-lysosomal proteinase complex abundantly present in the cytosol. Proteasomes have several proteolytically
active sites and are complexes of protein of high relative molecular mass (about 600 kD), consisting of about 20 - 30 subunits. At least one of these subunits is encoded by the mouse MHC in the region between the K locus and the MHC class II region, and is inducible by interferon-gamma. This raises the intriguing possibility that the MHC encodes not only the MHC class I molecules but also proteases involved in the formation of MHC - binding peptides (Figure-3)\textsuperscript{38}. In the human MHC class II region, four genes have been identified (RING4, RING10, RING12 and RING11) which are believed to encode the peptide transport proteins. These human proteasome-like genes are expressed at a very low level in some cells, but are inducible with interferon-gamma, they may be specifically tailored to antigen presentation and could help recruit proteasome component for this function\textsuperscript{23}. In the mouse, there are two genes (called HAM1 and HAM2) which are polymorphic, at least these two genes encoding subunits of the low - molecular mass polypeptide (LMP) complexes. In this region proteins are encoded which are postulated to be involved in the transport of peptide fragments into the ER for association with newly synthesized class I molecules\textsuperscript{30}.

Processed antigens interact with MHC molecules and with the T-cell antigen receptor via different amino acid residues as shown in Figure-4. The part of the antigen which interacts with the MHC molecules is the "agretope"; the part which interacts with the T-cell antigen receptor is the epitope. In this scheme the part of the MHC molecule which interacts with the antigen is the desetope, and the part which interacts with the T-cell antigen receptor is the histotope. MHC of different haplotypes will have different desetopes. Consequently they will bind different agretopes on the antigen, and this will result in different
epitopes becoming exposed to the T-cell antigen receptor in animals of different MHC haplotype\textsuperscript{(39)}.

Figure-3: (a) Representation of the class II region showing the linkage relationships of proteasome component genes (P) and transporter genes (T). (b) An intact antigen is shown binding to a proteasome which degrades peptide transporters across the membrane of the endoplasmic reticulum where they bind to newly synthesized class II MHC glycoproteins causing the stable assembly of transmembrane heavy chain with $\beta_2$-microglobulin. Only after the assembly of the three components can the class I molecule be expressed on the cell surface. ABC, ATP-binding cassette transmembrane transporters\textsuperscript{38}. 
Figure-4: T-cell antigen recognition involves a 3-way interaction involving the T-cell factor, MHC molecule and processed antigen. To facilitate understanding of the interaction, the various interacting parts are named as shown. The antigen’s aleptode binds to MHC destope while its epitope binds to the T-cell receptor paratope. The MHC molecule and T-cell receptor may also interact separately via their histotope and restitope.\(^3\)

T-cell receptors (TCRs):

The mechanism by which a single T-cell receptor (TCR) recognizes simultaneously a peptide antigen and elements of the MHC structure (restriction) is still an enigma. The TCRs fall into two main groups defined by the nature of the heterodimeric receptor chains (αβ or γδ) expressed. Both receptors are associated with a complex of polypeptides making up the CD3 complex. This complex is present on the surface of all mature T-
cell and is thought to be involved in passing the signal from surface of an antigen-activated T-cell to its anterior\textsuperscript{2,11}.

A TCR heterodimer is composed of an $\alpha$ and a $\beta$ polypeptide chain, both of which are glycosylated. Each chain is about 280 amino acid residues long, and its large extracellular part is folded into two immunoglobulin like domains- one variable (V) and one constant (C). From an analysis of amino acid sequences deduced from cDNA clones, it is thought that an antigen-binding site formed by a V$\alpha$ and V$\beta$ domain is similar in its overall dimensions and geometry to the antigen-binding site of an antibody molecule. Unlike antibodies, however, which have two binding sites for antigen TCRs have only one (probably because they are always bound to the plasma membrane, where they can act cooperatively). The $\alpha/\beta$ heterodimer is non-covalently associated with an invariant set of membrane proteins called the CD3 complex. A typical T-cell has 20,000 to 40,000 $\alpha/\beta$ receptor proteins on its surface\textsuperscript{2,11}.

A second type of TCR heterodimer, composed of $\gamma$ and $\delta$ chains, has recently been discovered. The overall structure of TCR$\gamma$ and $\delta$ polypeptides are similar to those of the TCR$\alpha$ and $\beta$ chains. Both $\gamma$ and $\delta$ chains have V and C regions with weak, but significant, homologies Ig domains, and the trans-membrane regions contain positively charged residues, two for TCR$\alpha$ and one for TCR$\gamma$. These receptors are expressed on subpopulations of cells in the thymus, epidermidis and gut epithelium and the functions of cells in the thymus, epidermidis and gut epithelium and the functions of TCR$\gamma/\delta$ T-cells are unknown\textsuperscript{2,28}.

The $\alpha\beta$TCR is expressed by at least 95% of peripheral blood T-cells and up to 5% of blood T-cells express $\gamma\delta$TCR. The $\alpha\beta$TCR can be subdivided further into two distinct non-
overlapping populations; the $T_h$ subset which is $CD4^+$ and the $T_{c/s}$ subset which is $CD8^+$, CD4$^+$ T-cells recognize antigens in association with MHC class II molecules, while CD8$^+$ T-cells recognize antigens in association with MHC class I molecules (Figure-5)$^{29}$.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{cd7_marker_diagram.png}
\caption{Major T-cell markers in man and mouse. The molecule CD7 is bracketed to indicate that it is only detected thus far in man. Markers in square brackets are specific for mouse (thy-1) or mouse equivalents$^{39}$.}
\end{figure}

Murine T-cells express markers similar to those detected on human T-cells (Figure 5). In addition, all murine T-cells carry a molecule, Thy-1, with a molecular weight of 19-35 KD. With regard to suppressor cells in the mouse, a small proportion of T-cells carry I-J molecules, the expression of which is controlled by genes in the MHC.$^{40}$
Viral antigens:

Viruses consist of a central core of nucleic acid which may be single or double-stranded RNA or DNA. This is surrounded by a coat (capsid) of repeating protein subunits (capsomers); the virus may also have a lipoprotein envelope derived from the host cell membrane into viral glycoproteins are inserted.

Viral infection begins with the attachment of the virus to a component of the cell membrane which acts as its specific receptor, such as the CD4 molecule on T-cells to which human immunodeficiency virus (HIV) binds or sialic acid for the influenza virus haemagglutinin (HA). Enveloped viruses may penetrate the cell by fusion with the cell membrane (mediated by fusogenic viral glycoproteins, e.g. Sendai virus) or by endocytosis after binding to their specific receptor (e.g. influenza virus). In the latter case, the virus then enters the cytoplasm by fusion with the endosomal membrane consequent upon low pH dependent cleavage of viral glycoproteins. Viruses then uncoat allowing transcription of viral nucleic acids (except single positive-stranded RNA viruses which are translated directly). In more complex viruses, some viral proteins may be nonstructural (i.e. not from part of the virion) and serve functions such as shutting down host cell protein synthesis and regulating viral transcription. Other viral proteins are structural and are incorporated into new virions. Following viral nuleic acid replication, virus particles are assembled by aggregation of structural proteins around the nucleic acid. Non-enveloped viruses may be released from the cell by lysis, whereas enveloped viruses insert their viral glycoproteins
into host cell membranes and bud from such membranes.$^{4,33,36}$

**Infection of immune-cells by viruses:**

Most virus diseases involve infection of the immune system; this may lead to severe immunodeficiency and/or lymphocytic or myelogenous malignancies. Many viruses replicate in macrophages, but few viruses have macrophage-specific tropism or bind to macrophage-specific receptors. Lactic dehydrogenase (LDH) virus, which causes a persistent infection in mice, has a predilection for infecting subsets of macrophages expressing Ia molecules as receptors. Some macrophages display CD4 antigens, which leave them permissive to HIV. Infection of macrophages by vaccinia virus normally results in entry of virus into the cytoplasm, followed by productive replication; antibody coated vaccinia virus suffers a different fate, as it is engulfed in a phagolysosme and degraded. Many viruses, such as herpes simples virus (HSV) and influenza virus, grow poorly in activated macrophages, but others such as mouse cytomegalovirus (MCMV) or LDH virus may grow better in activated macrophages.$^3$

Unstimulated B- and T-cells have small, relatively inactive cytoplasms and serve as poor hosts for productive virus infections. Some viruses, such as measles, will infect lymphocytes but remain dormant until the lymphocytes are stimulated with mitogens, at which time measles viral proteins are produced and there is a conversion to a lytic infection. The ability of Varicella-Zoster virus (VZV) to replicate in and lyse only stimulated dividing lymphocytes has been used as a means to quantitate the number of T-cells responding to an antigen; the rational is that only the stimulated T-cell will become an infective centre and give rise to a viral plaque on a monolayer of susceptible cells. Some viruses,
such as HIV, are T-cell tropic, whereas others, such as Epstein-Barr virus (EBV), are B-cell tropic. When such tropism occurs, it usually involves cell-type dependent receptors, such as CD4 for HIV, and the CR2 complement receptor for EBV\textsuperscript{4,42}.

Viruses which lyse stimulated lymphocytes have the potential to be immunosuppressive and many have been shown to inhibit lymphocyte responses in vitro. For example, the feline leukemia virus p15E blocks the ability of T-cells to respond to IL-2; similar proteins are found in murine and human retroviruses. The mechanism of immunosuppression in vivo is a much more complicated process, often involving cytokines and autoimmunity. The immunodeficiencies in man caused by HIV or in mice caused by lymphocytic choriomeningitis (LCM) virus are actually associated with the infection of a very low percent of lymphocytes\textsuperscript{33,47}.

In contrast to non-proliferating T- and B-cells, natural killer (NK) cells have large, active cytoplasms capable of supporting virus growth. Little is known about the frequency or significance of virus infections of NK cells in vivo, but human CMV, measles and influenza viruses infect human NK cells in vitro. The infections are non-lytic, and influenza virus does not inhibit NK cell mediated cytotoxicity. In contrast, both human CMV and measles virus inhibit the ability of NK cells to mediate natural cytotoxicity but do not impair their ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC). The reason for this selective inhibition in lytic function is not known\textsuperscript{2,33}.

\textit{T-cells recognize fragments of viral proteins:}

Tc cells are generated during most viral infections. They are
detected in vitro by their ability to lyse virus-infected cells and probably act in the same way in vivo\textsuperscript{47}, although they may also release lymphokines including interferon-gamma\textsuperscript{34}. In acute infections such as with influenza A virus, T\textsubscript{c} cells have been shown to terminate infection and to contribute to clearing of virus\textsuperscript{19,50}. This was most clearly demonstrated in experiments in which virus-specific T\textsubscript{c} cell clones were transferred to lethally infected mice\textsuperscript{19}. The level of specific T\textsubscript{c} cell responses has been shown to correlate with virus-clearing in humans\textsuperscript{32}. In EBV infection in vitro, T\textsubscript{c} cells have been shown to cause regression of the outgrowth of transformed B-cells, and in vivo they probably inhibit infection by persisting virus\textsuperscript{42}. The importance of T\textsubscript{c} cells in vivo has been demonstrated in mice depleted of CD4 cells by specific monoclonal antibody. These animals generated a weak antibody response to infecting influenza virus, because they lack T\textsubscript{h} cells, but a good T\textsubscript{c} cell response was demonstrated and influenza virus-infected irradiated mice were cured by transfer of these T\textsubscript{c} cells\textsuperscript{18}. Similarly, mice that are genetically incapable of making a T\textsubscript{c} cell response to a virulent strain of Sendai virus are more likely to die during acute infection\textsuperscript{22}.

Most virally infected cells display viral antigens on the surface of their plasma membranes which are recognized by T\textsubscript{c} cells. Furthermore, it may be demonstrated that T\textsubscript{c} cells recognize the viral antigens in association with their recognition of the H-2K and D antigens present on the surface of the infected cells. In this way T\textsubscript{c} cells of a particular H-2 haplotype from an animal infected with a virus are primed to kill cells infected with that virus. However, it is found that they will not kill cells of a different haplotype infected by the same virus. In effect the H-2 molecules on the surface of the virally infected cell act as a code, guiding the
Tc cell to its target, and allowing it to differentiate the target cell from other tissues carrying the viral antigen (Figure-6).\(^ {39} \)

![Diagram of viral infection and Tc cell activity]

**Figure-6: Killing of virally infected target cells and haplotype restricted killing.\(^ {39} \)**

Virus specific T\(_c\) cells recognize viral antigens which have been processed and presented as peptides on the surface of infected cells in conjunction with the appropriate MHC molecules. Processing and presentation of viral antigens allows viral proteins not otherwise expressed on the cell surface to be
exposed to T-cells e.g. influenza virus nucleoprotein (Figure-7)\textsuperscript{44,47}. Hence an infected cell can be killed before the virus can replicate, and viral spread may thus be limited. With a few exceptions, such as reovirus, T\textsubscript{c} cells are not serotype specific, i.e. do not recognize the same epitopes as antiviral antibodies. Protection mediated by T\textsubscript{c} cells can be adoptively transferred: for example naive mice are protected from influenza A virus by transfer of an influenza A T\textsubscript{c} cell clone\textsuperscript{33}.

Figure-7: A cytotoxic T-cell will kill a virus infected cell when it recognizes fragment of viral protein bound to class I MHC molecules on the surface of the infected cell. In the case shown, the peptide fragments are derived from the nucleoprotein (NP) of the influenza virus; for simplicity, this is the only internal viral protein shown. Only a very small proportion of the viral proteins synthesized in the target cell are degraded. It is not known how they are degraded, how the resulting peptide fragments get to the cell surface, or where the fragments is associated with the MHC glycoproteins\textsuperscript{44}. 
$T_h$ cells augment T-cell, B-cell and NK cell responses to viral proteins; $T_h$ cells recognize multiple epitopes on a viral protein, such as influenza virus HA, which may differ from those recognized by antibody.

T-cells mediating delayed type hypersensitivity (DTH) respond to specific viral antigens by secreting cytokines which produce an inflammatory reaction characterized by a mononuclear cell infiltrate. This may be modulated by subsets of both $T_h$ and $T_c$ cells. The exact role of DTH in viral infections in man is poorly understood due to the difficulty of any in vitro assay, but there is evidence for its importance in some experimental virus infections. Herpes simplex virus (HSV) inoculated into the ear pinna in mice results in a local infection - CD4 lymphocytes from draining lymph nodes proliferate in response to HSV antigens, mediate DTH and can transfer protection. However, in mice infected with influenza virus and previously exposed to non-infectious virus, adoptive transfer experiments have shown that DTH may be responsible for increased mortality.\(^3\)

$T_s$ cells have been studied in experimental models and are thought to limit the immune response to viruses, possibly thus preventing immune-mediated host damage. $T_s$ cells have been shown to specifically limit DTH activity in mice after experimental HSV infection. It has been suggested that increased $T_s$ activity might favour persistence of certain viruses.\(^3\)

_Cytomegalovirus specific immune recognition and immunoregulation:_

$T_c$ cells are predominantly directed against the major IE antigen as is found with other viruses such as HSV. The role of $T_c$
cells in CMV infection has been studied in detail in the mouse CMV model. In human CMV, Borysiewicz and colleagues (1983-1988) showed that there are precursors of CMV-specific Tc cells present in peripheral blood lymphocytes (PBL) of seropositive individuals and that most of these are directed against non-structural immediate early antigens\textsuperscript{6,7}. They first stimulated production of Tc cells by coculturing CMV infected fibroblasts with PBL. The fibroblasts were obtained by skin biopsies from the same patients from which Tc cells were obtained and hence were autologous and HLA compatible with the effector cells. Predominantly Leu2a\textsuperscript{+} lines of Tc cells were generated which lysed \textsuperscript{51}Cr-labelled CMV-infected cells in virus-specific and HLA-restricted manner. They further showed that CMV-specific Tc cells were present in PBL of seropositive subjects at a frequency of one in 500 to 20,000 E-rosette-positive lymphocytes. To differentiate Tc cells recognizing different viral specificities, targets that expressed only IE and E antigens were produced by infecting fibroblasts in the presence of phosphonoformate to inhibit viral DNA synthesis and late antigen synthesis. The majority (60\%) of Tc cell clones developed from PBL lysed cells expressing only IE and E antigen\textsuperscript{6}. The Tc cell precursor cells of infected B-cells with CMV were also analyzed\textsuperscript{7}. It was found that 43\% and 58\% of the CMV Tc cell precursors of two different donor respectively lysed IE-antigen expressing targets, whereas less than 6\% lysed targets expressing gB\textsuperscript{7}.

In murine CMV, protein pp89, which is encoded by genes IE1, is a non-structural regulatory protein expressed in the IE phase of the viral replication cycle and located mainly in the nucleus of infected cells. Tc cells recognize the IE protein pp89, specifically a nonapeptide which is presented by the MHC have revealed that CMV has the capacity to interfere with antigen presentation. Del
Val et al. have suggested that the recognition of pp89 by T\textsubscript{c} cells is abolished after expression of E genes\textsuperscript{13}. The failure of pp89 presentation appeared to be selective in that MCMV E antigens could be presented. Since pp89 synthesis, stability and nuclear transport remained unchanged in the E phase, they hypothesized that characteristics of the protein or its regulatory function affected pp89 processing during the E phase. They defined the step at which MCMV E gene products interfere with the natural pathway of pp89 processing and peptide presentation. First, the inhibition of further glycosylation indicates that the transport of MHC class I molecules through the Golgi compartment is generally inhibited by MCMV E gene function. Second, because cells with arrested transport of MHC class I molecules contain already the correctly processed nonapeptide of pp89, these results suggest the ER/cis-Golgi compartment represents the site of antigenic peptide binding to MHC class I molecules\textsuperscript{13,24}.

The suggestion in HCMV, that sequestration of beta-2 microglobulin (β\textsubscript{2}m) would result in a block of peptide presentation by MHC class I molecules and predict an escape from cellular immune control, is different in the mechanisms of MCMV\textsuperscript{27}. Koszinowski and his co-workers (1988, 1991, 1992) did not see an inhibition of MHC class I molecule assembly, and only at later stage was the maturation of the trimolecular complex inhibited. They also observed in HCMV-infected cells that HLA class I molecules were synthesized but remained retained intracellularly\textsuperscript{3, 12, 24}.

In contrast to T\textsubscript{c} cell. HCMV-specific T\textsubscript{h} cells appear to recognize primarily envelope glycoproteins comprising the gcI and gcII complexes and the abundant matrix- tegument protein, pp65. Gehrz et al. (1993) showed that HLA-DR restriction of T\textsubscript{h}
cell response to HCMV-gB. This process is associated with limited T-cell receptor diversity: (1) high proportion of $T_h$ clones restricted by HLA-DR7 and recognizing gB contain TCR$\alpha\beta$ heterodimer with VP13 in association with VP14; (2) comparative analysis of TCRVDJβ sequence of HCMV-specific $T_h$ clones suggest that five specificity for HLA-DR7-gB is defined by the junctional region. Alternatively, gB-specific $T_h$ precursors may not be expanded due to the presence of antigen-specific $T_s$ cells or lack of antigenic stimulation due to sequence polymorphisms in certain strains of HCMV which modify or delete the immunodominant epitopes of the gB$^{25}$.

The role of macrophage during CMV infection has not been clearly defined. But in MCMV, infection of mouse macrophages resulted in the alteration of phagocytic functions of the macrophages while supporting MCMV replication. Carney and Hirsch (1981) showed that monocytes infected in vivo or in vitro with CMV could suppress the proliferation responses of lymphocytes to concanavalin A$^9$. Schrier et al. (1986) showed that suppression of NK cell activity by CMV infected mononuclear cells could be attributed to the monocyte fraction. The two groups have found a reduction of IL-1 production after CMV infection, and at least one group has suggested that an IL-1 inhibitor is involved$^{35}$. Kapasi and Rice (1988) also showed that CMV infection impairs the ability of infected peripheral blood mononuclear cells and monocytes to produce IL-1 and IL-2, as well as their ability to respond to these ILs$^{21}$. Duran et al. (1985) showed that IL-1 is an upregulator for $T_h$ cells in vitro; it promotes the generation of lyt-1 positive $T_h$ cells and inhibits the

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generation of lyt-2 positive T\(_{c}\) cells. Impairment of IL-1 generation because of CMV infection might result in an imbalance in helper/suppressor cell ratios\(^{15}\).

A characteristic feature of the virus is its ability to establish latency for the life of the individual. This characteristic probably allows no or very minimal expression of virion proteins which could be presented as peptides in the context of MHC class I molecules. The cell with latent CMV genome would therefore be undetectable by circulating T\(_{c}\) cells. This virus has a novel way of avoiding antibody neutralization when it is extracellular. Soon after release from cells it binds the host protein \(\beta_2m\) and this coating protects the virus from neutralization. The presence of this \(\beta_2m\) coat also increases the infectivity of virions and allows them to bind preferentially to cells which express class I HLA molecules. The sequencing of the genome of HCMV has revealed a gene which, if expressed, would have considerable homology with HLA class I like molecules. There are several possible reasons why the virus may have this gene. One is that this protein within the cytoplasm may bind \(\beta_2m\) and so prevent peptides derived from virion proteins being presented at the cell surface by authentic class I molecules\(^{5, 8, 16}\).

The hypothesis in the lack of T\(_h\) and/or T\(_{c}\) cells to recognize viral antigens must involve: (1) a defect in an antigen processing and presentation; (2) lack of association of viral peptides with particular HLA molecules; (3) tolerance due to negative selection or lack of positive selection of thymocytes expressing T-inducer and for viral peptides; or (4) antigen-specific suppression of T\(_h\)
reactive with HCMV peptides\textsuperscript{16}.

Gopal and Grundy (1993) used a model in which the cell surface expression of class I HLA molecules has been shown to be downregulated in some viruses, e.g., Adenovirus 2. They examined the processing of class I molecules using endoglycosidases. They found, at early times in HCMV infection, there is progressive loss of class I HLA molecules with the time from the surface of cells increased by intracellular accumulation coincident with an increase of gross cellular proteins. They suggested that the early decrease in cell surface expression of class I HLA on CMV infected cells is not due to decreased synthesis or altered glycosylation\textsuperscript{26}.
References


