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Herpes simplex virus infection. The roles of T-lymphocytes in host responses

M. Cholis
Department of Dermato-Venereology, Faculty of Medicine, Brawijaya University/
Dr. Saiful Anwar District Hospital, Malang

ABSTRACT

M. Cholis – ***Herpes simplex virus infection. The roles of T-lymphocytes in host responses***

T-lymphocytes are the most important component of the immune response to control recurrent infections. T-lumphocytes of CD_4+ and CD_8+ recognize a variety of viral proteins and produce lymphokines with antiviral and immunomodulatory effects. Both CD_4+ and CD_8+ bearing T-cells can kill HSV infected host cells. The relation between specific T-cells responses and severity of HSV disease have not been consistently detected. Interaction between T-cells responses and HSV and host cells result in a dynamic state of latency. HSV has evolved special mechanisms for evasion of host immunity. Reactivation can result in recurrences with the implication of transmission and/or disease. Molecular definition of T-cell responses for HSV may lead to immunological intervention to prevent HSV disease. Impaired T-cell immunity should be considered as a risk factor for severe infections.

Key words: herpes simplex – T-cell role – latency – immunocompromised – vaccine

ABSTRAK

M. Cholis – ***Infeksi virsus herpes simpleks. Peranan limfosit-T terhadap respon pejamu***

Limfosit-T merupakan komponen utama respon imun dalam mengendalikan infeksi rekuren. Sel-T CD_4+ dan CD_8+ dapat mengenal protein-protein virus dan memproduksi limfokin yang mempunyai sifat antivirus dan imunomodulator. Sel-T CD_4+ dan CD_8+ mampu membunuh sel pejamu yang terinfeksi. Hubungan antara respon sel-T yang spesifik dan derajat penyakit belum dapat dipastikan. Interaksi antara respon sel-T dengan virus dan sel pejamu menyebabkan keadaan laten sebagai keadaan yang dinamis. Virus herpes simplek (HSV) mempunyai kemampuan khusus untuk menghindar dari imunitas pejamu. Reaktivasi HSV laten menyebabkan kekambuhan dengan implikasi terjadinya penularan dan atau penyakit. Dasar molekular dari respon sel-T terhadap HSV dapat digunakan dalam tindakan intervensi imunologik untuk pencegahan infeksi HSV. Kelumpuhan imunitas sel-T merupakan faktor risiko terjadinya infeksi yang hebat.

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INTRODUCTION

Both humoral and cellular immune responses develope during the first week following acquisition of Herpes simplex virus (HSV) infection and persist for life. Cell mediated immune responses appear more important than humoral immune responses in controlling the severity of mucocutaneous HSV infection. Persons with congenital, acquired, or iatrogenic cellular immunodeficiency have more frequent, severe, and prolonged herpetic infections.

High levels of antibody and strong CD_4+ T-lymphocytes reactivity are present in the peripheral blood of infected patients, leading to the apparent paradox of continuing infection in the presence of a vigorous immune response. Accumulating evidence indicates that T-lymphocytes are perhaps the most important components of the immune response to recurrent infections.

HSV has evolved a specific mechanism to evade or attenuate host CD_8+ T-cell recognition of the virus, consistent with a significant pathophysiologic role for these responses. [1]

The present paper reviews the roles of T-lymphocytes in host responses to HSV and their clinical implications.

COMPONENT OF T-CELL IMMUNITY

The specificity of T-cell responses is due to the presence of a genetically unique T-cell receptor (TCR) on the surface of each T-cell. After initially contacting their specific viral peptide antigen, properly processed and presented on surface of the APC, 'naive' T-cells are stimulated to undergo cell division and differentiation into mature and memory cells. Thus the number of T-cells in the body specific for a virus increases dramatically after the initial infection. These virus-reactive T-cells may also kill the neighbouring antigen-presenting cells, and thus, any virus contained therein and stimulate B lymphocytes to produce antiviral antibody. [2]

Most T-cells utilize specific genes, termed as and α as ß, to encode their TCR complex. These α and ß genes are very complex and combine in literally millions of ways to produce a repertoire of T-cells capable of recognizing all the diverse components of the microbial (and allergenic) environment. Most TCR ß-bearing cells in adults also express either the CD_4 or CD_8 molecule on their cell surface. These 'accessory' molecules bind to human leukocyte antigen (HLA) class II and class I, respectively, and assist the recognition step between the APC and the T-cell, and the signalling within the T-cell where recognition of antigen has occurred.

Natural killer cells are thought incapable of recognizing specific viral peptides.

Viral peptides are combined within the APC with HLA molecules. Peptides/HLA complexes are exported to the surface of the APC for exposure to the surrounding milieu. Direct cell-to-cell contact between the APC and the T-cell is required, and three molecular contacts are made at the point of antigen recognition. [3]

Since individuals inherit differing HLA molecules, a peptide region of a viral protein may bind to HLA and thus trigger T-cell in some patients but not others. CD_4- and CD_8- bearing T-cells isolated from HSV lesions display this phenomenon of HLA restriction. Vaccine design is, thus, complicated, since HLA differences may preclude universal recognition of spesific viral proteins or peptides by some members of the population.

Generally, viral proteins that are newly synthesized within a cell are cleaved into component peptides, transported to the endoplasmic reticulum, and there loaded into the empty cleft of HLA class I molecules. The complex of HLA class I molecules and viral peptide is then moved to the cell membrane for surveilance, and possible recognition by host CD_8+ T-cell. The delivery process for viral peptides, from the cytoplasm of infected cells to the endopasmic reticulum, involves a complex of proteins, termed as transporter associated with antigen processing (TAP). Interference with TAP may contribute to HSV evasion of the immune system.

In contrast to HLA class I molecules, only B-lymphocytes and the family of blood and tissue monocyte-derived cells, including Langerhans cells of the skin, normally display HLA class II molecules. HSV skin lesion are marked by HLA class II expression on the surface of normally negative cell types, especially keratinocytes. These class II - expressing keratinocytes may be able to present HSV antigen to CD_4+ T-cells. [3,4]

FUNCTIONAL ROLES OF T-CELLS IN HSV INFECTION

Both CD_4 and CD_8 bearing T-cells can kill HSV infected host cells, and in doing so interrupt viral replication. CD_8 bearing T-cells are the classic cytotoxic T-lymphocytes (CTL) and human CD_4 bearing HSV specific T-cells are heterogenous in their CTL activity. [5]

It is of interest for vaccine design to determine which type (CD_4 versus CD_8) of CTL are associated with clearance of infectious HSV in normal human. Live-virus vaccines provoke CD_8+ T-cell responses, while inactivated virus and sub unit vaccines typically induce CD_4+ responses.

Koelle [6] has consistently recovered CD_4+ specific T-cells from recurrent HSV skin lesions sampled on days 3 - 7 of evolution. These T-cells recognize a variety of viral proteins, including

glicoproteins B, C, and D, and the viral tegument protein, VP 16, and some have CTL activity and secrete lymphokines, including interferon-γ and interleukin-4. CD_4+ T-cell responses against some of these proteins have also been described in blood-derived T-cells. CD_8+ T-cell responses against glycoprotein B and several other viral proteins can be detected in blood from HSV seropositive patients. It is likely that so many diverse HSV proteins are recognized by CD_4+ and CD_8+ T-cells.[6]

To date, associations of HLA type or specific T-cells responses measured in the peripheral blood and HSV disease severity have not been consistently detected. T-cells and NK cells are sources of interferon-γ, a lymphokine with potent immunomodulatory and some direct antiviral effects.

THE HOST RESPONSE IN LATENCY

The immune system has an important role in limiting the effect of primary HSV infection and in constraining the infection to a latent state. The primary aims of the host response are to promote host survival, rescue infected cells and establish lifelong immunity to reinfection. In achieving these aims, the virus may be contained or eliminated.

Antibody-dependent cell mediated cytotoxicity (ADCC) is an important component of the host response to infection (FIGURE 1).[7]

Virally-encoded proteins are processed into peptides and presented by major histocompatibility complex (MHC) class I molecules to the T-cell receptors of CD_8+ cytotoxic T-lymphocytes, with subsequent lysis of the infected cell. Although neurones normally express low levels of MHC class I molecules, recent data suggests that they can rapidly up-regulate the transcription of class I genes in response to HSV. Theoretically, down regulation of the MHC class I molecules, which are vital for immune recognition, would be a valuable means of evading the immune response.

The classic antiviral response, lysis of infected cells by cytotoxic T-lymphocytes is essential when the host needs to destroy an infected cell.

Numerous cytokines are secreted by cellular immune cells, e.g. γ-interferon, which can affect the transcriptional environtment of neighbouring cells. In this way, lytic infection may be prevented and cellular function maintained in a delicate balance with the latent state [7,8]

Virus contain in the body may be important for effectiveness of the immune system, maintaining antibody levels, against disease throughout life.

EVASION OF THE IMMUNE SYSTEM BY HSV

After infection by HSV, there is a profound down regulation of the sysnthesis of HLA class I. Since viral peptides are loaded primarily onto newly synthesized HLA class I, this has an effect of decreasing the amount of mature HSV peptide-HLA class I molecules complexes present on the surface of the infected cell.

At least two specific proteins of HSV contribute to this down regulation of HLA class I synthesis. One protein, termed the virion host shut-off protein, does not specifically reduce the synthesis of host cellular proteins, and is thought to help indirectly the protein synthesis machinery of the infected cell towards synthesis of viral proteins. A second protein, termed ICP-47, prevents newly synthesized HLA class I molecules from maturing in the endoplasmic reticulum, perhaps by inhibiting the function of one of the TAP proteins. The presence of this specific anti-CD_8 T-cell evasion method may indicate that CD_8 responses to HSV are, potentially, important.

HSV encodes a pair of glycoproteins, labeled E and I (gE and gI) which form a complex capable of binding the Fc portion of human IgG. The HSV infected cells may bind HSV specific antibody in this fashion and thus avoid opsonization. HSV glycoprotein C (gC) also binds the third component of complement, and HSV inhibits macrophage function.

Paul[9] reports that the killer T-cells may also act by producing molecules that elicit a form of cell death called apoptosis effect. These signals tell the infected cell that it should kill itself.

Thompson[10] describes that HSV infection is a disease associated with the inhibition of apoptosis. The suicide of an infected cell may be viewed as a cellular defense mechanism to prevent viral propagation.

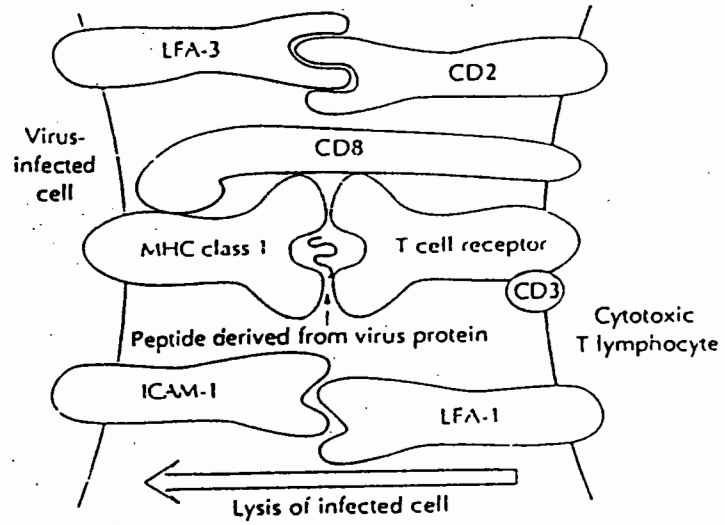

FIGURE 1: – Interaction between the immune system and a virally-infected cell. CD_8+ cytotoxic T-lymphocyte (CTL) recognition of a virus-infected cell. A short peptide fragment derived from a virus protein is presented to T-cell receptor in association with a particular MHC class I molecule. The CTL-target cell interaction is stabilized by CD_8 binding to the MHC class I molecule and by the specific binding of various adhesion molecules (only the LFA- 1-ICAM-1 and LFA3-CD2 interaction are shown). (Whitley RJ and Sandstrom E., 1995). [7]

Recent evidence has demonstrated that T-cells can induce cell death by activating the target cell's endogenous cell death program. Cytotoxic T-cells induce apoptosis either by activation of the Fas receptor on the surface of the target cell or by introduction of proteases, such as granzyme B, which activate the cell death program from the cytoplasm. [9,10]

CLINICAL IMPLICATIONS

HSV infection - a global challenge

HSV are extremely common human pathogens which may cause a broad spectrum of illness, ranging from asymptomatic infections to fulminant disseminated diseases resulting in death.

HSV infection is associated with latency and may result in reactivation. Reactivation leading to recurrent disease can be disabling. Asymptomatic carrier remains undetected, undiagnosed and uncounselled. [11]

As T-cell immunodeficiency causes worsening of recurrent HSV, variations in T-cell function might logically account for the great spectrum of disease severity.

It is possible that an early, effective, localized host response may prevent lesion formation. The T-cell response within lesions may, therefore, represent secondary viral clearance mechanisms after an early immunologic failure. [12]

A continuing study of local and systemic T-cell responses to HSV, including innate and acquired antiviral effector mechanisms, will be required to understand the immunologic correlations of HSV disease severity.

HSV infection in the immunocompromised patients

Depending on the degree of immunosuppression either the activity of the underlying diseases or the length of immunosuppressive therapy,- HSV infection may recur more frequently and have a more severe and prolonged course. [13]

Any patient with impaired T-cell immunity should be considered as a risk factor for severe HSV infection. Patient in immunocompromised group should be considered for prophylactic administration of agents that are active against HSV. It was reported that antiviral therapy could be dramatically effective in reducing morbidity in this patient, both with early recognition and treat-

ment of disease and in the wider use of prophylactic and suppressive therapy. [13]

Conversely, severe or frequent HSV disease should prompt a search for causes of T-cell dysfunction, especially HIV infection.

Immunoprophylactic and immunotherapy

Current vaccine formulations lead to levels of B-cell and CD_4+ T-cell immunity similar to those seen in natural infection. While neutralizing antibody responses are likely to be important in the prevention of primary infection, as suggested by the studies of neonatal disease, the interdependence of B and T-cell responses suggests that HSV specific T-cell will have an indispensible role in a succesful prophylactic vaccine.

Immunotherapy of established infection has been successful in the guinea pig model of recurrent vaginal HSV-2 infection, and initial results in human using recombinant HSV-2 glycoprotein-D have been encouraging. CD_4 T-cells specific for viral glycoproteins B and D localize to recurrent HSV-2 lesions, and both CD_4 and CD_8+ T-cells specific for these antigens are present in the blood. Phase III trials of both immunoprophylaxis and immunotherapy using glycoproteins B and D are underway.

Nevertheless, the understanding of the molecular basis of T-cell responses is developing rapidly and promises to illuminate new ways to minimize tissue damage and to control HSV infections.

CONCLUSION

The relative importance of lymphocytes, natural killer cell markers, and the functional importantce of the T-lymphocyte effector functions of cytotoxicity, B-cell help and lymphokine production has not been fully defined in human.

CD_4 T-cells recognize a variety of viral proteins, including glycoproteins B, C and D, and the viral tegument protein, VP16, and some have CTL activity and secrete lymphokines, including interferon-γ and interleukin-4.

CD_8 T-cell responses against glycoprotein B and several other viral proteins.

HSV has evolved special mechanisms for evasion of host immunity.

Any patient with impaired T-cell immunity should be considered as a risk factor for severe HSV infections.

Trials of both immunoprophylaxis and immunotherapy using glycoproteins B and D are underway.

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