

CELLULAR IMMUNITY IN HUMAN HERPES VIRUSES 6 AND 7 INFECTED GASTROINTESTINAL CANCER PATIENTS

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CD4+ T lymphocytes appear to be the preferential target for replication of HHV-6 (human herpes virus) as well as HHV-7 viruses in vivo. In addition, CD8+ T cells, monocytes/macrophages, natural killer cells, epithelial, endothelial, neural cells and fibroblasts may be infected. By definition, however, even a tumour designated by pathologists to be early stage may be late stage when considered by the immune system. Certainly, even early stage tumours have evaded immune control, suggesting that they have acquired many immunosuppressive characteristics. The aim of the study was to clarify the influence of beta-herpes viruses on cellular immune response. In 95 gastrointestinal cancer patients we determined the immunocompetent cell level CD3, CD4, CD8, CD19, CD38, CD95, CD25 using laser flow cytometer and B-herpes viruses HHV-6, HHV-7 presence using a nested polymerase chain reaction method. Our data showed no statistically significant difference in immunocompetent cell level between negative, latent and active HHV-6, HHV-7 infection. Patients with immunocompromised immune status (lymphopenia) had a tendency to decreased CD4+, CD19+ absolute count. It may be suggested that virus-mediated immune response inhibition seems to be similar to cancer mediated, but differences in immune response among the same group of individuals had no influence on the average number of the immunocompetent cells in the group. Therefore, to characterise host-virus-tumour interactions, individual interpretation of each case is needed.

Key words: HHV-6, HHV-7, gastrointestinal cancer, cellular immunity.

INTRODUCTION

Cellular immunity is the most important part of the immune system in anticancer immune response. Numerous innate and adaptive immune effector cells and molecules participate in the recognition and destruction of cancer cells, a process that is known as cancer immunosurveillance. However, cancer cells avoid such immunosurveillance through the outgrowth of poorly immunogenic tumour cell variants, called immunoselection, and through suppression of the immune system (Zitvogel *et al.*, 2006). Cancer-associated immunosuppression is mediated by evaluation of an immunosuppressive network that extends from the primary tumour site to secondary lymphoid organs and peripheral blood immunocompetent cells. Chronic stimulation of T cells by tumours leads to activation-induced cell death and insufficiency of cellular immune response.

It could be expected that each additional immunosuppressive factor contributes to the tumour escaping from immunological control and promotes cancer growth.

Human herpes viruses (HHV) are frequently present in patients with a compromised immune system and are described as immunotropic viruses that can infect several cells implicated in the generation of both cell-mediated and humoral immune response. Beta-herpes viruses HHV-6 and HHV-7 have some similar biological properties and both viruses are often recognised concomitantly, suggesting that viral syndromes may often be due to a combination of these viruses (Hall *et al.*, 2006). HHV-6 and HHV-7 can induce immunosuppression by various mechanisms and triggering of apoptosis in lymphocytes is one of the most important (Mirandola *et al.*, 2006).

CD4+ T lymphocytes appear to be the preferential target for replication of HHV-6 as well as HHV-7 viruses *in vivo*. In addition, CD8+ T cells, monocytes/macrophages, natural killer (NK) cells, epithelial, endothelial, neural cells and fibroblasts may be infected (Clark, 2002; Dockrell, 2003; De Boele *et al.*, 2005; Miyake *et al.*, 2006).

An effective CD4+ T cells response is believed to prevent tolerance induction by effective function of tumour antigen

on cytotoxic CD8+ T cells, thereby preventing tumour escape from immunological control. Lack of CD4+ T cells help is also involved in the deletion of cytotoxic T Ly in the chronic viral infection. The persistent presence of low levels of antigens in these cases is similar to some cancers. Therefore, it is possible that cytotoxic T Ly against tumour antigens are deleted when T helper responses are absent (Kennedy and Celis 2006). Induction of T cells apoptosis by viruses is one of the mechanisms to destroy host immune system. Based on previous studies, it is known that resting T cells are not susceptible to Fas (CD95)-dependent apoptosis, but Fas-triggered T cells death happens in activated effector T cells upon encountering their antigens. Thus, active effector T cells will be eliminated and less active or suppressed T cells (CD95-) will be preserved (Lenardo, 1991; Russell *et al.*, 1991).

Beta-herpes viruses frequently reactivated under immunosuppressive conditions, and reactivation of HHV-6 plays a significant pathologic role in immunocompromised patients. The pathogenic significance of HHV-7 reactivation remains uncertain, however, indirect effects of HHV-7 replication may include interactions between HHV-6 and -7, and the development of cytomegalovirus disease (Smith *et al.*, 2001; Moussa *et al.*, 2002).

By modulating specific antiviral immune response, beta-herpes viruses can facilitate their own spread and persistence *in vivo* as well as contribute to the pathogenic effect of the other agents (Lusso, 2006). The risk of reactivation of HHV-6 and HHV-7 in different conditions of immunosuppressions has been clearly showed, and clinical attention should be paid to immunocompromised patients with reactivated and persistently active HHV-6, HHV-7 infections at later ages (Cassula *et al.*, 2001). HHV-6 and HHV-7 are frequently present in patients with various lymphoproliferative disorders including multiple myeloma, Hodgkin's disease, T-cell lymphoma and myeloproliferative syndromes. Additionally, HHV-6 has been linked to precancerous lesions of the uterine cervix (Tran-Thanh *et al.*, 2002). Immuno-modulating processes between host and virus during HHV-6 and HHV-7 infection in solid tumour patients were not widely investigated.

The interactions between beta-herpes viruses and the immune system have been extensively characterised using *in vitro* and *ex vivo* models while *in vivo* studies are still limited, as concluded by Lusso (2006).

Our aim was to clarify the influence of beta-herpes viruses on cellular immune response in gastrointestinal (GI) cancer patients before any antitumour treatment.

MATERIALS AND METHODS

We examined 95 gastrointestinal (GI) cancer patients before antitumour treatment. Patient age was from 38 to 75 years. Patients were divided into two groups according to lymphocyte count in peripheral blood: Ly > 1400 per 1 mm³ and

Ly < 1400 1 mm³ (group I and II, respectively). HHV-6 and HHV-7 were detected in both groups. Lymphocyte subpopulations were determined by a laser flow cytofluorimeter Becton Dickenson with corresponding monoclonal antibodies to CD3+, CD4+, CD8+, CD16+, CD19+, CD38+, CD25+, CD95+ lymphocytes. Nested polymerase chain reaction (nPCR) was used for the identification of viral sequences in DNA isolated from peripheral blood leukocytes (PBL) and plasma (markers of latent/persistent and active infection, respectively). Total DNA was isolated from 0.5 ml of fresh whole blood by phenol-chloroform extraction, QIAamp DNA Blood Kit (Qiagen) was used for DNA purification from 200 µl of cell free blood plasma. The plasma samples were treated with Deoxyribonuclease I before DNA purification. To assure the quality of the PBLs DNA as well as exclude contamination of plasma DNA by cellular DNA, a globin PCR was performed. PCR amplification for the viruses was carried out in the presence of 1 µg of PBL DNA and 10 µl of plasma DNA (corresponding to 100 µl of plasma). The detection of HHV-6, HHV-7 and CMV DNA was performed according to Secchiero *et al.* (1995) Berneman *et al.* (1992), and Studahl *et al.* (1995), respectively. Positive (virus genomic DNA) and negative (DNA without virus-specific sequences) and water controls were included in each experiment.

The investigation was carried out with approval of Ethics Committee of Rīga Stradiņš University and all patients gave their informed consent prior to the examination.

As statistical method, Fisher's exact test, NPar, Kruskal Waller test for statistical evolution of the results were used.

RESULTS

Patient distribution with HHV-6, HHV-7 is shown in Table 1. There was no statistically significant difference between leukocyte, lymphocyte, monocyte, neutrophile and CD3, CD4, CD8, CD38, CD16, CD19, CD95, CD25 cell absolute counts and CD4/CD8 ratio between negative, latent and active HHV6 and HHV7 infection groups in GI cancer patients (Table 2). However, we observed a tendency that the number of CD3+, CD4+, CD8+, CD38+ and CD95+ cells increased in peripheral blood in GI cancer patients with active beta-herpes virus infection. It was surprising that the total count of CD16+ cells was not influenced by virus infection in our patients. Average count of the determined parameters in patients with Ly > 1,400 (group I) and pa-

Table 1
HHV-6 AND HHV-7 IN GASTROINTESTINAL CANCER PATIENTS

Infection stage	HHV-6	HHV-7	HHV-6/HHV-7
	n of patients (%)	n of patients (%)	n of patients (%)
Negative	83 (87.4)	33 (34.7)	32 (33.7)
Latent	11 (11.6)	39 (41.1)	39 (41.1)
Active	1 (1.1)	23 (24.2)	24 (25.3)

HHV, human herpes virus

Table 2

ABSOLUTE COUNT (MEAN \pm SD) OF LYMPHOCYTE SUB-POPULATIONS DEPENDING ON HHV6 AND HHV7 INFECTION IN GASTROINTESTINAL CANCER PATIENTS

HHV6+ HHV7 infection	Ly $\times 10^3$ in mm $^{-3}$	Mo	CD3	CD4	CD8	CD19	CD16	CD38	CD95	CD25
Negative	1.66 \pm SD 0.76	0.54 0.21	1150 610	660 380	490 330	140 120	340 250	480 250	800 430	130 80
Latent	1.85 \pm SD 0.53	0.54 0.17	1350 380	730 250	590 200	140 80	350 260	530 270	950 280	170 170
Active	1.96 \pm SD 0.91	0.56 0.25	1450 730	780 360	640 550	200 170	340 230	530 220	1030 560	140 70

HHV, human herpes virus; Ly, lymphocyte; Mo, monocyte

Table 3

COUNT (MEAN \pm SD) OF IMMUNOCOMPETENT CELLS IN GI CANCER PATIENTS GROUP I (Ly > 1,400)

HHV6+ HHV7 infection	Ly $\times 10^3$ in mm $^{-3}$	Mo	CD3	CD4	CD8	CD19	CD16	CD38	CD95	CD25
Negative	≥ 1.4 \pm SD 1.68	574 660	1489 407	857 408	616 83	164 287	430 252	618 436	1065 93	150
Latent	≥ 1.4 \pm SD 1.70	576 335	1461 234	795 188	634 80	156 272	388 272	592 272	1013 259	188 186
Active	≥ 1.4 \pm SD 2.78	622 635	1789 259	976 619	789 188	241 240	421 193	638 535	1267 82	152

HHV, human herpes virus; GI, gastrointestinal; Ly, lymphocyte; Mo, monocyte

Table 4

COUNT (MEAN \pm SD) OF IMMUNOCOMPETENT CELLS IN GI CANCER PATIENTS GROUP II (Ly < 1,400)

HHV6+ HHV7 infection	Ly $\times 10^3$ in mm $^{-3}$	Mo	CD3	CD4	CD8	CD19	CD16	CD38	CD95	CD25
Negative	<1.4 \pm SD 2.44	493 200	781 199	446 142	358 52	120 40	238 136	337 169	521 58	101
Latent	<1.4 \pm SD 1.02	413 166	890 76	479 147	404 52	118 31	159 54	285 145	644 29	76
Active	<1.4 \pm SD 1.42	460 264	758 164	400 189	356 71	107 35	197 58	312 165	543 38	103

HHV, human herpes virus; GI, gastrointestinal; Ly, lymphocyte; Mo, monocyte

tients with Ly < 1,400 (group II) are shown in tables 3 and 4, respectively.

Cellular immune parameters were determined in both immunocompetent (Ly > 1,400) and immunocompromised (Ly < 1,400) GI cancer patients groups, independently of beta-herpes virus infection. Number of T cells and NK cells was higher in patients without lymphopenia, as expected, while the total count of B cells and CD25+ cells was similar in both groups (Table 5).

Table 5

ABSOLUTE COUNT (MEAN \pm SD) OF IMMUNOCOMPETENT CELLS IN GI CANCER PATIENTS IN GROUPS I AND II

Parameters	Group I ly > 1400	Group II ly < 1400	P
L	7140 \pm 2044 587 \pm 199	5360 \pm 1962 460 \pm 190	< 0.001 *
Mo	1545 \pm 523	802 \pm 209	< 0.05 *
CD3	854 \pm 299	443 \pm 169	< 0.001 *
CD4	665 \pm 386	369 \pm 151	< 0.001 *
CD8	609 \pm 248	318 \pm 105	< 0.001 *
CD38	407 \pm 266	209 \pm 129	< 0.001 *
CD 16	175 \pm 19	117 \pm 115	0.31
CD19	1086 \pm 394	556 \pm 165	< 0.001 *
CD95	170 \pm 146	95 \pm 49	0.09

GI, gastrointestinal; * P < 0.05; Ly, lymphocyte; Mo, monocyte

Comparative analysis of Ly subsets between groups I and II was performed. Each group was subdivided into non infected, latent and active HHV-6 and HHV-7 infected patient subgroups. Patients with a normal Ly count (group I) and active viral infection tended to have increased counts of CD3+, CD4+, CD8+, CD19+ and CD95+ cells (Table 3). The number of CD4+ T as well as CD19+ B cells in the patients with a lower Ly count (group II) and active HHV-6, HHV-7 infection tended to be lower (Table 4).

GI cancer patients with latent HHV-6, HHV-7 infection had the highest number of CD25+ T cells and the lowest number of CD4+ T cells among patients in group I; however, a significant difference in absolute counts of immunocompetent cells was not observed (Table 4). In contrast with group I, immunocompromised patients (group II) had the highest number of CD4+ T cells and the lowest number of CD25+ T cells between subgroups. There was no significant difference between negative, latent and active HHV-6, HHV-7 infection subgroups in both immunocompetent and immunocompromised GI cancer patients groups.

Different immune response was observed among patients in the same subgroup. Average count of Ly subsets in each of the patients did not reflect individual immune response and intensity of cellular immune reactions.

DISCUSSION

Despite immune response HHV-6, HHV-7 viruses are never completely eradicated from the host. A key feature of both viruses life-style in the human host is their ability to infect

and survive, in a latent/persistent form, in the cells of the immune system. Modulation of functional properties of host immune factors is an important mechanism of evading the immune response or creating an environment in which the virus can survive (Clark, 2000; Dockrell, 2003). Our results show that patients with latent and active infection in comparison to negative had tendency to have higher number of CD3+, CD4+, CD8+, CD95+ cells. It may be explained by additional activation of immune cells due to viral infection. In beta-herpes viruses-infected patients persistent immune activation driven by constant supply of HHV-6 and HHV-7 antigens in chronic or latent infection was observed (Wang *et al.*, 2006). In comparison, our data showed that patients with latent infection had in average higher CD3, CD4, CD8, CD38, CD95, CD25 absolute count than patients with negative HHV-6 and HHV-7 infection.

Reduced Th1 immune response was observed in HHV-6 infected individuals (Morel *et al.*, 1998). We did not observe Th1 immune answer depression in our active, latent infection group. By definition, however, even tumour designated by pathologists to be early stage may be late stage when considered by the immune system. Certainly, even early stage tumours have evaded immune control, suggesting that they have acquired many immunosuppressive characteristics (Lu and Fink, 2008). Depression of cellular immunity could be observed at various stages of cancer and the absolute count of lymphocytes in peripheral blood could be the first and simple indicator of the immune system insufficiency. Therefore, we also look for our patients groups with different lymphocyte absolute counts. We found out, that GI patients with Ly ($< 1.4 \times 10^3$) and latent and active infection had suppressed inductor phase of cellular immune response and tendency to weaken humoral immune reactions.

Many studies have described beta-herpes virus ability to suppress T cell proliferation, to induce apoptosis of CD4+ T Ly, to alter the expression of some immune activation markers and to perturb the cytokine network (Peng *et al.*, 2000; Dockrell, 2003; De Bolle *et al.*, 2005). It has been observed that CD4+ T cells from HHV-6-infected individuals exert suppressive activity on the proliferation of native T cells (Wang *et al.*, 2006). The authors hypothesised that the suppressive capacity of these CD4+ T cells could be attributed to a high population of CD4+25+ T regulatory cells, which could be actively suppressing the immune response. Our data show that patients with latent infection had elevated CD 25+ cell absolute count, in comparison with negative and active infected patients. It is difficult to speculate on the role of CD 25+ in our case, as these changes are not so remarkable.

Saff *et al.* (2004) suggested that Fas (CD95+) or Fas-ligand (CD95-L+) deficient tumour-specific Th1 cells survive better in tumour-bearing mice. Moreover, these tumour-specific Th1 cells were more effective than wild-type Th1 cells at eliminating tumours. This implies that Fas-mediated activation-induced cell death could be a limiting factor in effective T-cell-mediated immunosurveillance and immune response. Our HHV-infected patients had a tendency to in-

crease Fas cell absolute count. We could suggest that such activation may lead to cell immunocompetent cell apoptosis and immune response functional inability. According to some reports, NK cells could be involved in host-virus interaction by different manner: NK could be infected by beta-herpes viruses and probably change their functional activity as well as T cells (Kruger, 1990; Clark, 2002; Migake *et al.*, 2006), and beta-herpes viruses could increase NK cell activity via the cytokine network (Atedroe *et al.*, 1997). Our patients did not show difference in CD16 absolute count. Lymphopenic patients with latent and active HHV-6, HHV-7 infection had decreased mean CD16+ absolute count in comparison with patients who were free from infection. We speculate that CD 16+ cells were deleted (or they were infected).

There were some attempts to find relationships between beta-herpes virus infections and carcinogenesis based on observations that HHV-6 can directly infect CD4+ cells and induce apoptosis in immunocompetent cells, and that the virus can also infect thymic epithelial cells, hematopoietic stem cells and NK cells which are very important for immune maturation and protection against cancer and viral infections. Thus, HHV-6 infection may contribute to cancer circuitously through immune suppression (Kruger *et al.*, 1990). Later studies were focussed on virus-induced immunosuppression or virus influence on the immune system of immunosuppressed patients. Gastrointestinal malignancies are associated with a compromised immune system and viruses may be able to utilise cellular mechanisms responsible for immune response inhibition. Our findings show that patients who are compromised (lymphopenic) and had HHV-6, HHV-7 infection had greater immune response deviations than patients who are not immunocompromised. Virus-mediated immune response inhibition seems to be similar with cancer mediated. The study combining both virus- and cancer-mediated immune suppressive mechanisms will help us to understand complicated host-tumour interactions *in vivo*.

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ŠŪNU IMUNITĀTE AR HHV-6 UN HHV-7 INFICĒTIEM ZARNU TRAKTA VĒŽA PACIENTIEM

Cilvēka herpes vīrusus konstatē cilvēkiem ar kompromitētu imūno atbildi. Herpes vīrusi spēj inficēt dažādas šūnas, ietekmējot gan šūnu, gan humorālo imunatbildi. HHV-6 un HHV-7 vīrusi spēj inficēt CD4 + T limfocītus, kā arī inficēt monocītus, makrofāgus, naturālos killerus, epiteliju, endotēliju, nervu šūnas un fibroblastus. Patologu noteiktā audzēja stadija ne vienmēr saskan ar imūnas sistēmas atbildes spēju, un jau agrīnās stadijās audzējs spēj pats radīt imūnsupresīvu vidi. Darba mērķis bija noskaidrot β herpes vīrusu ietekmi uz šūnu imūno atbildi. 95% zarnu trakta vēža pacientiem noteicām CD3, CD4, CD8, CD19, CD38, CD95, CD25 absolūto šūnu līmeni, izmantojot lāzera plūsmas citofluorometrijas metodi. HHV-6, HHV-7 vīrusu klātbūtni noteicām ar nPCR metodi. Pacientiem ar negatīvu, latentu, aktīvu HHV-6, HHV-7 infekciju nekonstatējām statistiski ticamu diferenci noteikto imūnkompetento šūnu līmeni. Pacientiem ar kompromitētu imūno atbildi konstatējām zemāku CD4, CD19 absolūto skaitu. Audzēja mediētā imūnā atbilde ir līdzvērtīga imūnatbildei pacientiem ar HHV-6, HHV-7 aktīvu infekciju un limpopēniju. Viena tipa (latentā, aktīva pasīva) HHV-6, HHV-7 infekcijas pacientiem grupas robežas varam konstatēt atšķirīgu imūnabildi katram individuādam, taču tas neietekmē grupas vidējos rādītājus. Tāpēc uzskatām, ka ir nepieciešams izvērtēt imūnabildi katram pacientam individuāli.