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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Virus-induced changes in peroxisomal markers among HIV-infected patients

Evgeny V. Butorov

Municipal Center for HIV/AIDS prophylaxis, *Surgut, Russian Federation*
✉ butorov888@gmail.com

Abstract. *Relevance.* It is been currently known that viruses rewire the metabolic machinery host's cell to promote successful viral replication via reprogramming host energy flows, resource, metabolic tools and further, the reorganization of cellular structures. Recent studies indicate that the human immunodeficiency virus significantly reduces the number of peroxisomes in infected cells. However, there is still no clear understanding of the reasons for this apparent HIV intervention. The aim of the study was to confirm the hypothesis about the causes of the decrease in the number of peroxisomes in HIV infection. In this study, changes in several hematological markers of peroxisomal metabolism were assessed in connection with data on the unique role of these organelles in the catabolism of the amino acid L-lysine, the level of which correlates with the level of viral RNA in the blood plasma of HIV-infected individuals. *Materials and Methods.* A study was conducted on the levels of total cholesterol, catalase, L-lysine, and its derivative L-carnitine among HIV-infected individuals (controllers and patients with rapidly progressive disease) in comparison with similar indicators in cohorts of HIV-infected patients and healthy individuals. *Results and Discussion.* The study confirms the presence of significant differences in plasma levels of markers associated with peroxisomal metabolism, such as catalase, cholesterol, and the amino acid L-lysine, in the compared groups of HIV controllers and patients with rapidly progressing disease. The most negative changes in peroxisomal markers were detected among patients with accelerated HIV disease progression and, to a lesser extent, in individuals from the overall cohort. *Conclusion.* The results of this study indicate that HIV interference with host peroxisome biogenesis is accompanied by a concomitant dysregulation of peroxisomal enzyme systems and L-lysine-related substrates. Virus-induced reprogramming of the catabolism of this essential amino acid indirectly confirms the hypothesis of a key role of L-lysine in the HIV life cycle and is a factor in the successful implementation of the reproductive strategy of the human immunodeficiency virus.

Keywords: HIV, peroxisomes, L-lysine amino acid, cholesterol, catalase, HIV controllers, HIV rapid progressors

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Introduction

Viruses do not possess their own metabolic tools. Therefore, they use and alter the metabolism of infected cells to ensure an optimal environment for their life cycle. The main goal of any virus is effective replication in a suitable host cell type and production of progeny for new infections. Reproductive strategies involve reprogramming cellular metabolic pathways to provide an increasing number of pools consisting of free nucleotides and amino acids. This is necessary for energy-intensive processes of viral genome synthesis and virions assembly[1–6].

The available data indicate common metabolic changes induced by most viruses studied, such as changes in central carbon utilization pathways, induction of aerobic glycolysis, also known as the Warburg effect, upregulation of fatty acid synthesis and glutaminolysis, manipulation of host protein metabolism, and related aminogram abnormalities [7–15]. Simultaneously, each virus species implements its own highly specific alterations in cellular metabolism that mirror the needs of the respective pathogen for certain molecular compounds.

It is also widely known that viral intervention and related metabolic changes are accompanied by the induction and development of oxidative stress and inflammation through mitochondrial and peroxisomal dysfunctions in cells. There is no doubt that the profound functional alterations in these important organelles of cellular metabolism are associated with their involvement in the antiviral signaling system and in the further implementation of the antiviral response by the host organism, which allows infected cells to survive and eliminate an infectious process [16–20].

On the other hand, reprogramming peroxisomes' functional activity and their significant quantitative variability may be an important part of viral strategy. It is also a supporting factor for the effective reproduction of viruses that cause long-lasting chronic infections. In particular, human cytomegalovirus (HCMV), herpes simplex virus type 1 (HSV-1), and Kaposi's sarcoma-associated herpesvirus induce biogenesis and morphological changes in peroxisomes and support their replication [3, 18, 21, 22]. In contrast, hepatitis C virus (HCV) [23]and some flaviviruses, such as West Nile, Dengue, and Zika, are known for their active inhibition of peroxisomal antiviral functions. They significantly decrease peroxisome number by sequestering and degrading a critical biogenesis factor [23–25].

It has recently become apparent that human immunodeficiency virus (HIV) has also been associated with the inhibition of peroxisome biogenesis factors. On average, HIV-infected cells contained 30–65% less peroxisomes compared to uninfected ones [26–28]. However, the reasons for multidirectional changes in the number of these organelles remain unclear. According to our assumption, the reasons are primarily associated with cellular metabolic reprogramming: to meet the energy and building needs of viruses, and not only to evade the host's antiviral response. Accordingly, the aim of our study was to answer the question: Why does HIV need to reduce the number of peroxisomes? To achieve this goal, we tried to assess the alterations in some hematological markers of peroxisome metabolism among HIV-positive patients in relation to the intensity of the infectious process, taking into account the data of our earlier studies [29, 30].

Previously, it was shown that there is an inverse correlation between HIV-1 ribonucleic acid (RNA) and L-lysine amino acid levels. Excess intake of this essential substrate causes an increased viral load, and vice versa. We assumed that viral load-dependent plasma fluctuations in the levels of L-lysine in HIV-infected persons are associated with viral intervention in peroxisomal activity, because the initiation of L-lysine catabolism occurs only in these organelles.

Materials and methods

We conducted a case-control cohort study among HIV-infected patients followed up at the Surgut Municipal Center for HIV/AIDS prophylaxis, Russian Federation. Samples were obtained from forty-six individuals, classified into two groups: a group of two elite controllers and 18 viremic controllers, hereafter referred to as HIV controllers (*n* = 20), and a group of patients with fulminant disease progression as HIV rapid progressors (*n* = 26).

According to the accepted classification [31], patients with undetectable charge or less than 50 copies/ml and CD4 cells counted as more than 800 cells/μL for more than 20 years of follow-up in the absence of antiretroviral therapy (ART) were considered elite controllers. The subgroup of viremic controllers included HIV-infected persons with a mean viral load less than 50 copies/ml, rare blips up to 2000 copies/ml, and CD4 cell counts > 500 cells/μL for more than 18 years of follow-up, also without ART. The key criterion for identifying patients with rapid progression of the disease was the period from the onset of verified HIV infection to death from AIDS, the average duration of which was, unfortunately, only 2.5 years. Therefore, with the mean number of viral particles of more than 500.000 in ml of plasma and CD4 cell counts less than 350 cells/μL for the entire observation period.

Viral load and hematological, immunological, and peroxisomal markers were measured at the start of the study and every subsequent 3 months among HIV controllers (166 samples) and HIV rapid progressors (139 samples). The patients' baseline characteristics and targeted hematological parameters were compared with those of HIV-infected individual and healthy donors as controls. The HIV-positive cohort included 250 individuals with analogical age, sex, and an average verified disease duration of 7.4 years. Patients on ART were excluded from the comparison groups and controls, with the exception of HIV rapid progressors, about 50% of whom received therapy in the last months of their lives in the AIDS stage. Reference values for the analyzed parameters were established in an HIV-negative cohort of 85 regional donors.

The ethics committee of the Surgut Municipal Center for HIV/AIDS prophylaxis approved of the study, and blood samples were obtained after informed consent from all participants. All methods were performed in accordance with the relevant guidelines and regulations of the ethics committee of the Surgut Municipal Center for HIV/AIDS prophylaxis. Detailed characteristics of the groups and controls are presented in Table 1.

Overnight fasting venous blood samples for measurement of hematological and immunological parameters, HIV-1 RNA levels and amino-acid profiles were collected in 5 ml tubes containing 1.6 mg/ml K^2 EDTA (BD Vacutainer®, USA). For targeted l-lysine analysis, venous blood was deproteinized with 3% sulfosalicylic acid, carefully mixed, and immediately centrifuged at 3500 rpm; 10 min to remove plasma proteins. Aliquots (200 µL) were pipetted into Eppendorf tubes, stored, –40 °C and analyzed within the following fortnight. Each metabolite was detected spectrophotometrically after a post-column reaction with the ninhydrin reagent using an automatic amino acid analyzer (L-8800, Hitachi, Japan). Blood samples for measurement of HIV-1 RNA levels were centrifuged (3500 rpm; 10 min), and aliquots plasma of 1.0 ml were pipetted into Eppendorf tubes and stored at –40 °C til ready for use.

Quantification of HIV-1 RNA was performed by quantitative competitive reverse-transcriptase polymerase chain reaction (RT-PCR) using the commercially available Amplisens® HIV-monitor-FRT kit (Amplisens®, Russian Federation) with a sensitivity limit of 50 HIV-1 RNA copies/ml and a real-time PCR cycler (Rotor-Gene Q, QIAGEN, Germany). A laboratory survey of immune function was conducted using a flow cytometer according to the method of defining CD3, CD4, and CD8 lymphocyte counts (Coulter Epics XL, Beckman Coulter, USA).

Plasma total L-carnitine levels were measured using an enzymatic UV test kit (Roche Diagnostics GmbH, Germany). Serum catalase activity was determined spectrophotometrically at 240 nm using the method described by Abei H. [32].

The Student’s t-test with a 95% confidence interval was applied to compare the hematological, immunological, and virological parameters and peroxisomal markers among HIV controllers, HIV rapid progressors, and controls. The correlation between HIV-1 RNA and CD4 and cholesterol levels was estimated using Pearson’s correlation coefficient. Data are reported as mean ± standard deviation (SD), and *P* values 0.05 were considered to indicate statistical significance. Statistical analyses were performed using the statistical software package.

Results and discussion

Baseline clinical characteristics of comparison groups

We ascertained patients’ general attributes among HIV controllers and HIV rapid progressors: age (40.9 ± 2.3 and 40.8 ± 5.4 years, respectively), sex (only males), co-infection HCV (100% and 92%) and drug use (95% and 84%). However, HIV-infected patients from compared groups have obvious differences in such criteria as, duration of HIV infection (18.7 ± 3.1 and 2.5 ± 1.4 years), the presence of progressive stages [B, C] of the disease (15 and 84%, respectively) and purpose of HAART (only in 50% of HIV rapid progressors). In the control group 1 (HIV-positive cohort) were included only men (mean age 42.4 ± 5.8 years), average duration of the disease was 7.4 ± 3.2 years, without HAART, 94% of patients had experience of drug use, HCV co-infection was detected in 90% of cases, at stages A (90%) and B (10) of HIV infection (according CDC guidelines, 1993). Control group 2 (HIV-negative cohort) consisted of healthy male donors with an average age of 38.3 ± 6.2 years.

Baseline clinical characteristics of comparison groups and controls are summarized in Table 1.

Immunological and virological parameters of HIV-infected patients in comparison groups

The obtained data showed obvious differences in basic immunological and virological disease markers between HIV controllers and HIV progressors (Table 2). In the combined group of controllers and slow progressors, the average viral load was 2.707 ± 197 copies/ml over the next 18 years. At the same time, the average number of HIV-1 RNA copies in rapid progressors was 607.600 ± 82.440 copies/ml over 2.5 years of observation from the moment of infection to death due to HIV (*P*<0.001). The mean level of viral load in samples of the HIV-positive cohort was 136.000 ± 9.614 copies/ml (*P*<0.001 for all comparison groups).

Table 1

Clinical data of HIV-infected patients in comparison groups and healthy control subjects

Clinical data	HIV controllers and slow progressors (*n*=20)	HIV rapid progressors (*n*=26)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n*=250)	HIV-negative cohort (donors) (*n*=85)
Age (years)	40.9 ± 2.3	40.8 ± 5.4	42.4 ± 5.8	38.3 ± 6.2
Sex (male/female)	20/0	26/0	250/0	85/0
Duration of the disease (years)	18.7 ± 3.1	2.5 ± 1.4	7.4 ± 3.2	–
CDC stages of HIV infection A (1, 2, 3)/B (1, 2, 3)/C (1, 2, 3)	17/ 3/0	4/2/20	226/24/0	–
Prescribing highly active antiretroviral therapy (without/under HAART)	20/0	12/14	250/0	–
Drug use (yes/no)	19/1	22/4	235/15	0/85
HBV/HCV	0/20	2/24	26/224	0/0
BMI (kg/m^2)	24.65 ± 3.72$^{1, 2, 5}$	22.23 ± 2.46$^{3, 4}$	23.31 ± 2.34	23.96 ± 2.67

Note:

[1] HIV controllers *versus* controls 1, *P*<0.05 or less;
[2] HIV controllers *versus* controls 2, *P*<0.05 or less;
[3] HIV progressors *versus* controls 1, *P*<0.05 or less;
[4] HIV progressors *versus* controls 2, *P*<0.05 or less;
[5] HIV controllers *versus* HIV progressors, *P*<0.05 or less.

We found significant differences in absolute CD4 cell counts among patients in the compared groups. The plasma average value of this immunological parameter in HIV controllers (931 ± 307 cells/μL) was considerably higher than that in rapid progressors (329 ± 187 cells/μL, $P < 0.001$), HIV entire cohort (481 ± 199 cells/μL, $P < 0.001$), and lower than our reference values (1231 ± 389 cells/μL, $P < 0.01$). The present study shows that the mean absolute CD4 cell counts markedly decreased in HIV rapid progressors (329 ± 187 cells/μL) compared with controls 1 (481 ± 199 cells/μL, $P < 0.001$) and 2 (1231 ± 389 cells/μL, $P < 0.001$).

The plasma average levels of CD8 lymphocytes were higher in the group of HIV controllers (1164 ± 450 cells/μL) than in rapid progressors (1048 ± 434 cells/μL, $P < 0.05$) and healthy controls (813 ± 310 cells/μL, $P < 0.05$). Hence, we detected that the mean values of CD8 lymphocytes in HIV rapid progressors were evidently lower than those in donors ($P < 0.05$). At the same time, no significant differences were found between the average absolute CD8 cell counts in controllers and rapid progressors compared to HIV-positive cohort ($P > 0.05$).

The lowest CD4/CD8 ratio was detected in HIV-infected males from the group of rapid progressors (0.31 ± 0.19) compared with the same parameters in HIV controllers (0.90 ± 0.39, $P < 0.001$), the control group 1 (0.50 ± 0.24, $P < 0.01$), and healthy controls (1.58 ± 0.51, $P<0.001$). We retrospectively observed

Table 2

Virological and immunological parameters of HIV-infected patients in comparison groups and healthy control subjects

Immunological parameters	HIV controllers and slow progressors(*n* = 20) (number of samples = 166)	HIV rapid progressors(*n* = 26) (number of samples = 139)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n* = 250) (number of samples = 250)	HIV-negative cohort(donors) (*n* = 85) (number of samples = 85)
Viral charge (copies/ml)	2.707 ± 197[1, 5]	607.600 ± 82.440[3]	136.000 ± 9.614	–
CD4 (cells/μl)	931 ± 307[1, 2, 5]	329 ± 187[3, 4]	481 ± 199	1231 ± 389
CD8 (cells/μl)	1164 ± 450[2, 5]	1048 ± 434[4]	1075 ± 463	813 ± 310
CD4/CD8 ratio	0.90 ± 0.39[1, 2, 5]	0.31 ± 0.19[3, 4]	0.50 ± 0.24	1.58 ± 0.51

Note:

[1] HIV controllers *versus* controls 1, $P<0.05$ or less;

[2] HIV controllers *versus* controls 2, $P<0.05$ or less;

[3] HIV progressors *versus* controls 1, $P<0.05$ or less;

[4] HIV progressors *versus* controls 2, $P<0.05$ or less;

[5] HIV controllers *versus* HIV progressors, $P<0.05$ or less.

that the mean CD4/CD8 ratio was mildly decreased among HIV controllers and slow progressors, with the exception of two elite controllers with constant immunological parameters.

Hematological markers related to the functional activity of peroxisomes in compared groups of HIV-infected patients and controls

The concentrations of total cholesterol, catalase, L-lysine (Lys), and its derivative (L-carnitine), as hematological peroxisome-related markers, were evaluated between HIV controllers and HIV rapid progressors in comparison with the entire patient cohort and healthy donors.

The present survey showed that the average levels of total cholesterol (Chl) in rapid progressors were significantly lower than those in HIV controllers ($P < 0.01$), control 1 ($P < 0.01$), and control 2 ($P < 0.01$). At the same time, the mean Chl values in the controllers were higher than those in the control group 1 ($P < 0.05$) and lower than those in the control group 2 ($P < 0.05$).

We found that the mean L-lysine amino acid levels were significantly decreased in both HIV controllers ($P < 0.001$ for all controls) and rapid progressors ($P < 0.001$ for all controls) compared to the controls. The lowest concentrations of Lys were detected among patients with accelerated progression of HIV infection (118.5 ± 111.7 μmol/L). The same tendencies were observed for the average plasma levels of L-lysine derivative (total L-carnitine (TC)) in HIV rapid progressors.

Our data revealed that the average concentrations of TC were evidently decreased compared to those in controls 1 and 2 ($P < 0.001$ for all parameters). At the same time, the mean L-carnitine level was markedly higher in the controllers than in the entire HIV cohort ($P < 0.05$) and lower than that in healthy donors ($P < 0.05$).

The average level of serum catalase (CAT) was significantly lower in the HIV rapid progressors' study group (1.72 ± 1.15 specific activity in U/mg of protein) than in HIV controllers ($P < 0.001$) and controls 1 and 2 ($P < 0.001$ and $P < 0.001$, respectively). At the same time, the mean level of CAT in the HIV controllers group (2.97 ± 1.32) was evidently higher than that in the control group 1 ($P < 0.05$) and did not differ from the level of our reference values ($P > 0.05$).

In the present study, we observed a weak negative correlation between serum cholesterol and HIV-1 RNA levels and, conversely, a positive correlation between Chl and absolute CD4 cell counts in the HIV-positive cohort ($r = -0.13$, $P < 0.036$ and $r = 0.11$, $P < 0.047$, respectively). A comparison of peroxisomal markers in HIV-infected patients and healthy control subjects is shown in Table 3.

Table 3

Hematological markers related with peroxisomes' functional activity

Peroxisomal markers	HIV controllers and slow progressors (*n* = 20) (166 samples)	HIV rapid progressors (*n* = 26) (139 samples)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n* = 250) (number of samples = 250)	HIV-negative cohort(donors) (*n* = 85) (number of samples = 85)
Total cholesterol (Chl) (mmol/l)	$4.26 \pm 0.79^{1, 2, 5}$	$3.44 \pm 0.49^{3, 4}$	3.91 ± 0.96	4.90 ± 0.48
L-lysine amino acid (μmol/L) (Lys)	$146.0 \pm 117.2^{1, 2, 5}$	$118.5 \pm 111.7^{3, 4}$	236.1 ± 148.7	265.6 ± 143.2
Total L-carnitine (TC) (μmol/l)	39.1 ± 5.6	19.5 ± 5.4	32.4 ± 6.7	44.8 ± 6.3
Catalase (CAT) (IU/L)U/mg of protein	$2.97 \pm 1.32^{1, 5}$	$1.72 \pm 1.15^{3, 4}$	2.57±1.94	3.21±1.46

Note:

[1] HIV controllers ***versus*** controls 1, $P<0.05$ or less;
[2] HIV controllers ***versus*** controls 2, $P<0.05$ or less;
[3] HIV progressors ***versus*** controls 1, $P<0.05$ or less;
[4] HIV progressors ***versus*** controls 2, $P<0.05$ or less;
[5] HIV controllers ***versus*** HIV progressors, $P<0.05$ or less.

Despite substantial progress in HIV science and antiretroviral therapy (ART) in the past years, HIV infection is the leading cause of morbidity and mortality worldwide, and the goal of eradicating the disease remains elusive. Many links between the virus replication cycle, the mechanisms of chronic immune inflammation, and the formation and reactivation of latent viral reservoirs that sustain HIV persistence remain relatively obscure. Arguably, the key to these tasks is a thorough understanding of the metabolic interactions between the human immunodeficiency virus and host target cells with respect to HIV infection pathogenesis.

There is no doubt that an increase in HIV comorbidities, including changes in brain tissue [33–35], dyslipidemia, insulin resistance, cardiovascular, liver, kidney, bone, and nonalcoholic fatty liver diseases in both naïve and HIV-infected persons under ART [36–38]is the result of final metabolic alterations at the organism level due to the unknown biochemical details of virus-host relationships at the molecular level.

Similar to all viruses, HIV is an obligate intracellular parasite that relies entirely on the energy, nucleotides, amino acids, or lipids of the host to copy its own genetic material, synthesize viral proteins, and assemble new virions. Pathogenic changes in infected cells ultimately reflect the implementation of a reproduction virus strategy via reprogramming host resources, metabolic tools, and reorganization of cellular structures. Recent studies have shown that some viruses actively alter peroxisomal biogenesis.

Peroxisomes are essential subcellular and highly dynamic metabolic hubs that contain over 50 different enzymes and perform variety cellular functions [3, 39–41]. It is also known that in humans, catabolism of the essential amino acid L-lysine is initiated only in peroxisomes containing unique L-lysine oxidase. While the precise role of peroxisomes in the life cycle of most viruses is unclear, recent data suggest their critical importance in the host antiviral defense system.

At the same time, it is unlikely that these multifunctional cellular hubs are involved only in the host innate immune response and antiviral signaling system. The plastic nature of peroxisomes allows them to play dual roles in the progression of human viral infections. Peroxisomes rewire their metabolism, structure, and biogenesis.

Both the host and pathogen may leverage the functions of these multifunctional organelles to achieve antiviral defense or support cellular processes for virus replication and spread [42–43]. In connection with this, the roles of peroxisomes in HIV biology are diverse.

Virus-induced dysfunction and loss of these organelles are fundamental aspects of the viral reproductive strategy and HIV infection pathogenesis.

To answer the goal of our research, we tried to connect the available data on the unique importance of peroxisomes in the metabolism of L-lysine amino acids and the results of previous findings that showed an inverse correlation between plasma Lys and HIV-1 RNA levels. We assumed that a decrease in the number of peroxisomes and their functional activity are associated with targeted viral intervention in L-lysine amino acid catabolism.

The priority of the present study was to analyze certain peroxisomal markers among HIV-infected individuals in relation to the intensity of the infectious process. To accomplish the assigned task, we formed two contrasting groups of patients according to the criteria for disease progression. We enrolled in the first group the so-called HIV controllers (*n*=20), with an average duration of HIV infection 18.7 years. The second group included patients (*n*=26) with fulminant disease progression within 2.5 years from the moment of infection to AIDS-related death.

The obtained data showed significant differences in immunological and virological parameters between the compared groups of HIV controllers and progressors. We also observed that the average levels of peroxisomal markers, such as total cholesterol (Chl) and catalase (CAT), were evidently decreased among patients with fulminant progression of HIV infection compared to those capable of controlling virus replication.

Cholesterol plays a key role in the pathogenesis of many infectious agents that modify their metabolism to meet their needs at different stages of the life cycle and weaken the host's immune response. Although the participation of peroxisomes in the pathogenesis of cholesterol remains unclear, the mevalonate pathway or pre-squalene segment of this multistep process is localized in these organelles [44–47]. In addition, recent findings indicate that the peroxisome proliferator-activated receptor (PPARs) system is involved in cholesterol metabolism and the maintenance of homeostasis in humans [48].

Available data indicate that HIV relies on cholesterol at many stages of its replication cycle including entry, assembly, and release. It is clear that membrane-associated Chl in target cells is critical for HIV infection and syncytium formation [49–52]. Inhibition of Chl synthesis by lovastatin was followed by a decrease in the number of HIV particles. This confirms the importance of intracellular cholesterol in viral assembly [55, 54]. Undoubtedly the active use of this substrate's resources by HIV leads to the development of hypocholesterolemia, which correlates with a high viral load in infected patients.

It is assumed that the depletion of cholesterol resources is associated with demyelination processes and the development of HIV-associated neurocognitive disorders, severity of the inflammatory response, metabolic dysregulation, organ dysfunction, and disease prognosis [55]. In regard to this, the worst Chl levels correspond to the terminal stages of HIV infection and to the group of patients with a rapid disease progression.

The next step of our study was to assess the plasma changes of a unique peroxisomal marker, L-lysine amino acid (Lys), the catabolism of which is triggered only in peroxisomes. The mean concentrations of this substrate were evaluated in groups of HIV controllers and rapid progressors versus HIV-positive and HIV-negative cohorts. We found that the average levels of Lys were significantly reduced in both patient groups that were able to control HIV replication and those with accelerated progression of the infection compared to the two controls. However, the mean concentration of this amino acid among HIV controllers was markedly higher than that among HIV rapid progressors.

The low plasma levels of Lys and its derivatives in HIV-infected patients [58] can be explained by consider the available data on the limiting function of host amino acids in the replicative cycle of viral systems. It is well known that deficiency of these host substrates leads to a fundamental changes in infected cells' metabolism, especially in the control of successful viral reproduction. Based on this reliable information, we hypothesized that the host's essential L-lysine amino acid plays a key role in the HIV life cycle.

In this regard, a decrease in Lys levels among HIV rapid progressors is the result of the endless huge production of viral particles, which requires sufficient resources for this amino acid. In fact, the human immunodeficiency virus interferes with the biogenesis of peroxisomes to reduce their number and enzymatic activity, in particular L-lysine oxidase [58, 59], and redirect the flow of L-lysine amino acids for their own needs.

Based on the obtained data, it is possible to answer the question about the reasons for the impact of HIV on peroxisome biogenesis with the following statement: a targeted reduction in the number of peroxisomes and their metabolic activity is associated with viral intervention in the catabolism of L-lysine amino acid for its intracellular accumulation and subsequent use in the virus life cycle.

In the context of this hypothesis, some topics and open questions concerning the biology of HIV and the pathogenesis of the disease acquire completeness or other interpretations.

In particular:

- The effects of reducing the viral load and preventing HIV-associated brain inflammation in infected persons after treatment with thiazolidinediones, in particular rosiglitazone, etc. [18, 60–68]. These antidiabetic drugs are known to enhance peroxisomal activity through peroxisome proliferator-activated receptors-γ (PPARs-γ), which are also involved in the control of systemic inflammation and is suppressed by the HIV-1 accessory protein R (Vpr) [69]. The relative recovery of the pool of these organelles' and their enzymatic activity contributes to the redirection of L-lysine to the needs of the infected organism and the limitation of its use by the virus, followed by a noticeable decrease in HIV-1 RNA blood levels.
- Negative changes in L-carnitine plasma concentrations in HIV-infected patients [18, 70–72]. Arguably, the reason for this imbalance also lies in the active consumption of L-lysine resources by the human immunodeficiency virus, which reduces the synthesis of LC, despite their partial intake from food. The role of this Lys derivative in the processes of cellular apoptosis and metabolism is well known, and its deficiency may be related to premature age-related changes in HIV-infected persons.
- The recurrence of varicella-zoster virus (VZV) is associated with high HIV-1 RNA and low L-lysine plasma levels [73–76]. Undoubtedly, the infectious processes trigger a large-scale reprogramming of cellular metabolic pathways that are accompanied by noticeable alterations, including the amino acid profile. The concentration of L-arginine (Arg) is important in the life cycle of VZV, and it is likely that a change in the Lys/Arg ratio may cause disease relapse. In this regard, data on the effectiveness of restricting dietary L-arginine and prescribing high doses of L-lysine amino acids in the treatment of recurrent herpes zoster are becoming more convincing.
- HIV tropism towards certain body tissues. The gray matter in the brain, Peyer's patches, and lymph are very attractive for the human immunodeficiency virus [18, 62–84, 77]. We assume that this phenomenon is associated with the access of immune target cells to Lys located in these lysine-rich tissues or their participation in the assimilation and transportation of this essential amino acid after its intake with food. For this reason, macrophages and long-lived infected cells form potential reservoirs of HIV, primarily in the brain and lymph nodes, where the necessary resources are available for virus replication [78–82].
- High levels of HIV-associated neurocognitive disorders (HAND) [18, 27, 83–90]. It was recently established that virus-induced loss of peroxisomes is associated with the development of HAND in HIV-infected patients. The proposed mechanism of these disorders includes the altered expression of miRNAs in infected cells, subsequent depletion of the pool of peroxisomes responsible for myelin formation, and functioning of the central nervous system. Therefore, it is not surprising that the most pronounced consequences of HIV intervention in the biogenesis of these cellular metabolic hubs are manifested in a large percentage of brain tissues sensitive to both virus-induced Lys deficiency and concomitant peroxisomal dysregulation of plasmalogen and cholesterol synthesis.
- Antiviral effects of L-lysine-α-oxidase (LysOx) in vitro and in vivo. It is well known that this enzyme is

highly selective for L-lysine amino acids, in addition to antitumor, antimetastatic, and antibacterial properties, and has unique antiviral activity, particularly against herpes simplex virus 1 and 2 (HSV-1 and HSV-2), tick-borne encephalitis virus (TBEV), and HIV [58, 91, 92]. An in vitro study showed that the production of viral particles and the level of Lys in HIV-infected cells are significantly reduced when LysOx is added to the medium [93, 94]. Similar results were obtained in an in vivo experiment. It is assumed that the cytotoxic and antiviral effects of this enzyme are associated with its attachment to the cellular surface, local accumulation of hydrogen peroxide, and development of apoptosis and necrosis of the affected cells. In our opinion, L-lysine play an important role in HIV biology, and the depletion of Lys is the main reason for the decrease in viral load, taking into account the fact that H_2O_2 activates the processes of HIV transcription.

- To date, unanswered questions remain regarding the role of uncharged tRNALys packed in the HIV capsid [95–97]. It is well known that the human immunodeficiency virus requires cellular tRNALys as a primer to initiate reverse transcription on entry into a target cell. Undoubtedly, the start of this process will be successful after the activation of this highly specific primer with free covalent L-lysine. In this regard, the presence of a sufficient concentration of this amino acid in the cytosol facilitates initiation of the HIV reproductive cycle. Moreover, several uncharged primers are packaged in a capsid to increase the chances of survival of virus progeny during the formation of new virions.

Overall, our results indicate that HIV intervention in the biogenesis of host' peroxisomes is accompanied by the concomitant dysregulation of peroxisomal enzyme systems and substrates. The most pronounced negative changes were found in catalase, cholesterol, and L-lysine amino acid levels in HIV rapid progressors and, to a lesser extent, among persons from the total HIV-positive cohort.

There is also no doubt that the so-called disease' controllers have certain mechanisms that prevent viral reprogramming of these organelles, which is confirmed by CD4 cell counts within reference values, undetectable viremia, and unchanged concentrations of the analyzed markers, with the exception of Lys. It is likely that the decrease in L-lysine levels among HIV controllers is a genetically determined process that makes it difficult to use this essential amino acid for the virus's needs. At the same time, among HIV rapid progressors, this mechanism seems to be lost, which allows the virus to redirect Lys flux for the production of viral particles.

In connection with this, there is evidence that excessive Lys consumption may increase the risk of high HIV replication and vice versa [29]. Limited dietary L-lysine intake is also a metabolic factor that determines the non-pathogenic course of simian immunodeficiency virus (SIV) infection and the absence of AIDS-like symptoms [98–105] in its natural hosts.

Conclusion

In summary, the results of this study confirmed significant differences in the plasma levels of certain hematological markers related to peroxisomes, such as catalase, cholesterol, L-lysine amino acid, and its derivatives [L-carnitine] in compared groups of HIV controllers, rapid progressors, and controls. The most negative changes in these peroxisomal substrates were observed in patients with accelerated disease progression. We tried to connect the results of the present study with the data on the unique role of peroxisomes in catabolism of L-lysine, the recent findings on a significant reduction in the pool of cellular peroxisomes due to HIV infection, and the evidence of an inverse correlation between the plasma concentrations of this amino acid and viral load. It is obvious that virus-induced metabolic reprogramming of peroxisomes occurs to create an excess of L-lysine in the cell cytosol for the successful implementation of the HIV reproductive strategy. Thus, our current findings support the hypothesis that L-lysine definitely plays a limiting role in the human immunodeficiency virus life cycle, and its access to the resources of this essential amino acid increases the risk of high levels of HIV-1 RNA, immunosuppression, and AIDS development. A better understanding of this fact may contribute to the development of novel approaches for the therapy and regulation of HIV infection through metabolic intervention.

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Вирусиндуцированные изменения пероксисомальных маркеров при ВИЧ-инфекции

Е.В. Буторов

Центр профилактики и борьбы со СПИД, *г. Сургут, Российская Федерация*
✉ butorov888@gmail.com

Аннотация. *Актуальность.* Общеизвестно, что для успешной реализации своего жизненного цикла вирусы перестраивают метаболический аппарат клетки хозяина посредством перепрограммирования потоков энергии, ресурсов и метаболических инструментов клетки с последующей реорганизацией клеточных структур. Результаты недавних исследований свидетельствуют, что вирус иммунодефицита человека значительно снижает количество пероксисом в инфицированных клетках. Однако до сих пор нет четкого понимания очевидного вмешательства ВИЧ в этот процесс. Цель нашего исследования — подтвердить предположение о причинах снижения количества пероксисом при ВИЧ-инфекции. В настоящем исследовании проведена оценка изменений некоторых гематологических маркеров метаболизма пероксисом в связи с данными об уникальной роли этих органелл в катаболизме аминокислоты L-лизина, уровень которого корреллирует с уровнем РНК вируса в плазме крови ВИЧ-инфицированных лиц. *Материалы и методы.* Проведено исследование уровней общего холестерина, каталазы, L-лизина и его производного L-карнитина среди ВИЧ-инфицированных (контролеры и пациенты с быстро прогрессирующим заболеванием) в сравнении с аналогичными показателями когорт ВИЧ-инфицированных пациентов и здоровых лиц. *Результаты и обсуждение.* Исследование подтверждает наличие существенных различий в плазменных уровнях маркеров, связанных с метаболизмом пероксисом, таких как каталаза, холестерин и аминокислота L-лизин в сравниваемых группах ВИЧ-контроллеров и пациентов с быстро прогрессирующим заболеванием. Наиболее негативные изменения пероксисомальных маркеров были выявлены среди пациентов с ускоренным прогрессированием ВИЧ-инфекции и, в меньшей степени, у лиц из общей когорты. *Выводы.* Результаты настоящего исследования свидетельствуют о том, что вмешательство ВИЧ в биогенез пероксисом хозяина сопровождается сопутствующим нарушением регуляции систем пероксисомальных ферментов и субстратов, связанных с L-лизином. Вирусиндуцированное перепрограммирование катаболизма данной эссенциальной аминокислоты косвенно подтверждает гипотезу о ключевой роли L-лизина в жизненном цикле ВИЧ и является фактором успешной реализации репродуктивной стратегии вируса иммунодефицита человека.

Ключевые слова: ВИЧ, пероксисомы, аминокислота L-лизин, холестерин, каталаза, ВИЧ-контроллеры, ВИЧ-прогрессоры

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Ответственный за переписку: Буторов Евгений Владимирович — врач-эпидемиолог КУ ХМАО-Югры «Центр по профилактике и борьбе со СПИД», филиал в г. Сургуте; 628412, а/я 500 г.Сургут, ХМАО-Югра, Российская Федерация, E-mail: butorov888@gmail.com
Буторов Е.В. SPIN 6162-9574, ORCID 0000-0003-2822-1297

Corresponding author: Evgeny Vlad. Butorov — epidemiologist of the The Municipal Center for HIV/AIDS prophylaxis; 628412, P.O. Box 500, Surgut, Russian Federation, E-mail: butorov888@gmail.com
Butorov E.V. ORCID 0000-0003-2822-1297