Title

Soluble CD14 is subtype-dependent in serum but not in cerebrospinal fluid in people with HIV

Authors

de Almeida, Sergio Monteiro

Tang, Bin

Vaida, Florin

et al.

Publication Date

2022-05-01

DOI

10.1016/j.jneuroim.2022.577845

Peer reviewed

ScienceDirect

Journal of Neuroimmunology

Volume 366, 15 May 2022, 577845

Soluble CD14 is subtype-dependent in serum but not in cerebrospinal fluid in people with HIV

Sergio Monteiro de Almeida MD, PhD [a], Bin Tang PhD [b], Florin Vaida PhD [d], Scott Letendre MD [c], Ronald J. Ellis MD, PhD [e, f], the HNRC Group [f]

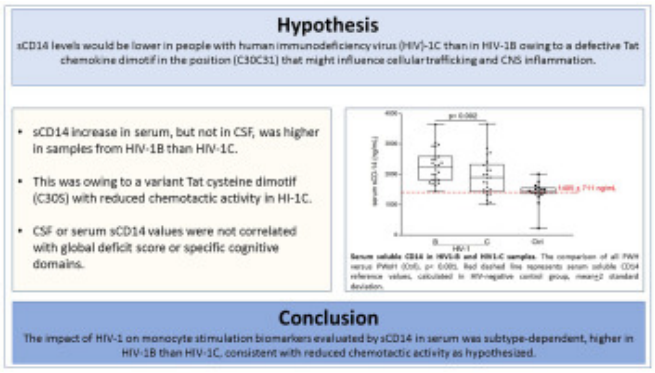
Show more

https://doi.org/10.1016/j.jneuroim.2022.577845

Abstract

Monocytes and macrophages activation are crucial in human immunodeficiency virus (HIV) central nervous system (CNS) infection and HIV associated neurocognitive disorders (HAND) pathogenesis. The soluble form of CD14 (sCD14) is a marker of monocyte activation. We hypothesized that sCD14 levels would be lower in people with HIV-1 subtype C (HIV-1C) than in HIV-1B owing to a variant Tat cysteine dimotif (C30S31) with reduced chemotactic activity. A total of 68 paired cerebrospinal fluid (CSF) and blood samples from people with HIV (PWH); 27 samples of the HIV-1B subtype and 40 of the non-B HIV-1 subtypes (including 26,HIV-1C), and 18 HIV-negative controls were included. sCD14 levels were quantified using a high-sensitivity enzyme-linked immunosorbent assay. sCD14 increase in serum, but not in CSF, was higher in samples from HIV-1B than HIV-1C ($p = 0.002$; Cohen's d, 0.7). CSF or serum sCD14 values were not correlated with global deficit score or specific cognitive domains. The impact of HIV-1 on monocyte stimulation biomarkers evaluated by sCD14 in serum was subtype-dependent, higher in HIV-1B than HIV-1C, consistent with reduced chemotactic activity as hypothesized.

Graphical abstract



Download : Download high-res image (295KB) Download : Download full-size image

Introduction

Persistent central nervous system (CNS) inflammation and chronic immune activation, which are accompanied by the production of proinflammatory cytokines, play important roles in neuronal damage associated with human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) (Zipeto et al., 2018; Ruhanya et al., 2021).

Monocytes and macrophages activation are crucial in HIV CNS infection and HAND pathogenesis. These cells are central in HIV transport from periphery to brain, in establishing and maintaining reservoirs in specific tissues as CNS, as well as in maintaining neuro-inflammation (Burdo et al., 2013; Campbell et al., 2014; Wong et al., 2019; León-Rivera et al., 2021).

Many studies on inflammatory biomarkers of HIV-1 infection, including the soluble form of CD14 (sCD14) a marker of monocyte activation, have been carried out in settings where the HIV-1B subtype predominates (Lyons et al., 2011; Kamat et al., 2012; Shive et al., 2015; Gianella et al., 2019; Jumare et al., 2020). However, little is known about these markers in non-B HIV subtypes.

The HIV Tat protein upregulates the expression of several cytokines (Chen et al., 1997; Bennasser and Bahraoui, 2002), this is attributed to the C30C31 dicysteine motif (Albini et al., 1998; Beall et al., 1996). Tat-B (C30C31) is associated in vitro with higher inflammation and higher monocyte expression of inflammatory biomarkers, such as TNF-α, interleukin (IL)-6, IL-10, and C—C chemokine ligand 2 (CCL2) (Campbell et al., 2007; Wong et al., 2010). The expression of higher levels of CCL2 may support a pro-inflammatory state in the CNS; cerebrospinal fluid (CSF) CCL2 levels are associated with increased sCD14 levels (Thames et al., 2015). IL-10, which is upregulated by HIV-Tat (Gee et al., 2007), enhances CD14 expression in monocytes (Sandanger et al., 2009) and positively correlates with sCD14 (Williams et al., 2018). On the other hand, in vitro, Tat-C (C30S31) showed lower inflammation with lower monocyte expression of IL-6 and TNF-α (Campbell et al., 2007; Gandhi et al., 2009). Furthermore, HIV Tat C does not induce calcium influx, which results in lower levels of IL-10 in monocytes (Wong et al., 2010; Williams et al., 2020). All these can result in lower levels of sCD14 in HIV-1C subtype. However, CD14 activation was not studied yet in HIV-1C CSF or serum samples compared with HIV-1B.

Our group, studying human CSF and serum samples from people with HIV (PWH), described comparable CSF level of inflammation biomarkers between HIV-1 subtypes C and B, as well as no differences in the frequency of HAND (de Almeida et al., 2013; de Almeida et al., 2016a; de Almeida et al., 2020a; de Almeida et al., 2021b), in contrast with the previous in vitro studies.

We hypothesized that stimulation of sCD14 levels would be lower in samples with HIV-1C than in those with HIV-1B, due to a defective Tat chemokine dimotif (C30S31). To investigate this hypothesis, we conducted a cross-sectional survey analyzing stored CSF and blood samples. This study aimed to: (a) to compare the effects of HIV-1 subtypes B and C infection on sCD14 in CSF and serum, (b) assess sCD14 levels in PWH compared with HIV-negative controls (people without HIV; PWoH). (c) Secondary exploratory comparisons were performed to assess the relationship between the sCD14 in both compartments (i.e. CSF and serum) in neurocognitive impairment in PWH.

Section snippets

CSF and blood samples

In this study, 86 CSF and paired serum samples were collected purely for research purposes from PWH ($n = 68$) and PWoH, ($n = 18$).

PWH were recruited from Hospital de Clínicas–Universidade Federal do Paraná (HC-UFPR), Brazil. All volunteers underwent serological testing to confirm the HIV status before enrollment. Exclusion criteria included opportunistic CNS infections, loss of consciousness for greater than 30 min, non-HIV-related neurologic injury or disorder (e.g., epilepsy, stroke, and...

Results

Demographic, clinical, and laboratory characteristics were compared between PWH and PWoH and individuals infected with HIV subtypes B and C (Table 1). Subtype B- and C-infected individuals were similar in age, sex, and years of education. Subtype B-infected participants had nonsignificantly lower nadir CD4 counts (median, 82 cell/mm^3 vs. 159 cell/mm^3, $p = 0.29$) and were more likely to be on ART (89% vs. 69%; $p = 0.099$). ART included non-nucleoside reverse transcriptase inhibitors for nine of...

Discussion

We evaluated sCD14 in CSF and serum in PWH with chronic infection and without CNS opportunistic infections, compared with a group of PWoH. The sCD14 levels were higher in PWH than in PWoH in the serum, but not in the CSF. The sCD14 increase was subtype-dependent higher in HIV-1B than HIV-1C, which was in accordance with our hypothesis. The *p*-values were adjusted for plasma HIV viral load suppression and nadir CD4 count. The sample size was sufficient for power analysis of the comparisons of the ...

Sources of funding

This study was supported by grant from the National Institutes of Health (R21 MH76651, RE and SMA), and CFAR International Pilot Grant P30 AI036214 (principal investigator: S. de Almeida)....

Role of funding source

Funding organizations did not contribute to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication....

Ethics committee approval

This study was a cross-sectional survey using stored blood and CSF samples, was approved by UCSD (San Diego, CA, USA) IRB, HC-UFPR (Curitiba, Paraná, Brazil) IRB, and the National Commission of Ethics in Research (CONEP, Brazil). All participants signed informed consent forms approved by the IRBs in the United States and Brazil....

Authors' contributions

SM de Almeida participated in the conception and design of the study, patient recruitment, acquisition, statistical analysis and interpretation of clinical and laboratory data, as well as drafting, revision, and finalization of the manuscript.

B Tang participated in the statistical analysis, as well as the revision and finalization of the manuscript.

F Vaida participated in the statistical analysis.

S Letendre participated in the conception and design of the study.

RJ Ellis participated in the...

Conflicts of Interest and Source of Funding

The authors declare that there are no conflicts of interest regarding the publication of this article.

This research was supported by NIH R21 MH76651 (principal investigators: R. Ellis and S. de Almeida) and CFAR International Pilot Grant P30 AI036214 (principal investigator: S. de Almeida). Funding organizations did not contribute to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and...

Declaration of Competing Interest

The authors declare that there are no conflicts of interest regarding the publication of this article....

References (56)

J.K. Wong *et al.*
Differential induction of interleukin-10 in monocytes by HIV-1 clade B and clade C tat proteins
J. Biol. Chem. (2010)

M.E. Williams *et al.*
Signatures of HIV-1 subtype B and C tat proteins and their effects in the neuropathogenesis of HIV-associated neurocognitive impairments
Neurobiol. Dis. (2020)

M.J. Wang *et al.*
Oligomeric forms of amyloid-β protein in plasma as a potential blood-based biomarker for Alzheimer's disease
Alzheimers Res. Ther. (2017)

P. Chen *et al.*
The tat protein of HIV-1 induces tumor necrosis factor-alpha production. Implications for HIV-1-associated neurological diseases
J. Biol. Chem. (1997)

A. Albini *et al.*
Identification of a novel domain of HIV tat involved in monocyte chemotaxis
J. Biol. Chem. (1998)

P. Ancuta *et al.*
Microbial translocation is associated with increased monocyte activation and dementia in aids patients
PLoS One (2008)

A. Antinori *et al.*
Updated research nosology for HIV-associated neurocognitive disorders
Neurology (2007)

C.J. Beall *et al.*
Site-directed mutagenesis of monocyte chemoattractant protein-1 identifies two regions of the polypeptide essential for biological activity
Biochem. J. (1996)

B. Becher *et al.*
Regulation of CD14 expression on human adult central nervous system-derived microglia
J. Neurosci. Res. (1996)

G. Bello *et al.*
Origin and evolutionary history of HIV-1 subtype C in Brazil
AIDS (2008)

View more references

Cited by (0)

Recommended articles (6)

Research article

To the editor: Response to Kao et al.

Seminars in Arthritis and Rheumatism, Volume 55, 2022, Article 151990

Research article

Role of C-terminal Membrane-proximal Basic Residues in Cell Surface Trafficking of HIV Coreceptor GPR15 Protein

Journal of Biological Chemistry, Volume 288, Issue 13, 2013, pp. 9189-9199

Show abstract

Research article

A Comment on Anti–*Helicobacter pylori* Therapy and Autoimmune Diseases

Clinical Gastroenterology and Hepatology, Volume 17, Issue 8, 2019, p. 1647

Research article

Astrocyte Elevated Gene-1 Is a Novel Modulator of HIV-1-associated Neuroinflammation via Regulation of Nuclear Factor-κB Signaling and Excitatory Amino Acid Transporter-2 Repression

Journal of Biological Chemistry, Volume 289, Issue 28, 2014, pp. 19599-19612

Show abstract

Research article

Up-regulation of the Neuronal Nicotinic Receptor α7 by HIV Glycoprotein 120

Journal of Biological Chemistry, Volume 287, Issue 5, 2012, pp. 3079-3086

Show abstract

Research article

Geologic position, age, and petrogenesis of plagiogranites in northern Rudny Altai

Russian Geology and Geophysics, Volume 54, Issue 10, 2013, pp. 1305-1318

Show abstract

View full text