

The role of IFN- γ production during retroviral infections: an important cytokine involved in chronic inflammation and pathogenesis

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ABSTRACT

Interferon-gamma (IFN- γ) plays a crucial role in viral infections by preventing viral replication and in the promotion of innate and adaptive immune responses. However, IFN-gamma can exert distinct effects in different persistent viral infections. The long-term overproduction of IFN- γ in retroviral infections, such as the human immunodeficiency virus (HIV), human T-lymphotropic virus type 1 (HTLV-1), and human endogenous retroviruses (HERVs), resulting in inflammation, may cause neuronal damage. This review is provocative about the role of IFN- γ during persistent retroviral infections and its relationship with the causation of some neurological disorders that are important for public health.

KEYWORDS: Retroviruses. HIV. HTLV-1. HERVs. Interferon- γ . Immune regulation.

INTRODUCTION

Interferons (IFN) are a group of cytokines that induce the production of antiviral factors during viral infections. IFN- γ belongs to IFN type 2; its genes are located on chromosome 12, and the gene (IFNGR1) encodes the ligand-binding chain (alpha) of the heterodimeric gamma interferon receptor, which is found in macrophages¹. It induces the immunoregulation for the recognition of the antiviral and antitumor antigens²; it also stimulates T cell differentiation for the Th1 type response and clonal expansion, capable of acting in an autocrine and paracrine way, and the overexpression of IFNGR can induce pro-apoptotic phenotypes³.

Interferon- γ is secreted by B lymphocytes, Natural Killer (NK) cells, Natural Killer T lymphocytes (NKT), and antigen-presenting cells (APCs), resulting in inflammation and cellular recruitment⁴. This cytokine can interfere with viral replication⁵ by activating the stimulated interferon genes, which induce the production of antiviral factors such as APOBEC-3G, TRIM5 alpha, MIP-1 alpha, and MIP-1 β . IFN- γ signalling activates the antigen-presenting cells (APCs) to upregulate the expressions of cytokines (IL-12 and IL-18) and CD86 costimulatory molecule that enhances the Th1 differentiation and cytotoxic T lymphocyte (CTL) function^{7,8}. Therefore, IFN- γ is related to the class I main histocompatibility complex (MHC) and to the presentation of class II antigens; it also controls the differentiation of naive TCD4 cells into Th1 effector⁹. Those events mediate cellular immunity against intracellular agents. On the other hand, excess IFN- γ is related to chronic inflammatory and autoimmune diseases, such as multiple sclerosis and diabetes mellitus⁹⁻¹¹.

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The IFN- γ is antagonistic to the production of immunosuppressive and anti-inflammatory interleukins, such as IL-10, and is directly responsible for down modulating the presentation of antigens by MHC class II, during the virus immune response in general. There is a lack of this regulatory mechanism and constant influence of the IL-2^{8,12} and no limitation of the intensity of inflammatory response^{8,13}. IFN- γ and IL-2 play a crucial role in the replication of host cells and may be a biomarker to monitor disease progression in infections^{6,14}. This chronic overexpression of IFN- γ in different tissues can initiate several inflammatory disorders and excessive damage to tissues. This review intends to raise and analyze the information regarding the role of IFN- γ in persistent viral infections, particularly human retroviral infections with epidemiological importance¹⁵.

MATERIALS AND METHODS

The bibliographic research reported here followed some criteria for surveying, selecting and analysing the literature, as described below.

Sources for obtaining the information

The NCBI Pubmed electronic database was used for result retrieval. The searched terms such as Retroviruses; HIV; HTLV-1; HERVs; Interferon- γ (INF- γ) were adapted in order to meet the specific demands of the database. The latest search update was conducted on December 31, 2021.

After obtaining the articles that addressed the topic, texts were selected based on the content of their abstracts which reflected the objective outlined in the present review. Among all, 60 articles that met the thematic criterion were obtained and 14 of them discussed the role of the immune response and role of IFN- γ ; 17 discussed the role of IFN- γ and HTLV-1 infection; 21 texts addressed the role of IFN- γ and HIV infection; and 13 highlighted the role of IFN- γ and HERV; some of them were included in more than one category.

Eligibility criteria

Cross-sectional and review studies; the role of IFN- γ and HTLV-1, HIV and HERV infection; English language.

Exclusion criteria

Were excluded: Abstracts and conference proceedings, study protocols, editorials or commentaries, and letters to the editors not including any original data; co-infection

studies in an already known infected population; and not in the English language.

Reading and analysis of texts

We performed an analytical and comparative reading of the information obtained. The reading had two phases: (a) recognition reading and analysis of the content of each manuscript; (b) new reading in order to punctuate the relevant aspects about the role of IFN- γ and retroviruses infection.

The role of IFN- γ was firstly characterised, then followed the identification of the interferon-gamma response pathways and retrovirus infections. Thereafter, important data about the topic in general were evaluated. At the end, the possible mechanisms involved in retrovirus infection and stimulated by IFN- γ were identified. The following is the result of the survey and the bibliographic analysis performed with a view to systematise the knowledge about IFN- γ and retrovirus infection in the form of a literature review.

Interferon-gamma (IFN- γ) and its role in HTLV-1 infection

The Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus associated with several chronic inflammatory diseases such as uveitis, polymyositis, arthritis, alveolitis, infective dermatitis as well as some types of skin lesions, susceptibility to some opportunistic infections, and the HTLV-1 associated myelopathy (HAM)^{16,17}.

HAM is potentially considered an immune-mediated disease, mainly due to the increase of cytokines and chemokines, and it stands out for the elevation of IFN- γ levels^{18,19}. The production of IFN-gamma by CD8+ T cells is considerable in the central nervous system (CNS) due to the volume of cells expressing MHC class I antigens; it is also related to MHC class II involved in the production of IFN- γ ^{6,20}. Therefore, the spontaneous IFN- γ production is more likely due to TAX activation over certain genes in the hosted cells^{14,21} (Figure 1).

Some genes are over-expressed in the white blood cells of patients with HAM (HTLV-1-associated myelopathy), but not in asymptomatic HTLV-1 carriers or patients with the disease clinically similar to multiple sclerosis^{22,23}. The expression of these genes is induced by interferons, usually beneficial to the host protection, but it can also cause inflammation^{20,22}. It was noted that interferons do not efficiently suppress HTLV-1 protein expression in vitro and do not control chronic HTLV-1 infection, but instead contribute to the development of HAM²⁴. In addition,

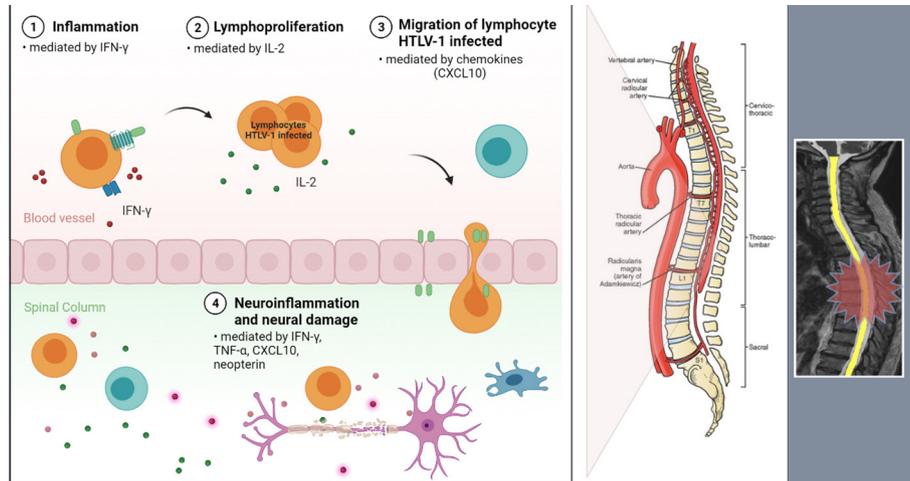


Figure 1 - Hypothesis of neuroinflammation process during HTLV-1 infection: 1) Activation of inflammation process; 2) T-cell proliferation; 3) Migratory process of infected T cells; 4) Pro-inflammatory cytokines and chemokines secreted during the neurodegeneration process. This inflammatory process will induce the release of cytokines in the spinal cord (thoracic segment). Initially, there is a proinflammatory local involvement, driven mainly due to IFN- γ . Over a few years, this process is ongoing and chronic with the outcome being degenerative damage to the myelin membrane.

disorders of the p53 signalling pathway are hallmarks of HTLV-1 infection²⁵.

In contrast, a subset of IFN-stimulated genes is overexpressed in HAM cases but not in asymptomatic carriers and patients with a similar disease like multiple sclerosis²³. The IFN-inducible signature was present in all circulating leukocytes and its intensity is correlated with the clinical severity of HAM, where T and B cells from HAM cases were primed to respond strongly to stimulation with exogenous IFN²². However, while the type I IFN suppressed expression of the HTLV-1 structural protein Gag, it failed to suppress the highly immunogenic viral transcriptional transactivator Tax²⁶. Taken altogether, the overexpression of a subset of IFN-stimulated genes in chronic HTLV-1 infection does not constitute an efficient host response, but instead contributes to the development of HAM²⁷.

HTLV-1 can induce the infected cells to migrate, a property linked to cytoskeleton reorganisation induced by the viral Tax protein, the “virological synapse” (VS) promoting direct transmission based on cell-cell contacts⁵. Viral proteins of HTLV-1, such as Tax, can activate various signal pathways including the NF- κ B and AP-1 pathways¹⁸. The major histocompatibility complex class I (MHC-I) antigen presentation pathway plays a central role in the development of host immunity against pathogens, where MHC-I molecules are expressed on the surface of all nucleated cells and present peptides to the TCRs of cytotoxic T lymphocytes²⁰. Effector CD8+ T-cells specifically recognize viral peptides via the TCR to destroy infected cells. Consequently, many viruses have evolved proteins whose main function is to interfere with this pathway²⁸.

The inflammatory process activated by HTLV-1 could be related to anatomical characteristics of the lumbar thoracic medulla due to the angulation of the radicular thoracic arteries and the Adamkiewicz-surge artery, causing local inflammation due to the production of cytokines, mainly an overproduction of IFN- γ (Figure 1)^{27,29}. One study found the production of a significant range of interferon levels ($p=0.0001$) in an asymptomatic patient (ASY) compared with patients who have HTLV-associated myelopathy (HAM) and (0.0009) in an asymptomatic patient (ASY) vs patients that did not have a complete framework for classification as HAM, and was named Intermediate Syndrome (SI), even as a very early phase of HAM³⁰. This shows that IFN- γ can be the pillar for a prognostic marker, as well as an indicator for anti-inflammatory treatment, as recommended in the last International Retroviral Association (IRVA) guideline³¹.

In summary, HTLV-1 leads to dysregulation of the immune system. Several studies have reported interferon- γ as a central mediator of inflammation in patients with neurological damage associated with HTLV-1¹⁶. Different immunological aspects are involved in virus/host interaction, and the way this interaction develops will determine whether the patient will be asymptomatic or afflicted with some condition, such as HAM²⁰. In this sense, IFN can be a potential marker to predict early disease development, since HAM is an immune-mediated disease, and may be of greater prognostic value when compared to HTLV-1 proviral load¹⁴. The immune response during viral infection is one of the important parameters that can determine the degree of infection. There is currently no cure for HTLV, however, partially blocking the production/

action of IFN can be a palliative strategy for patient disease management³¹. The drugs currently used in clinical practice, for example, corticosteroids, can temporarily alleviate the pain that patients feel but are not effective for preventing long-term neurological damage³¹.

Role of the IFN- γ levels among HIV-1-infected subjects

Human immunodeficiency virus (HIV) is also a retrovirus, but unlike HTLV-1 it leads to the progressive loss of cells, resulting in Acquired Immunodeficiency Syndrome (AIDS). In this infection, there is a high production of pro-inflammatory cytokines, which in turn trigger apoptosis; they are important factors for modulating HIV-1 infection and in the replication rate of the virus during disease progression³².

Among those pro-inflammatory cytokines, the interferons produced during viral infections act on T and B lymphocytes, natural killer cells (NK), and phagocytic cells. They play a crucial role in the prevention of early replication from binding IFN- γ to its IFNGR-1 and IFNGR-2³², triggering intracellular signalling to induce apoptosis of the infected cells, and regulating post-transcription and translation processes. This recognition could help in the development of new therapies to prevent infection and regulate innate and acquired immunity, controlling the spread of HIV in the early stages of infection³³.

People living with HIV (PLWH) can also have neurological symptoms. The virus can cross the blood-brain barrier during the acute phase, with the migration of infected monocytes from the bloodstream into the CNS and infect

neighbouring cells, such as microglia and astrocytes³⁴. The antiviral cytokines present in the brain during infection control the viral replication in the CNS³⁵. In contrast, IFN- γ plays a protective role in uninfected children of mothers with HIV-1³⁶, who have a higher concentration of IFN- γ and IL-10 than infected children. Exposure in the uterus to HIV-1 may increase the amount of IL-10 in the umbilical cord that is associated with protection against perinatal infection³⁶.

An interesting study on patients receiving interferon-alpha (IFN- α) therapy and in systemic lupus erythematosus patients demonstrated that elevated CSF levels of IFN- α are associated with cognitive dysfunction³⁷. In this direction, another manuscript observed that these high productions were significantly elevated in the CSF of PLWH with dementia compared to those without this diagnostic compared to controls, suggesting that the significant amounts of this protein³⁸. This detection in the CSF of HAND cases is derived from intrinsic brain cells such as macrophages and astrocytes. The increased local production of IFN- γ during HIV infection may contribute, directly or indirectly, to the pathogenesis of HIV-associated dementia (HAD)³⁹ (Figure 2).

On the other hand, there is evidence that the deficit of the signal transducer and activator of transcription 5 (STAT5) in HIV-infected patients can be restored with antiretroviral therapy^{40,41}. This is evident with the characterization of those transcription factors in the population and their correlation with the treatment and genotyping of the virus; some genes in the HIV-1 envelope are associated with resistance to IFN- γ function, resulting in greater infectivity due to the possibility of replication of viral particles⁴⁰.

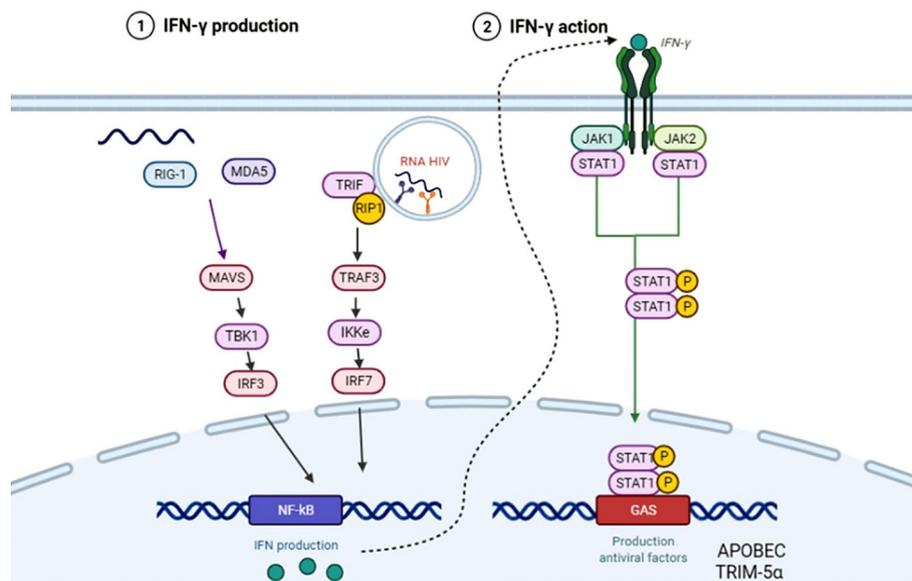


Figure 2 - Role of IFN secretion during HIV-1 infection. The presence of HIV RNA in endosomes activates Toll-like receptors, thus activating the NF-kappa beta pathway. The production of IFN-gamma promotes the JAK-STAT activation and consequently signaling of interferon-stimulated genes. After that, antiviral factors such as APOBEC, and TRIM-5alpha are produced.

The difficulty in assessing the real contribution of serum IFN- γ levels in PLWH stems from their antagonistic role, acting both as an inflammatory cytokine and as an enhancer of antiviral immunity⁴². During the acute stage of HIV-1 infection, the host immune system mounts an inflammatory response resulting in a cytokine storm³⁷. If not appropriately controlled, it enhances HIV-1 infection and may cause a higher viral set point before T cell immunity can control the HIV-1 load. Remarkably, low levels of IFN- γ are detected throughout HIV-1 infection, correlating with persistent HIV-1 replication⁴³. Furthermore, many of the HIV-1 proteins can directly stimulate T cells to produce IFN- γ , leading to chronic immune activation and ultimately to the exhaustion of the immune system and waste of IFN- γ production. However, IFN- γ therapy does not affect HIV-1 load or AIDS progression whereas ART has a dramatic effect on both, even if long-term ART does not completely restore the immune responses⁴⁴. Hence, IFN- γ may still play an important role as a product of HIV-specific polyfunctional CD4⁺ T cells, which may serve to enhance the anti-HIV antibody production as well as CTLs against HIV-1 infection⁴⁴.

HIV proteins are found in the central nervous system of patients progressing to HIV-associated neurocognitive disorder (HAND), along with high IFN- γ levels. Those HIV proteins lead to high activation of the JAK/STAT1 pathway that regulates the inflammation and apoptotic signalling associated with neuronal damage⁴⁵. Most HIV patients remain asymptomatic for years, albeit up to 60% of them present some degree of neurological disorder. Among those neuropsychiatric deficiencies, HIV-associated dementia (HAD) is the most severe form with an average survival of only six months after the onset of symptoms⁴⁵. Antiretrovirals are not able to control HIV replication in the CNS, but an early start of antiretroviral treatment may decrease the incidence of neurological diseases⁴⁶.

Neurons are not killed directly by a viral infection, but viral proteins induce the production of cytokines such as IFN- γ , TNF- α , and IL-1 β which are neurotoxic. A study found that the JAK/STAT pathway, a key regulator of inflammatory and apoptotic signalling, is elevated in HIV-1-infected brains progressing to HAND³⁴. This pathway can be inhibited by the epigallocatechin-3-gallate (EGCG) present in green tea, resulting in a decrease of inflammatory cytokines and the consequent mitigation of neuronal damage in the cortical regions of mouse brains, as compared to controls⁴⁵. These observations suggest the use of IFN- γ for monitoring patients that tend to progress to HAND and it can be an important therapeutic target, as an adjunct to ART, to prevent it. Immunological pathways that activate the production of pro-inflammatory cytokines and chemokines should be investigated in order to help in

the development of a treatment strategy to prevent patients from becoming dependent^{34,46}.

Some people remain negative for HIV infection despite having unprotected sex with viremic HIV-positive patients. They show a higher production of IFN- γ in CD3⁺-CD56⁺ bright (NK) and CD3⁺/CD56⁺ (TNK) cells in their plasma, which can be their protector factor⁴⁷. In this sense, approximately 30% of HIV-positive patients, treated with ART for four years, have high levels of IFN- γ in their plasma and low amounts of circulating CD4⁺ T lymphocytes⁴². Since HAND may occur in up to half of the HIV-positive individuals, even with cART, adjunctive therapies are needed⁴⁸.

Human endogenous retroviruses (HERVs) as regulators of neuroinflammation

Most of the human endogenous retroviruses (HERVs) are not capable of encoding functional proteins (junk DNA). They are considered remnants of exogenous retrovirus, since they have 5'LTR, GAG, POL, ENV, and 3'LTR^{49,50}. HERVs have retroviral envelopes that are composed of glycoproteins, such as syncytin-1, that bind to ASCT1 and ASCT2, located in neurons and glia, responsible for modulating the neurotoxic and neurotrophic effects⁵⁰. The overexpression in astrocytes increases pro-inflammatory cytokines responsible for causing neuroinflammation, neurodegeneration, and stress response of the endoplasmic reticulum, being harmful to the oligodendrocytes involved in the formation of myelin. The regulatory factor of interferon 1 (IRF1) and NF- κ B can trigger the expression of HERV-K through the response stimulated by interferon in neurons of the motor cortex, suggesting the potential role of HERVs in the mediation of inflammation in neuropsychological disorders^{49,50}.

Despite the association of HERVs with neuroinflammation, there are few studies in the literature that report the influence of HERVs in the production of interferon-gamma. In this sense, the greater exposure to IFN gamma seems to generate a positive feedback loop for the activation of STAT1 and to induce the expression of CXCL10, IFN- β , PD-L1, and ERVs, in cases of mesenchymal tumours with high expression of AXL/MET and low levels of EZH2⁵¹. As for HTLV infection and the onset of HAM, no relationship was found between the expression of HERVs and the cause of this disease⁵². In addition, IL-12 produced by macrophages and dendritic cells promotes the differentiation of T lymphocytes into Th1 and the activation of NK cells, both responsible for secreting interferon- γ (IFN- γ), which acts in the activation of macrophages and lymphocytes⁵².

Thousands of endogenous retroviruses (ERV), viral fossils of ancient germ line infections, reside within the human genome. Evidence of ERV activity has been observed widely in both health and disease⁵³. While this is most often cited as a bystander effect of cell culture or disease states, it is unclear which signals control ERV transcription. Bioinformatic analysis suggested that the viral promoter of ERVK is responsive to inflammatory transcription factors⁵⁴. For example, ERVK upregulation in amyotrophic lateral sclerosis (ALS) is the presence of functional interferon-stimulated response elements (ISREs) in the viral promoter⁵⁵. Transcription factor overexpression assays revealed independent and synergistic upregulation of ERVK by interferon regulatory factor 1 (IRF1) and NF- κ B isoforms. Thus, neuroinflammation is a key trigger of ERVK provirus reactivation in ALS. It has been well established that the inflammatory signalling pathways in ALS converge at NF- κ B to promote neuronal damage⁵⁵. Therefore, quenching ERVK activity through antiretroviral or immunomodulatory regimens may hinder virus-mediated neuropathology and improve the symptoms of ALS or other ERVK-associated diseases, such as HAND mechanisms⁵⁶.

Endogenous retrovirus can also be related to the incidence of HAND, since HIV may activate two human endogenous retroviruses. The human endogenous retrovirus (HERV)-W is associated with multiple sclerosis (MSRV)⁵⁷. HERV-k II is highly expressed in human neurons, especially in seropositive people, due to the release of HIV proteins such as Vpr, Tat, Env, and the proliferation of glial infected cells and leukocytes⁵⁸ (Figure 3). This product is toxic

to neurons in the long term, and when added to host susceptibility factors leads to enhanced inflammation, with a consequent increase of apoptosis and necrosis⁵⁹. On the other hand, the expression of HERV-K (II) in neural cells can also exert neuroprotective effects, as it prevents the neurotoxicity measured by HIV-1, and can exert adaptive effects in the pathophysiological stress⁵⁸.

The introduction and integration of retroviruses in the chromosome of our genome are considered a final stage of parasitism and the hallmark of immunity evasion⁶⁰. There is a large number of endogenous viral sequences of different origins along the vertebrate genomes. Some of those sequences can still maintain viral characteristics, such as replication and the ability to activate innate and adaptive immune responses, which may or may not cause beneficial and/or pathogenic effects in humans⁵⁷.

In addition, viral sequences inherited by the germline that are part of our genome represent 5% of it and can act as restriction factors. ERV Gag proteins interfere with the exogenous retrovirus infection cycle, which consequently modulates the immune system *cis-pro* inflammatory regulators⁶⁰. These mechanisms can improve the levels of interferon, triggering the activation of T cells and also suppressing the immunological effects on the immune system⁶⁰.

Limitations of the study

The current study has several major limitations since it was not a systematic review. Hence, the results of studies

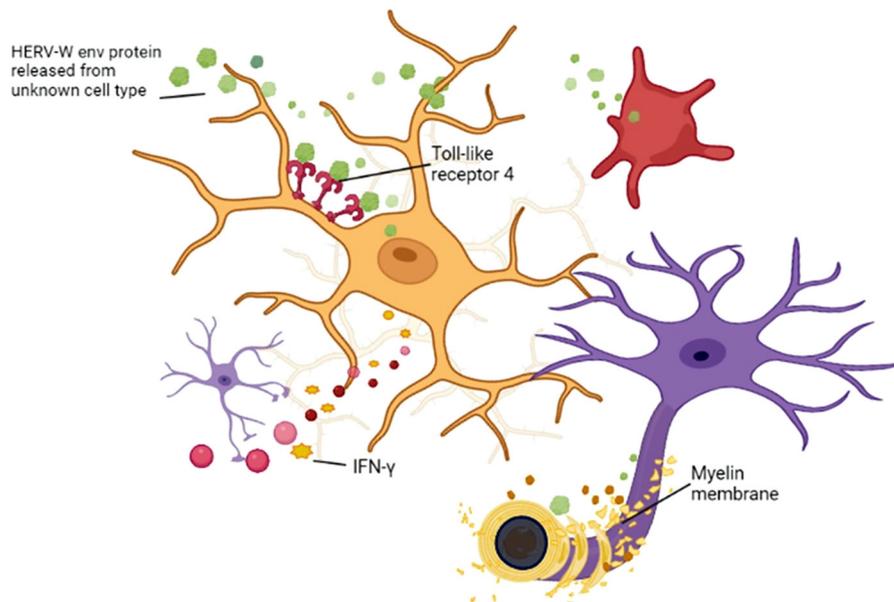


Figure 3 - Endogenous retrovirus expression in the central nervous system. The HERVs are expressed in several cell types. In astrocytes, regarding the viral chronic infection context, there is a major expression of the HERV proteins that, when added with inflammatory molecules, promote neuronal damage.

using bibliographic research methods need to be interpreted with caution, and the reliability and validity issues should be taken into account when interpreting their results.

CONCLUSION

The IFN- γ can be considered a double-edged sword, therefore it is essential to understand its biological functions in the face of infections. Different actions are at play to achieve a balance between control of infections with retroviruses and the host. As such, understanding the host-pathogen interaction is essential for the development of drugs and viral therapeutic measures aimed at patients, to achieve cures and prevent progression to life-threatening diseases. These viruses are broadly disseminated worldwide and the neurological outcomes should be of concern as nowadays it has epidemiological importance.

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REFERENCES

- Samuel CE. Antiviral actions of interferons. *Clin Microbiol Rev.* 2001;14:778-809.
- Stow JL, Murray RZ. Intracellular trafficking and secretion of inflammatory cytokines. *Cytokine Growth Factor Rev.* 2013;24:227-39.
- Ge Y, Huang M, Yao YM. Autophagy and proinflammatory cytokines: interactions and clinical implications. *Cytokine Growth Factor Rev.* 2018;43:38-46.
- Laurent X, Bertin B, Renault N, Farce A, Specq S, Milhomme O, et al. Switching invariant natural killer T (iNKT) cell response from anticancerous to anti-inflammatory effect: molecular bases. *J Med Chem.* 2014;57:5489-508.
- Dörries R. The role of T-cell-mediated mechanisms in virus infections of the nervous system. *Curr Top Microbiol Immunol.* 2001;253:219-45.
- Matsuura E, Yamano Y, Jacobson S. Neuroimmunity of HTLV-I infection. *J Neuroimmune Pharmacol.* 2010;5:310-25.
- Burke JD, Young HA. IFN- γ : a cytokine at the right time, in the right place. *Semin Immunol.* 2019;43:101280.
- Kak G, Raza M, Tiwari BK. Interferon-gamma (IFN- γ): exploring its implications in infectious diseases. *Biomol Concepts.* 2018;9:64-79.
- Rönblom L. The importance of the type I interferon system in autoimmunity. *Clin Exp Rheumatol.* 2016;34 Suppl 98:21-4.
- Clanet M, Blancher A, Calvas P, Rascol O. Interferons and multiple sclerosis. *Biomed Pharmacother.* 1989;43:355-60.
- Marroqui L, Perez-Serna AA, Babiloni-Chust I, Santos RS. Type I interferons as key players in pancreatic β -cell dysfunction in type 1 diabetes. *Int Rev Cell Mol Biol.* 2021;359:1-80.
- Sanders CM, Cruse JM, Lewis RE. Toll-like receptors, cytokines and HIV-1. *Exp Mol Pathol.* 2008;84:31-6.
- Frucht DM, Fukao T, Bogdan C, Schindler H, O'Shea JJ, Koyasu S. IFN-gamma production by antigen-presenting cells: mechanisms emerge. *Trends Immunol.* 2001;22:556-60.
- Prates G, Assone T, Corral M, Baldassin MP, Mitiko T, Silva Sales FC, et al. Prognosis markers for monitoring HTLV-1 neurologic disease. *Neurol Clin Pract.* 2021;11:134-40.
- Douville RN, Hiscott J. The interface between the innate interferon response and expression of host retroviral restriction factors. *Cytokine.* 2010;52:108-15.
- Martin F, Taylor GP, Jacobson S. Inflammatory manifestations of HTLV-1 and their therapeutic options. *Expert Rev Clin Immunol.* 2014;10:1531-46.
- Kitze B, Usuku K. HTLV-1-mediated immunopathological CNS disease. *Curr Top Microbiol Immunol.* 2002;265:197-211.
- Futsch N, Prates G, Mahieux R, Casseb J, Dutartre H. Cytokine networks dysregulation during HTLV-1 infection and associated diseases. *Viruses.* 2018;10:691.
- Araujo AQ. Update on neurological manifestations of HTLV-1 infection. *Curr Infect Dis Rep.* 2015;17:459.
- Enose-Akahata Y, Jacobson S. Immunovirological markers in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Retrovirology.* 2019;16:35.
- Brites C, Grassi MF, Quaresma JA, Ishak R, Vallinoto AC. Pathogenesis of HTLV-1 infection and progression biomarkers: an overview. *Braz J Infect Dis.* 2021;25:101594.
- Puccioni-Sohler M, Yamano Y, Rios M, Carvalho SM, Vasconcelos CC, Papais-Alvarenga R, et al. Differentiation of HAM/TSP from patients with multiple sclerosis infected with HTLV-I. *Neurology.* 2007;68:206-13.
- Oger J. HTLV-1 infection and the viral etiology of multiple sclerosis. *J Neurol Sci.* 2007;262:100-4.
- Bidkhor HR, Hedayati-Moghaddam MR, Mosavat A, Valizadeh N, Tadayon M, Ahmadi Ghezeldasht S, et al. The IL-18, IL-12, and IFN- γ expression in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients, HTLV-1 carriers, and healthy subjects. *J Neurovirol.* 2020;26:338-46.
- Matsuura E, Yamano Y, Jacobson S. Neuroimmunity of HTLV-I infection. *J Neuroimmune Pharmacol.* 2010;5:310-25.
- Rocamonde B, Futsch N, Orii N, Allatif O, Penalva de Oliveira AC, Mahieux R, et al. Immunoprofiling of fresh HAM/TSP blood samples shows altered innate cell responsiveness. *PLoS Negl Trop Dis.* 2021;15:e0009940.
- Tattermusch S, Bangham CR. HTLV-1 infection: what determines the risk of inflammatory disease? *Trends Microbiol.* 2012;20:494-500.

28. Sarkis S, Galli V, Moles R, Yurick D, Khoury G, Purcell DF, et al. Role of HTLV-1 orf-I encoded proteins in viral transmission and persistence. *Retrovirology*. 2019;16:43.
29. Tattera D, Skinningsrud B, Pękala PA, Hsieh WC, Cirocchi R, Walocha JA, et al. Artery of Adamkiewicz: a meta-analysis of anatomical characteristics. *Neuroradiology*. 2019;61:869-80.
30. Haziot ME, Gascon MR, Assone T, Fonseca LA, Luiz OC, Smid J, et al. Detection of clinical and neurological signs in apparently asymptomatic HTLV-1 infected carriers: association with high proviral load. *PLoS Negl Trop Dis*. 2019;13:e0006967.
31. Araujo A, Bangham CR, Casseb J, Gotuzzo E, Jacobson S, Martin F, et al. Management of HAM/TSP: systematic review and consensus-based recommendations 2019. *Neurol Clin Pract*. 2021;11:49-56.
32. Sauce D, Elbim C, Appay V. Monitoring cellular immune markers in HIV infection: from activation to exhaustion. *Curr Opin HIV AIDS*. 2013;8:125-31.
33. Zuo W, Zhao X. Natural killer cells play an important role in virus infection control: antiviral mechanism, subset expansion and clinical application. *Clin Immunol*. 2021;227:108727.
34. Minosse S, Picchi E, Di Giuliano F, Sarmati L, Teti E, Pistolesse CA, et al. Functional brain network reorganization in HIV infection. *J Neuroimaging*. 2021;31:796-808.
35. Liu H, Zhou RH, Liu Y, Guo L, Wang X, Hu WH, et al. HIV infection suppresses TLR3 activation-mediated antiviral immunity in microglia and macrophages. *Immunology*. 2020;160:269-79.
36. Kuhn L, Coutsooudis A, Moodley D, Mngqundaniso N, Trabattini D, Shearer GM, et al. Interferon-gamma and interleukin-10 production among HIV-1-infected and uninfected infants of HIV-1-infected mothers. *Pediatr Res*. 2001;50:412-6.
37. Shiozawa S, Kuroki Y, Kim M, Hirohata S, Ogino T. Interferon-alpha in lupus psychosis. *Arthritis Rheum*. 1992;35:417-22.
38. Rho MB, Wesselingh S, Glass JD, McArthur JC, Choi S, Griffin J, et al. A potential role for interferon-alpha in the pathogenesis of HIV-associated dementia. *Brain Behav Immun*. 1995;9:366-77.
39. Cassol E, Misra V, Morgello S, Gabuzda D. Applications and limitations of inflammatory biomarkers for studies on neurocognitive impairment in HIV infection. *J Neuroimmune Pharmacol*. 2013;8:1087-97.
40. Rihn SJ, Foster TL, Busnadiego I, Aziz MA, Hughes J, Neil SJ, et al. The envelope gene of transmitted HIV-1 resists a late interferon gamma-induced block. *J Virol*. 2017;91:e02254-16.
41. Bourke NM, Napoletano S, Bannan C, Ahmed S, Bergin C, McKnight A, et al. Control of HIV infection by IFN- α : implications for latency and a cure. *Cell Mol Life Sci*. 2018;75:775-83.
42. Watanabe D, Uehira T, Suzuki S, Matsumoto E, Ueji T, Hirota K, et al. Clinical characteristics of HIV-1-infected patients with high levels of plasma interferon- γ : a multicenter observational study. *BMC Infect Dis*. 2019;19:11.
43. Marras F, Casabianca A, Bozzano F, Ascierto ML, Orlandi C, Di Biagio A, et al. Control of the HIV-1 DNA reservoir is associated in vivo and in vitro with NKp46/NKp30 (CD335/CD337) inducibility and Interferon Gamma production by transcriptionally unique NK cells. *J Virol*. 2017;91:e00647-17.
44. Roff SR, Noon-Song EN, Yamamoto JK. The significance of interferon- γ in HIV-1 pathogenesis, therapy, and prophylaxis. *Front Immunol*. 2014;4:498.
45. Giunta B, Obregon D, Hou H, Zeng J, Sun N, Nikolic V, et al. EGCG mitigates neurotoxicity mediated by HIV-1 proteins gp120 and Tat in the presence of IFN-gamma: role of JAK/STAT1 signaling and implications for HIV-associated dementia. *Brain Res*. 2006;1123:216-25.
46. Sanford R, Fellows LK, Ances BM, Collins DL. Association of brain structure changes and cognitive function with combination antiretroviral therapy in HIV-positive individuals. *JAMA Neurol*. 2018;75:72-9.
47. Montoya CJ, Velilla PA, Chougnet C, Landay AL, Rugeles MT. Increased IFN-gamma production by NK and CD3+/CD56+ cells in sexually HIV-1-exposed but uninfected individuals. *Clin Immunol*. 2006;120:138-46.
48. Gascon MR, Lima M, Cheutchuk PM, Oliveira EA, Oliveira GS, Gualqui F, et al. High prevalence of HIV-associated neurocognitive disorders (HAND) in São Paulo City, Brazil. *Rev Bras Neurol*. 2021;57:6-12.
49. Antony JM, Ellestad KK, Hammond R, Imaizumi K, Mallet F, Warren KG, et al. The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes. *J Immunol*. 2007;179:1210-24.
50. Wang X, Huang J, Zhu F. Human endogenous retroviral envelope protein syncytin-1 and inflammatory abnormalities in neuropsychological diseases. *Front Psychiatry*. 2018;9:422.
51. Cañadas I, Thummalapalli R, Kim JW, Kitajima S, Jenkins RW, Christensen CL, et al. Tumor innate immunity primed by specific interferon-stimulated endogenous retroviruses. *Nat Med*. 2018;24:1143-50.
52. Jones RB, Leal FE, Hasenkrug AM, Segurado AC, Nixon DF, Ostrowski MA, et al. Human endogenous retrovirus K (HML-2) Gag and Env specific T-cell responses are not detected in HTLV-I-infected subjects using standard peptide screening methods. *J Negat Results Biomed*. 2013;12:3.
53. Grandi N, Tramontano E. Human endogenous retroviruses are ancient acquired elements still shaping innate immune responses. *Front Immunol*. 2018;9:2039.
54. Medstrand P, Mager DL, Yin H, Dietrich U, Blomberg J. Structure and genomic organization of a novel human endogenous retrovirus family: HERV-K (HML-6). *J Gen Virol*. 1997;78:1731-44.
55. Curzio DD, Gurm M, Turnbull M, Nadeau MJ, Meek B, Rempel

- JD, et al. Pro-inflammatory signaling upregulates a neurotoxic conotoxin-like protein encrypted within human endogenous retrovirus-K. *Cells*. 2020;9:1584.
56. Manghera M, Ferguson-Parry J, Lin R, Douville RN. NF- κ B and IRF1 induce endogenous retrovirus K expression via interferon-stimulated response elements in its 5' long terminal repeat. *J Virol*. 2016;90:9338-49.
57. Uleri E, Mei A, Mameli G, Poddighe L, Serra C, Dolei A. HIV Tat acts on endogenous retroviruses of the W family and this occurs via Toll-like receptor 4: inference for neuroAIDS. *AIDS*. 2014;28:2659-70.
58. Bhat RK, Rudnick W, Antony JM, Maingat F, Ellestad KK, Wheatley BM, et al. Human endogenous retrovirus-K(II) envelope induction protects neurons during HIV/AIDS. *PloS One*. 2014;9:e97984.
59. Küry P, Nath A, Créange A, Dolei A, Marche P, Gold J, et al. Human endogenous retroviruses in neurological diseases. *Trends Mol Med*. 2018;24:379-94.
60. Weiss RA. Human endogenous retroviruses: friend or foe? *APMIS*. 2016;124:4-10.