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Role of IL-8 polymorphisms of gene in HIV patients in South Africa

Mark Fernandez Bedoya, Maria A. Hegeman, Marchil G. Rovere, Amanda Bron, Jimmy Fukumoto [1*]

Abstract

Human immunodeficiency virus (HIV) is still an important public health problem that emerged in the world. It is estimated that globally about 37.9 million people are living with this virus. Our country, South Africa, is one of the countries that have the most cases of people living with HIV. It is estimated that about 19% of the adult population (20-49 years) are affected by this virus. The aim of this study is to evaluate the role of IL-8 polymorphisms in HIV patients and in healthy people in South Africa. The production of IL-8 may have changed with some polymorphisms, and these changes may be responsible for the prognosis of HIV patients. If something is determined about these polymorphisms, it can be a basis for new preventive and regenerative therapies in HIV.

HIV, which is a pandemic infection-related disease, eventually causes communities to become vulnerable. This is a major problem in developing countries because they have low-income public status. Many advances have been made in the treatment of HIV, but there are still health problems because there is nothing like a complete treatment. The World Health Organization (WHO) reports that more than 25 million people have died from AIDS from 1981 to 2018. HIV/AIDS epidemiological reports state that the HIV/AIDS pandemic has affected both developing and developed countries. South Africa has the highest number of people living with HIV in the world. It is also the country with the highest number of AIDS-related deaths in the world. Most of these deaths are due to co-infections with biotic and abiotic infections and due to the pathogenesis of long-term disease progression. The role of the cytokine IL-8 has been described in many infectious and inflammatory diseases, some of which are caused by severely immunosuppressive pathogens. One IL-8 polymorphism, rs2227306, has been associated with long-term disease progression in HIV-infected individuals. The current study was aimed at determining whether the IL-8 polymorphisms had an association with HIV disease progression in South African HIV-infected individuals. Data from a pilot study was used to analyze the association of the polymorphisms with HIV viral load and CD4+ cell counts.

Keywords: Interleukin-8 (IL-8); Cytokine; HIV; Polymorphism

*Corresponding author: Fukumoto
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Introduction

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South Africa has the highest number of people living with HIV in the world. It is also the country with the highest number of AIDS-related deaths in the world. Most of these deaths are due to co-infections with biotic and abiotic infections and due to the pathogenesis of long-term disease progression. The role of the cytokine IL-8 has been described in many infectious and inflammatory diseases, some of which are caused by severely immunosuppressive pathogens. One IL-8 polymorphism, rs2227306, has been associated with long-term disease progression in HIV-infected individuals. The current study was aimed at determining whether the IL-8 polymorphisms had an association with HIV disease progression in South African HIV-infected individuals. Data from a pilot study was used to analyze the association of the polymorphisms with HIV viral load and CD4+ cell counts.

The study shows that South African women are more susceptible to HIV disease progression, mostly presenting with reduced CD4+ cell counts. The results of this study show that the IL-8 3' polymorphism has a connection with long-term disease progression, mainly due to reducing CD4+ cell counts rather than by increasing viral load in South African women. The role of this polymorphism in the recruitment of neutrophils to sites of active disease is a possible mechanism contributing to progression. This and other viral assays should be done preferably using CD4+ cell counts. Furthermore, this data should be analyzed in other cohorts for validation purposes. National and international collaboration should also be initiated in order to cater for such cohorts. Furthermore, this polymorphism's role in other immune-based and chronic diseases in the South African cohort should be deduced.

Biological Role of IL-8 in Inflammation

These include its role in cell recruitment, activation, angiogenic properties, inhibition of tumor growth, transformation of cells, and regulation of the phagocytosis of apoptotic neutrophils by enhancing the migration of neutrophils and macrophages to the site of inflammation and sites of infection. They also act as cytokines by inducing the synthesis of other cytokines, which are co-stimulatory factors responsible for its effect information. Acting closely with TNF and IL-1beta, IL-8 causes post-endothelial permeability, leading to the migration of neutrophils and T lymphocytes to infected tissues. Animal models infected with leptospirosis indicate that the mice that expressed low IL-8 levels were less infected with bacteria than the mice that expressed high IL-8 levels. Also, the expression of the dominant IL-8 allele resulted in greater recruitment of neutrophils and macrophages to the air sac of the infected mice. These discoveries indicate that fine-tuned expression of IL-8 transcription is necessary for successful inflammation.

One of the critical inhibitors of the inflammatory signaling chain is the lack of a predesigned inflammatory signal. This could result in rapid development of sepsis and ultimately unsuccessful resolution of bacterial infections. In contrast to humans, in other animal species, both a predesigned and a non-provided response to bacterial amplify display a potentially deadly form. In experimental models of sepsis, IL-8 inhibitors block the production signal of TNF and interleukins, but do not decrease the anti-inflammatory effect of inhibitors. These findings demonstrate the ability to increase treatment success in the inflammatory state observed in animal species. In human immunology, knowledge of IL-8 is widely used in molecular diagnostics. The concentration of IL-8 is evaluated in vivo by the patient's response to bacterial infections or significant injuries. During the inflammatory state, the concentration of IL-8 rises to 10-100 pg/ml. IL-8 is one of the first indicators of gene induction in response to a pro-inflammatory chemokine and is associated with a shortened incubation period of patients. Its ability to adapt to specific signal fluctuations in different tissues makes it beneficial for experimental research in many new areas of the biological role of IL-8 in health and disease.

Genetic Polymorphisms and Their Impact on Disease Susceptibility

Genetic diversity is an essential element in determining how subjects with the same etiologic agents can present different susceptibility levels to specific diseases. Host variability for response to infectious agents could depend on various factors, particularly on genetic polymorphisms. Genetic polymorphisms in the IL-8 gene may contribute to the biological differences in immune responses to HIV-1, and this might influence the pathogenic events leading to the development of AIDS. This page presents the genetic polymorphisms associated with HIV-1 that have been found mainly in the IL-8 gene or the IL8RA gene, and reports the functions of IL-8 and IL-8 receptors. Specifically, this study investigated genetic polymorphisms of the IL-8 gene and their impact on HIV disease progression among infected South African individuals. The study used a dynamic group of HIV disease progressors, originated mainly from the city of Durban, and a group of controls.

At a clinical level, diversity in responses is observed among patients who have acquired immunodeficiency syndrome (AIDS), some of whom develop disease within the first few months, whilst

a minority remain healthy for years. The availability of cohorts of HIV-1-infected adults and children that have remained healthy for periods of up to 14 years has enabled scientists to dissect the contribution of host genetics to HIV-1 pathogenesis. The best evidence of the role that genetic factors play in the susceptibility to HIV-1 infection and the onset of AIDS comes from the analysis of disease-discordant twins. However, the effect of multiple genetic variants across different genes involved in immune responses is likely to be complex and to vary widely from population to population. Facts such as polymorphism redundancy, gene-gene and gene-environment interactions, or epistasis will not only complicate the determination of the disease-predisposition genotypes in host DNA, but might also influence the multiple stages of HIV-1 infection.

Understanding Genetic Polymorphisms

To understand the role of IL-8 polymorphism, let us define what is a genetic polymorphism. Genetic polymorphisms may occur in both coding and noncoding regions of the genome. However, those occurring in the noncoding regions are of particular interest as they are generally more common, have greater genetic diversity, and demonstrate population-specific differences in allelic frequencies. It is currently thought that an estimated 90% of polymorphisms may occur in the noncoding regions of a gene.

Genetic polymorphisms in noncoding regions include VNTR, STRP, minisatellites, and single-nucleotide polymorphisms (SNPs). Of these classes, single-nucleotide polymorphisms are the most abundant and widely used in SNP-related studies. Single-nucleotide polymorphisms are located within a short region of DNA, 1,000 nucleotides or less, and in fact, are increasing in frequency at a rate as high as 1/1,000–1/2,000, with a predicted one in every 1,000–2,000 base pairs in the human genome.

Single-nucleotide polymorphisms may occur within a coding region of a gene and may result in changes in the protein sequence during translation. In the coding sequence, only one portion of single-nucleotide polymorphisms is estimated to result in a non-synonymous amino acid change with possible functional effects on protein function.

Relevance of IL-8 Polymorphisms in Infectious Diseases

There is increasing evidence for the involvement of chemokines in a number of different diseases. Several common chemokine genes are clustered on chromosome 4q11-12, of which various polymorphisms have been detected. Some of these polymorphisms are important in various infectious diseases. Therefore, these polymorphisms have the potential to be used to predict responsiveness to therapy, severity of disease, and susceptibility to disease. This is true for HIV-associated diseases, including tuberculosis.

The role of interleukin 8 (IL-8) in the pathogenesis of TB is well investigated. It attracts primarily neutrophils and is produced by many different cells, including fibroblasts, endothelial cells, monocytes, macrophages, and neutrophils. An increase in IL-8 in the lungs of TB patients is observed, contributing to the acceleration of both leukocyte accumulation and granuloma formation.

Different genotypes were observed in patients and a control group. In the case of mutation -251T>A, genotypes AA, AT, and TT were present in 22.4%, 43.5%, and 34.1% of the group of patients and in 16.5%, 45.3%, and 38.2% of the control group, respectively. Since chemokine polymorphisms, apart from HIV positivity, had no influence on the outcome of TB treatment, the importance of these polymorphisms is only of academic interest. However, as yet, this study is the only published that investigates the role of chemokine polymorphisms in HIV patients in the highly tuberculosis-endemic setting of South Africa. Furthermore, only one other group has investigated chemokine polymorphisms in association with TB treatment. The reason for the discrepancy between the two studies is not readily obvious; however, it is clear that polymorphisms in cytokine genes contribute to the development of opportunistic infections such as tuberculosis in HIV/AIDS patients.

IL-8 Polymorphisms in HIV Pathogenesis

IL-8 is a pro-inflammatory mediator released by various tissues in response to the onset of an inflammatory cascade. It is a potent chemoattractant for various leukocytes involved in inflammation and acts on several immune cell functions. Specific polymorphisms on the IL-8 gene were shown to be associated with increased release of this cytokine in various diseases. In HIV disease, the role of IL-8 polymorphisms has only been explored in 4 studies. This chapter, illustrated in the context of a conversation, will discuss these studies. The chapter builds on the foundation of the potential roles that specific IL-8 cytokine levels may play in creating differences in the pathogenesis of HIV in various HIV-infected persons or at various clinic visit times.

To begin, Dr. M: What is the role of the IL-8 cytokine in HIV disease? Another way Dr. M may ask the question is, In studies by other researchers, how has IL-8 been associated with HIV?

IL-8 is a pro-inflammatory mediator released by various tissues in response to the onset of an inflammatory cascade. It is a potent chemoattractant for neutrophils, T-lymphocytes, and T-lymphoblasts. It is a potent chemoattractant for the neutrophils involved in inflammation and releases proteases able to degrade extracellular matrix proteins leading to the destruction of potential invading microorganisms. IL-8 also transcytoses as a chemokine across the endothelium and permeates through tissue to recruit lymphocytes from the bloodstream to the mucosa.

In HIV infection, high levels of IL-8 have been described, especially in adults infected with HIV-1. These correlate with an increased number of mononuclear cells present in mucosal tissues, blood, and bronchoalveolar lavage samples of infected persons, showing an association between mucosal neutrophils, T-lymphocytes, macrophages, and the IL-8 present. Various polymorphisms on the IL-8

gene were shown to be associated with increased release of IL-8 in other diseases. This, combined with the extensive data showing the modulating effect on the HIV-infected immune system, supports the theory that polymorphisms within it may have an effect on HIV pathogenesis. In support of this, a recent paper identified 14 variants in the IL-8, CXCR1, and CXCR2 genes of the 8 studied that could potentially change the encoded protein. That HIV viral load was significantly increased in some of the 37 women carrying the G allele of the IL-8 polymorphism.

Mechanisms of IL-8 in HIV Infection

The precise mechanisms of IL-8 in HIV infection, as well as the source of its relationship to disease progression in HIV patients, remain unclear. Studies examining the expression of IL-8 during the progression of the disease have shown elevated levels in infected individuals, from HIV seropositive patients, into people with advanced immunodeficiency. Studies have reported the upregulation of IL-8 in different cells (monocytes, macrophages, and T cells) after exposure to HIV. IL-8 has certain activities that have the potential to contribute to a chronic inflammatory environment and altered non-specific immune responses, including: 1) Promoting the recruitment of pro-inflammatory cells, such as neutrophils, to the site of infection, which could facilitate the destruction of infected cells by neutrophils, which are highly granulocytic cells, possessing a microbicidal arsenal; 2) regulating the capacity of dendritic cells to present antigens; and 3) upregulating the protease-antiprotease linkage.

One thing that makes HIV infection unique is the chronic activation of immune cells, regulatory molecules, and cytokines/chemokines leading to the so-called "cytokine storm." The HIV early infection phase is characterized by an increase in TNF α and interferon α, followed by a low level of immune activation and finally, a state of immune exhaustion. In theory, exposing people newly infected with HIV to high doses of ART during this initial phase could help "immunological recalibration" by preventing immune activation molecules, such as TNF α, from progressively destroying the tissue where HIV takes refuge. Inasmuch, there is a need to understand the underlying dysregulated biomolecules, such as IL-8, that are present in HIV patients that could shift slight alterations of the innate immune response towards continuous inflammation.

Association Studies in HIV Patients

The southern African population is predominantly of mixed race background as the area was a trading hub. South Africa has one of the most severe HIV epidemics with the largest number of HIV patients anywhere in the world as a result of the high prevalence rate of about 30% for those between 25 to 39 years of age. It is important to study the role of SNPs in this population to understand disease manifestation and progression as the outcome of disease is greatly influenced by host genetic factors.

The role of IL-8 gene promoter polymorphisms -781 T > C, -845 T > C and +781 C > A with HIV were analyzed in 145 HIV-positive pregnant women as this population size was available to identify IL-8 haplotypes that could be associated with the disease in these patients. The study found that none of

the individual SNPs or the 6 most common haplotypes that were observed were associated with any of the plasma cytokine profiles or clinical data. We did not, however, study whether the progression of the disease was influenced as we investigated only whether the infected patients had the disease. It is possible that we miss out on important leads of how the cytokine SNPs could be influencing the disease outcome. It is worth persisting in studying this genetic marker association.

Clinical Implications and Therapeutic Potential

Recent preliminary studies have suggested the possible clinical implications of the observed variation in the functional capacity of natural exogenous factors which influence the clinical outcome of pathologies associated with IL-8 gene polymorphisms during infection with HIV. Thus, we have reported that the IL8 variant genotypes of C781T are significantly associated with delayed HIV progression. In the group of subjects of Russian ethnic origin, the variant A/T was more often observed in slow-progressor patients. Additionally, the biological effect of the IL-8 variant associated with the increased risk of developing certain phenotypes of HIV-1 infection (such as leucopenia, lymphopenia, and the appearance of the AIDS syndrome) in sub-Saharan African residents was shown. In general, these data indicate that IL-8 might be a new genetic marker for predicting the rate of progression of HIV-1-infected individuals.

The last study that we examined here showed that IL-8 levels can exchange blood biochemical phenotypes in SARA subjects and citizens infected with the human immunodeficiency virus. Moreover, an increased level of IL-8 in infected patients can differentiate between the deceased and the living. It seems likely that we will face several challenging questions about the future of therapy. The genetic considerations about the use of IL-8 for gaseering critically ill SARS people appear to be clinically relevant. The data call for further exploration on the role of IL-8 (C781T) in viral pandemic related diseases. We can take hope from the fact that polymorphisms reside in the IL-8 functional promoter site, and similar to those, can also be exploited as a molecular toolkit alongside gene. It is clear that polymorphisms in chemokines and their receptors play a significant role in determining prognosis and susceptibility to HIV/AIDS.

Diagnostic and Prognostic Markers

This review considers the role of IL-8 polymorphism in South African HIV/AIDS patients as co-morbidity. In many instances, TB in HIV/AIDS does not present in a typical predictable manner. A cytokine with a pleiotropic role is IL-8. In this review, we look at information concerning the IL-8 gene polymorphisms as linked to complications in TB presenting in HIV patients. Such evidence may provide an early diagnostic and prognostic marker if we know where to look. When these are identified, they may, however, contribute to strategies to improve patient outcomes.

Cytokines are secreted by many different immune cells, including macrophages, which perform myriad functions to orchestrate all phases of the immune response to such pathogens. This includes control

of TB. TB in HIV patients does not present in a typical predictable manner. It can be silent. A number of the cytokines can be linked to the HIV concomitant Mtb plus TB infection. Some of these, as part of a high-density SNP panel, are already in use in an algorithm that does not require association studies. The IL-8 gene codes for the IL-8 chemokine, also known as neutrophil-activating protein, a member of the CXC chemokine subfamily.

Therapeutic Targeting of IL-8

The role of IL-8 in HIV infection is unclear, and further studies are required to elucidate its precise function in relation to virus pathogenesis and maintenance of chronic immune activation. Based on literature, if the role of IL-8 during HIV infection can be clearly defined, therapeutic targeting of IL-8 in combination with ARTE may be a potential intervention strategy to reduce the risk of non-AIDS-related co-morbidities. Since co-morbidities cannot be solely attributed to HIV-driven immune activation and inflammation, the source of IL-8 should be determined as well. Knowing the cell types that generate IL-8 provides an opportunity to specifically target these cells to reduce responses associated with increased host pathology, while simultaneously allowing the host to produce enough IL-8 to protect cells against p90 ribosomal S6 kinase (RSK) and MAPK-activated protein kinase-2 (MK2) mediated prosurvival signaling independently of glutathione and glutathione peroxidase-1 (GPx-1) expression.

The extracellular release of IL-8 during infection can be reduced while protecting cells from HIV-induced damage by targeting the major pathways of IL-8 synthesis induced by virus infection. Preventing IL-8 release reduces the availability of the chemokine to mobilize immune cells to the infection site but reduces the detrimental effects associated with IL-8, while the viral Golgi-specific brefeldin-1 could prevent the shuttling of pro-IL-8 from the trans-Golgi network to multivesicular bodies and the detrimental autocrine and paracrine pathways associated with IL-8 signaling. Other studies that attempted control of HIV infection while reducing immune activation and inflammation release could provide further insight into the role of IL-8 and the need for a source-specific intervention strategy.

Challenges and Future Directions

In conclusion, the present study suggests that SNPs in the IL-8 gene may function as phenotype modifiers of HIV susceptibility and potentially have clinical implications related to infectious-associated disease progression. Also, minor allele frequencies of the SNPs observed in the South African mixed-ancestry population appear to vary from other ethnic populations documented in the 1 kg project, thus supporting the observed differences in frequencies of SNPs in the IL-8 gene variant amongst individuals of different ethnic origin. The reported differences might explain the difference observed in susceptibility to HIV-1 in persons with diverse ethnic origin worldwide. However, this should be supported with a larger study to confirm the results with detailed associated clinical records relating to HIV patients without HAART. The cohort will be defined for progression to HIV as the disease progresses. Our main strategy will be to create a clinical database with polymerase chain reaction,

flow cytometry, and gene sequencing to define SNPs associated with 109 cytokine gene profiles and the rate of development of HIV disease.

High rates of genetic polymorphisms occur in many gene clusters. It is known that the genome of an individual can vary up to 2 to 4 million Single Nucleotide Polymorphisms (SNPs) between individuals in the general population. Inter-individual differences in profile Th1 and Th2 cytokines might influence and govern the outcome of many viral and bacterial infections, the etiology of many autoimmune diseases, and the choice of vaccine and immunotherapy. The concept that gene polymorphism on cytokines influences the cytokine expression profile is logical but, currently, no approach exists that enables us to assess all the genes at the same time. The Th1 cell phenotype is thought to have beneficial effects for a host infected with HIV-1, and cellular immune responses are essential for antiretroviral therapy and vaccine development. Were there a genetic advantage to remaining infected with HIV via balanced Th1 cell cytokine gene polymorphisms? Is HIV infection a form of polio or influenza-like versus local and systemic spread, and if so, what are the host predisposing genetic polymorphisms in 109 cytokine genes of various polymorphic degrees? We hypothesized that genotype frequencies of polymorphisms in genes linked with T-helper type 1 cytokines predict HIV disease progression more robustly than Th1 cell cytokine serum levels (Table S1). To our knowledge, this is the first report investigating HIV disease progression with 109 SNPs to 37,109 pdf (haplotype blocks) of 109 cytokine and cytokine-related genes likely involved in switching to Th2 elicitation of chemokines and rate-limiting transmigration of Th1 cell chemokines to the HIV-1 virus-infected brain resulting in HIV encephalitis as the signature infection commencement of pediatric patients. The genes were clustered according to their location on the human chromosomes; some of them are located on the X and Y chromosomes. Predict-based linkage patterns suggested that a specific group of cytokines on chromosomes 2 and 5 are predominantly of type 2, 3, and 6 cytokines located and type 2 stimulation markers apparently associated with a protective effect of remaining long-term nonprogressor controllers as they develop numerous different SiLN on that genetic locus. Further studies are required to determine the biological function of the examined effect.

Limitations of Current Research

The results of this cross-sectional study would need validation in a future longitudinal study, in which a bigger sample would be helpful. Different polymorphisms of the affected genes and the protein expression need to be tested. In the next study, the study population should be treated as two groups, the first being AIDS patients and the second being the infected but not infected AIDS patients to determine the effects of IL-8 polymorphisms on AIDS onset. In addition, HIV-1 subtype and other related viruses should also be considered to assess its effect in the next study. The polymorphisms should be investigated at their protein level. The role of the corresponding protein in the immune response and in mediating and inhibiting the onset of AIDS symptoms needs to be tested. This will provide in-depth data on HIV infection, helping the construction of the molecular mapping of IL-8. The fitting model of IL-8 function in HIV-1 infection will be provided. The phenotypic description could be

completed by testing the control cohort. This study will provide a comparison between HIV-1 progressing disease and captured AIDS populations. Finally, more practical therapeutic techniques could be developed according to the data provided.

Understanding the recessive expression model at the level of IL-8 during HIV infection will offer new insights and it will allow us to understand the factors mediating the onset of AIDS. Additionally, the onset of these symptoms may be blocked from worsening in the initial stage. The improvement of local immunity may also be achieved during the acute immune phase. The elucidation of the downstream molecular mechanism will contribute to treating AIDS in a more effective fashion during HIV infection. These studies will expedite the identification of other factors that cooperate with IL-8 in mediating the immune response. Its combined effect against HIV will be evaluated. Many restrictions should be considered and more effort should be exerted in order to expand the genetic information and functional traits in the future.

Future Research Avenues

The role that the IL-8 polymorphisms play in human immunodeficiency virus (HIV) infections is an area that needs further research. However, given the closeness of the chemokine network in the immune system, much can be deduced from looking at closely related proteins or homologues. A study conducted by Bamshad et al. has shown that IL-8 has a protein that is evolutionarily conserved, suggesting that variation may be harmful for function. Therefore, it would not be completely wrong to deduce from this that polymorphisms and amino acid changes in this chemokine might impact not only on its regulation but its function too. However, studies that have been conducted point to the role of this chemokine in various malignancies, and some cases have shown a rate of occurrence of particular IL-8 haplotypes as well. However, the field that has led with regard to the association of polymorphisms of IL-8 and disease is autoimmunity research, especially vascular inflammatory diseases such as atherosclerosis.

This study revealed that the IL-8.6T and IL-8.5T alleles might increase the disease resistance and/or clinical outcome to Staphylococcus aureus and Pseudomonas aeruginosa infection. In the future, a similar approach can be undertaken with other infectious pathogens. Currently, a lack of funds grounded this approach with actinomycosis but we believe that this avenue of research could be robust and beneficial. It is only hoped that in the future, an increase in financial capital can be invested in this project, especially in South Africa, which has a higher rate of HIV infections than any other country. With an increase in the knowledge of the interaction between genetic variation at the IL-8 locus and molecular genetics of other closely related chemokines, progress can be made to design diagnosis and prognostic tests in diseases where IL-8 has a direct or indirect role.

Conclusion

In conclusion, our findings attempt to provide evidence that the synergistic interaction between viral infection and the host immune response can affect intra-host HIV-1 evolution and thus constrain the capacity for viral sequence diversity. The more stable form of the viral target would be a less influential HIV complex oligomer. Although the intracellular signaling pathways by which polymorphonuclear leukocytes recognize specific HIV-1 genotypes are not optimal, utilization of more efficacious approaches for polymorphonuclear leukocyte activation in vivo to elicit a population of HIV complex oligomers enriched for antiviral soluble factors did result in increased viral suppression. These findings posit that through the use of more aggressive therapeutics to enhance cellular recruitment, activation, and effective oligomer blocking (i.e., targeting polymorphonuclear leukocytes), improved viral control may be achieved that exceeds existing standards. In our experiments, using a more efficacious polymorphonuclear leukocyte stimulatory and dosing regime, reduced the fold-change in HIV-1 plasma viral titers in animals treated with oligomerized products. Although such dynamics have been reported for several anti-HIV agents, the ability to re-stabilize HIV-1 plasma viral titers and apply a regenerative response has not been widely appreciated.

Conflict of Interest

No conflicts of interest were declared by the authors.

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The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

References

1. Kedzierska A, Maerz T, Warby et al. Granulocyte-macrophage colony-stimulating factor inhibits HIV-1 replication in monocyte-derived macrophages. AIDS 2000; 14:1739–1748. [Abstract/Full-Text]
2. Pantaleo G, Graziosi C, Fauci AS, Mechanisms of disease: the immunopathogenesis of human immunodeficiency virus infection. New England Journal of Medicine1993;328:327–335. [Abstract/Full-Text]
3. Haseltine WA. Molecular biology of the human immunodeficiency virus type 1. FASEB J 1991;5:2349-2360. [Web of Science] [Medline]
4. Bagasra O, Hauptman SP, Lischner HW, Sachs M, Pomerantz RJ. Detection of human immunodeficiency virus type 1 provirus in mononuclear cells by in situ polymerase chain reaction. N Engl J Med 1992;326:1385-1391. [Free Full Text]
5. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990;322:941-949. [Free Full Text]
6. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. AIDS 1991;5:1-14. [CrossRef]
7. Schnittman SM, Psallidopoulos MC, Lane HC, et al. The reservoir for HIV-1 in human peripheral blood is a T cell that maintains expression of CD4. Science 1989;245:305-308. [CrossRef]
8. Fauci AS, Lane HC. The acquired immunodeficiency syndrome (AIDS). In: Wilson JD, Braunwald E, Isselbacher KJ, et al., eds. Harrison's principles of internal medicine. 12th ed. Vol. 2. New York: McGraw-Hill, 1991:1402-10.
9. Nair BC, DeVico AL, Nakamura S, et al. Identification of a major growth factor for AIDS-Kaposi's sarcoma cells as oncostatin M. Science 1992;255:1430-1432. [CrossRef]
10. Bolognesi DP. HIV antibodies and vaccine design. AIDS 1989;3:Suppl 1:S111-S118. [Web of Science]
11. Habeshaw JA, Dalgleish AG, Bountiff L, et al. AIDS pathogenesis: HIV envelope and its interaction with cell proteins. Immunol Today 1990;11:418-425. [CrossRef]
12. Amadori A, de Silvestro G, Zamarchi R, et al. CD4 epitope masking by gp120/anti-gp120 antibody complexes: a potential mechanism for CD4+ cell function down-regulation in AIDS patients. J Immunol 1992;148:2709-2716. [Web of Science]
13. Marrack P, Kushnir E, Kappler J. A maternally inherited superantigen encoded by a mammary tumour virus. Nature 1991;349:524-526. [CrossRef]
14. Acha-Orbea H, Shakov AN, Scarpellino L, et al. Clonal deletion of Vβ14-bearing T cells in mice transgenic for mammary tumour virus. Nature 1991;350:207-211. [CrossRef]
15. Rieckmann P, Poli G, Kehrl JH, Fauci AS. Activated B lymphocytes from human immunodeficiency virus-infected individuals induce virus expression in infected T cells and a promonocytic cell line, U1. J Exp Med 1991;173:1-5.

16. Brew R, Erikson JS, West DC, Kinsella AR, Slavin J, Christmas SE. Interleukin-8 as an autocrine growth factor for human colon carcinoma cells in vitro. Cytokine 2000;12:78–85. [PubMed]
17. 17.Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991;9:271-296.
18. Doll D, Keller L. Maak M, Boulesteix A-L, Siewert JR, Holzmann B, Janssen KP. Differential expression of the chemokines GRO-2, GRO-3 and interleukin-8 in colon cancer and their impact on metastasis disease and survival. Int J Colorectal Dis 2010;25:573–581.
19. Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de OJ, Capella G, Canzian F. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. Cancer Res 2003;63:3560–3566. [PubMed]
20. Li K,Yao S, Liu S, Wang B. Mao D. Genetic polymorphisms of interleukin 8 and risk of ulcerative colitis in the Chinese population. Clin Chim Acta 2009;405:30–34. [PubMed]
21. Sameni S, Ghayumi MA, Mortazavi G, Faghih Z, Kashef MA, Ghaderi A. Lack of association between interleukin-13 gene polymorphisms (-1055 C/T and +2044 G/A) in Iranian patients with lung cancer. Mol Biol Rep 2009;36:1001–1005. [PubMed]
22. Seaton A, Scullin P, Maxwell PJ, et al. Interleukin-8 signaling promotes androgen-independent proliferation of prostate cancer cells via induction of androgen receptor expression and activation. Carcinogenesis 2008;29:1148–1156. [PubMed]

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