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MODULATION OF THE IMMUNE SYSTEM AGAINST THE CCR5 Δ-32 VARIANT IN HIV INFECTION

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ABSTRACT

After the isolation of the HIV virus by the virologist Luc Montagnier, types I and II were characterized with some peculiarities of behavior and geography. AIDS is a disease that affects all races, social classes, sex, religion and sexual orientation. It is expressed as the viral load increases, depressing the immune system propitiating opportunistic pathogens. Responsible for entry of the viral genome into the cells, this genetic mutation was named CCR5Δ-32 for the loss of 32bp encoding the wild-type CCR5. This genetic variant results in the production of non-functional CCR5 coreceptors, the CCR5 / CCR5 allele is predominant in the population homozygous individuals who inherit both copies of the parent CCR5Δ32 mutant gene have an allelic formation (CCR5Δ32 / CCR5 Δ-32). These appear to be highly resistant to the HIV virus. Heterozygous individuals who inherit only one copy of the mutant gene CCR5Δ32, have an allelic formation (CCR5 / CCR5Δ32), however, they will be infected but the evolution to the disease is delayed in relation to people who have two copies of CCR5 gene. The objective of the projectis to discuss the interaction of the coreceptor with the HIV virus by reviewing theories that explain the possible appearance of the mutation, physiological aspects of the normal gene and the mutant gene. It can be concluded that the spotlight is on the CCR5 chemokine receptor, which is the main protagonist of the elevation of HIV / AIDS infection. Efforts to eliminate HIV / AIDS are succeeding, opening up prospects for curing and immunological protection in drug development, engineering and gene therapy, with the CCR5 Δ-32 polymorphism basilar.

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INTRODUCTION

HIV (Human Immunodeficiency Virus) is a retrovirus that is part of the "Retroviridae" family and was first isolated in 1983 by French virologist Luc Montagnier and his team. This virus, which causes AIDS (Acquired Immunodeficiency Syndrome), has its primary genome composed of a single strand of RNA, which later inside the cell will be transformed into viral DNA by the action of the enzyme reverse transcriptase, which is part of its genetic material with two more enzymes: protease and integrase. Transmitted by blood, blood products, sexual contact, use of contaminated needles, mother to child at birth, transplacental or breastfeeding (Wiethäuper, 2003).

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Previously, HIV was known as HTLV-III (Human T-cell lymphotropic virus type III). Currently, there are two types: HIV-1, which is the most common among those infected, and HIV-2, which is found mainly in Africa. AIDS in HIV-2 has a peculiarity: its progression is slow in relation to HIV-1(Silva, 2012).AIDS has as its etiological agent the HIV virus and compromises the entire immune system of the infected individual. It leads to an immunodepression and propitiates opportunistic diseases that are likely to arise at large replication steps (increase in viral load), which can lead to serious infections, neoplasias and even compromise the Central Nervous System. Global statistical data from UNIAIDS (Brasil, 2015) show that by 2014 there were already 34.3 to 41.1 million people living with HIV worldwide. In Brazil (Brasil, 2017b), from 1980 to 2016, 842.710 AIDS cases were identified. In the early 80s, when the disease appeared in Brazil, a very high number of HIV / AIDS

individuals were found among male homosexuals, generating an exponential growth of prejudice, both by sexual orientation and by disease. It was then one of the biggest epidemics in the world. It was not a disease of a single social group but a disease that tests the limits and efforts of the whole world to fight against an infecting particle (Brasil, 2017a).Scientific studies in genetics, microbiology and epidemiology have improved their research by analyzing the behavior of the HIV virus against the population of infected individuals seeking the susceptibility or partial resistance to the virus. Research on uninfected individuals resulted in the discovery of the infection process by means of immune defense cells: CD4 + T lymphocytes and tropic macrophages. Their receptors, followed by two transmembrane coreceptors, respectively: CD4 + T, CCR5 and CXCR4, both cofactors that facilitate the insertion of the viral genome into the cell cytoplasm, expressed in the CD4 + T lymphocytes, and CCR5 that will also be present in the tropic macrophages. This important step will greatly assist in the evolution and consolidation of parameters for HIV infection and AIDS progression (Alkhatib, 1996).

Liu et al. (Liu, 1996) found that two individuals were highly resistant to HIV infection after being exposed to multiple HIV-1. These were tests performed in vitro, fully protecting human dignity and the health of these individuals in an inviolable way. With the incessant search of the main cofactor of this resistance, they discovered a genetic mutation, without phenotypic connections, treating a polymorphism in the genes that express the CCR5 coreceptor of these two individuals where they have inactive CCR5 transmenbranial coreceptors. This mutation was called the CCR5Δ32 variant, which prevents the fusion of lymphocytic and macrocytic cell membranes with HIV virus, since the virus can not release its genetic material into the cell cytoplasm, it will not replicate and these cells to death. The first genotype research was carried out in 1996, the year of several important discoveries for science, where it was found that the mutant allele CCR5Δ32 has a high frequency (0.092%) in the caucasian population, absent in the Japanese / Asian population and in the black population of central and West Africa[8]. A second survey was conducted in 1998, which revealed that individuals from Eurasia have 0% to 14% frequency for CCR5 Δ-32, being absent in East Asian, African and American ethnic individuals (Stephens, 1998).

The Δ-32 CCR5 variant is a genetic polymorphism in homozygous individuals who inherit from each of their parents a mutant gene forming a CCR5 Δ-32 / CCR5 Δ-32 allele. It is characterized by the deletion of 32 base pairs expressing the wild-type (normal) CCR5 co-receptor present resistance to HIV virus infection. Heterozygous individuals are those that only receive a mutant gene from one of their parents with a CCR5 / CCR5 Δ-32 allelic conformation. In these, there will be a delay in the progression of AIDS (Dean, 1996).The CCR5 coreceptor is one of the main cofactors responsible for the entry of the viral genome into CD4 + T lymphocytes and tropic macrophages, but its key role is to be a chemokine receptor. CCR5 is part of the extensive family of transmembrane receptors coupled to G proteins. Chemokines are small molecules of cytokines that participate in the process of trafficking cells from the immune system to the site of inflammation or infection and participate in the process of embryogenesis. The present work sought the relationship between the CCR5Δ32 variant and resistance in HIV infection (Raz, 2009 and Galvani, 2003).

Review

The first theory for the emergence of CCR5 Δ-32 dates back to the XIV century when the European continent was hit by theblack plague caused by the bacterium *Yersiniapestis*, which may have exerted an intrinsic pressure on the allelic formation of CCR5 Δ-32 / CCR5 Δ-32 leading to a higher frequency of that allele. According to Galvani (2004) and Slatkin (EUA, 2017), with the lack of probationary evidence to support the black plague theory, they think that the smallpox event in the XVII - XVIII century would be the most probable, since they used a population genetic pattern that includes a transient parameter of time, correlated closely with the age of different diseases. By using the pattern of population genetic structure, they were able to cross information important to the study developed such as: parameterization of the age group, historical data, burial certificates and statistical data about the population. Thus, performing an evaluation of the standard behavior of diseases to analyze the performance of the results between the plague of the black plague, including also the great London plague of 1665-1666, versus the records of people who died from smallpox between 1770 and 1812 in York, England, the lethality ratewas approximately 30%.

These relevant research results, with applications of calculations, formulas and according to the Hardy-Weinberg indices, have concluded that: 1º the change in "p" (final frequency of the resistant allele obtained until the end of the simulation) to periodicity of an allele with preponderant tenacity resulting from pest mortality, in relation to the black plague period in Europe, impels p <0.8%; and 2º the change in p, with periodicity relation to a preponderant tenacity allele, formed by smallpox mortality, would be a total of 680 years for "p" to achieve 10%.HIV and Orthopoxvirus (smallpox virus) show similarities in behavior, in the case of viral infection, the two uses practically the same vectors of our immune system, which would be: tropic macrophages and CD4 + T lymphocytes. They also use the same CCR5 coreceptor, which would be totally probable the explanation for a non-deleterious evolutionary mutation, thus expressing the CCR5Δ32 polymorphism. This contrasts with the hypothesis of bubonic plague, which has its etiological agent Yersiniapestis, with a totally different behavior from that of the HIV virus (Silva, 2004 and EUA, 2017).A mapping of the population periodicities of the CCR5 Δ-32 allele was performed comprehensively in Europe, where high periodicities were observed in northern Europe, and they were slowly shortening to the south, and no allelic formations were confirmed CCR5 Δ-32 / CCR5Δ -32 in other continents, countries and ethnic groups of the world, restricting themselves in a picturesque way, only in the European territory. Historical surveys indicated that the CCR5Δ32 polymorphism was caused by the Nordic people in which periodicity is high until today. They have been migrating little by little in century VIII and X, as the Vikings migrated towards the south (GUERREIRO, 2011 and Hutter, 2009).The wild-type (normal) CCR5 gene is identified on chromosome 3 at the locus (site of the chromosome where a gene is located) p21.31 (Benkirane, 1997). Wild CCR5 consists of 352 amino acids, with a molecular weight of approximately 40KDa, having seven transmembrane sites, the intracellular part consists of the C-terminal zone, which is composed of three intracellular loops responsible for the translation of the signal, and another extracellular part composed of the N-terminal zone containing 3 extracellular loops that operate on the

chemokine bonds (Brasil, 2012) (Figure 01). The CD4 + T lymphocyte or tropic macrophage cell must be subjected to an identification of its genetic material (genotyping), PCR amplification (chain reaction)and an identification by agarose gel electrophoresis, highlighting chromosome 3 at the p21.31 locus, will reach a mean with fractions of 200bp for the CCR5 allele (wild) and 168bp for the CCR5 allele Δ-32, however the values of the CCR5 allele base pairs and the CCR5 Δ-32 allele may vary due to the kits and software used (Brasil, 2002). (Figure2).The loss of 32bp (32 base pairs) gives rise to an incomplete protein, which will be retained in the endoplasmic reticulum and cannot be expressed on the surfaces of the cells and is now unable to intermediate the entry of the viral genome into the cell cytoplasm (GUERREIRO, 2011 and Hutter, 2009).

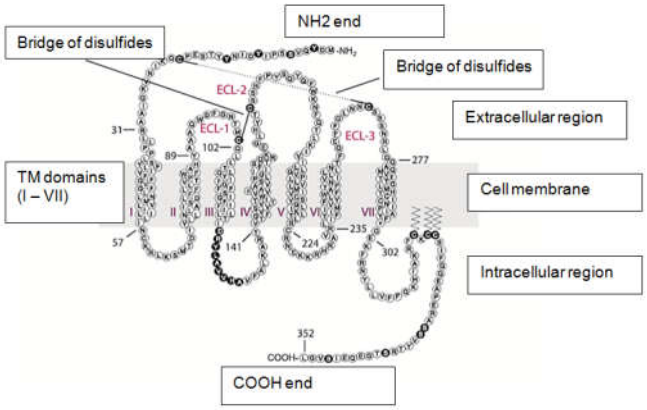

Figure 1. Scheme of the structure of the human chemokine receptor, CCR5. In black, the important amino acids in the interaction with the chemokines and the triggering of the intracellular response are marked. ECL, extracellular loop (the extracellular loops are numbered from 1 to 3); TM, transmembrane region (transmembrane regions are indicated by Roman numerals from I to VII)

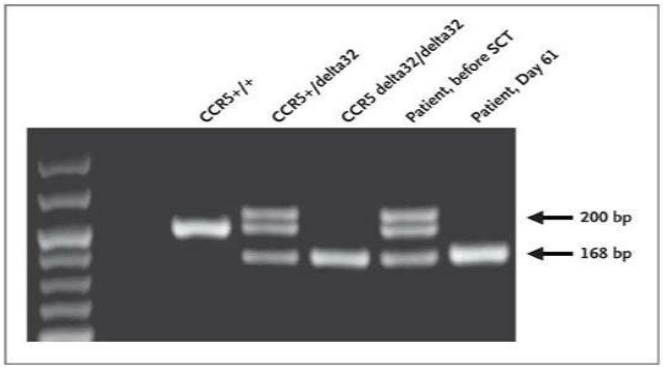

Figure 2. CCR5 electrophoresis in a patient after 61 days

Wild CCR5 first passes through the endoplasmic reticulum to be matured, where phosphorylation occurs and also a multimerization (arrangements of quaternary protein structures, formed from its subunits). Shortly after this post-translational chain, the wild-type CCR5 will be actively expressed on the cell surface. The same process will not occur with the CCR5 Δ-32 variant, where it will lose its phosphorylation capacity but will maintain its multimerization efficiency, which will confer the ability to interact with the wild CCR5 in its passage through the endoplasmic reticulum, causing CCR5 / CCR5 Δ-32 to delay AIDS for a few years[20].

The first step in the HIV life cycle is the connection of the viral surface with the cell surfaces, the next step is the insertion of the viral genome, which involves a cascade of molecular interactions between the viral envelope glycoproteins the primary (CD4 +) receptor and the CD4 + T-lymphocytes and the tropic macrophages (CCR5 / CXCR4). The gp120 subunit of the HIV virus envelope protein binds first to the primary receptor (CD4 +) of lymphocytic and macrocytic cells, leading to a change in the configuration of gp120, which allows it to bind to the CCR5 / CXCR4 coreceptor. Soon after binding to the CCR5 / CXCR4 co-receptor, a change in the configuration of the HIV virus gp41 subunit is triggered, leading to the incorporation of its viral fusion terminal peptide into the host cell membrane. This fusion results in the denudation of the virus, allowing the insertion of the viral genome into the cytoplasm of the cell (Stephens, 1998; Dean, 1996 and EUA, 2017). CCR5 and CXCR4 coreceptors are part of a wide family of G-coupled receptor receptors. More than a dozen chemokine receptors have been described, but only CCR5 and CXCR4 play the leading roles in HIV virus infection, since all HIV strains use these two co-receptors to incite increased viral load (Silva, 2012 and Brasil, 2017b; Alkhatib, 1999).There is a concept that coreceptors play a significant role in the evolutionary stages of disease, different strains of HIV vary while their abilities to use different co-receptors to enter cells. Some strains of HIV use only CCR5 coreceptors, others only use the CXCR4, while other strains are known as double tropism, because they use the two co-receptors (Galvani, 2003; Benkirane, 2006 and Brasil, 2002).

During the initial phase of infection, viruses using CCR5 are prevalent in most patients. In the intermediate phase of infection, HIV strains capable of using CXCR4 appear regularly because strains previously used had only the CCR5 coreceptors spend a long period of time without harming them, producing billions of virions per day, occultly waiting to leave, while their gp120 subunits undergo a metamorphosis to effectively bind the CXCR4 coreceptors. In the late phase of the infection there is a vertical increase of the double tropism stapes (GUERREIRO, 2011 and Hutter, 2009).Unlike reverse transcriptase inhibitors, protease and integrase inhibitors, they function within infected cells. Coreceptor antagonists work outside of the cells, therefore, coreceptor antagonists are classified as "inhibitors of entry". The mechanism of action of the antagonists of coreceptors are of genuine importance in relation to other antiretrovirals, since they only bind the host cells (Brasil, 2017 and Samson, 1996). This *sui generis* organization, demonstrates the beneficial clinical benefits of highly active antiretroviral therapy (HAART), all this bone of rigorous research, in the most diverse fields of science in relation to the CCR5 Δ-32 variant, culminated in the first antiretroviral entry inhibitor: Maraviroque, inspired by the resistance of the genetic mutation of the CCR5 Δ-32 allele (Huang, 1996).

Epidemiological data of Brazil: The researches were carried out in the South, North and Northeast regions in the respective cities and states: Joinville (Santa Catarina), in two amerindian settlements (natives of the American continent), Tiriyó (Pará), Waiampi / Wajãpi (Amapá) and Salvador (Bahia). All this scenario gives us a wide miscegenation of ethnic groups, which makes it more difficult to find the origin of the periodicity of the CCR5 Δ-32 allele; in this specific survey a

Table 1. Division of the three allelic formations in the Brazilian population: wild, heterozygous and homozygous, plus "df" (degree of freedom)

Region / city	Population	*n*	Genotipcs CCR5/CCR5 *n* (%)	CCR5/Δ-32 *n* (%)	Δ-32/Δ-32 *n* (%)	Alelic frequency Δ-32	X^2 (df=1)	P value
South/Joinville	Blood donors	99	87 (87.9)	11 (11.1)	1 (1)	0.065	1.022	0.20< P<0.50
Northest/Salvador	HIV Negative	549	520 (94.7)	29 (5.3)	0 (0)	0.026	0.404	0.50<P<0.80
	HIV Positive	113	103 (91.2)	10 (8.8)	0 (0)	0.044	0.242	0.50< P<0.80
North/Ameríndics	Tiriyó	180	180 (100)	0 (0)	0 (0)	0.0	-	-
	Waiampi/Wajãpi	221	221 (100)	0 (0)	0 (0)	0.0	-	-
Total		1.162	1.111 (95.6)	50 (4.3)	1 (0.1)	0.022	0.033	0.80<P <0.95

total of 1,162 blood samples were collected, in the most diverse profiles among the donors (Brasil, 2014 and Brasil, 2017a). In the southern region of Joinville, 99 blood samples were collected from individuals who were descendants of Germans, without HIV / AIDS, or any other STI (Sexually Transmitted Infections). 180 samples from the northern region of the indigenous peoples of Tiriyó and 221 Waiampi / Wajãpi samples; 549 samples from HIV negative individuals, plus 113 samples from HIV positive individuals in Salvador (Table1). The samples were collected between the years 1997 to 2001, all the samples collected underwent rigorous screening procedures, which were submitted to diagnostic testsELISA and Western Blot, flow cytometry, viral load measurement tests if the subject was diagnosed with HIV-1 / HIV-2 and the Hardy-Weinberg calculations and formulas were applied to give us the final frequency of the CCR5 Δ-32 resistant allele (Costa, 2009).

METHERIALS AND METHODS

This project was structured from a set of qualitative literary works about the "CCR5Δ-32 variant in the resistance of HIV infection." The project was based on an analysis of researches developed in the scientific field, to prove results that have helped science over the years, in the hope of elucidating the behavior of the HIV virus in the face of a genetic evolution that invigorates for possible cure of the disease. The research consists of investigating studies published in reliable databases, building a clear knowledge in the search for a logical and universal reasoning. In the same way, the objective was to comprehensively approach the acquired knowledge, managing to put into practice a constructive academic-scientific point of view. The data collection period was from 08/01/17 to 01/03/18 to gather published articles until 2017. Due to the shortage in the last 10 years of publications of substantial scientific articles and consistent with the object of research, the analysis of the last 25 years is taken as the time frame. Identifications were carried out in reference databases such as: MEDLINE (National Library of Medicine), BIREME (Latin American and Caribbean Center for Health Sciences Information), SCIELO (Scientific Electronic Library Online) and PUBMED (Public Medline). English and Portuguese languages, as well as in renowned scientific journals, that can contribute, adding more value to the article. In order to substantiate the maximum number of relevant articles, keywords such as: (Allele, CCR5, CCR5Δ32, Corrector, Gene, HIV, Mutation, Polymorphism, Chemokines, Receptor, Variant) were used in the search tool. In the construction and organization of the information of the articles found, it was extremely important to safeguard the authorship of the publications, without infringing in any way the laws of Intellectual Property and Copyright, always following a theme that corroborates the authenticity of scientific knowledge.

DISCUSSION

It is important to point out that a genetic mutation derives from a series of factors, and among them, the genetic variant can be emphasized, not being at first possible to be classified as beneficial or malefic, until, because, factors added to the genetic heritages of an individual, throughout life will alter the conformations making survival difficult. In addition, the main fact that will specify the nature of a genetic variation is its impact on reproduction (Yang, 2003). In general, antagonistic pleiotropy demonstrates that genes present in various animal species are beneficial in youth and have a negative impact at the end of life. The advantages can be accounted for by the carriers. The best known are the heterozygosity of the S allele for hemoglobin in regions with malaria and individuals who have two altered copies of the CCR5 gene - with a 32-base pair deletion (CCR5Δ32) that makes the carriers resistant or partially immune (HIV-1). If the individual has a copy, since the virus depends on this protein to infect the cells (Nazari, 2008).Among the different possibilities of polymorphisms, it is believed that this genetic variable can offer better performance and more than 200 of them are currently known, although their specific contribution and same relevance are still debated. An example of this type of polymorphism associated with angiotensin-converting enzyme, a protein bound to the physiological renin-angiotensin system that is apparently associated with physical resistance.

The D allele of the angiotensin converting enzyme (ACE) is associated with elevated serum and tissue levels of ACE, increased production of a vasoconstrictor molecule called angiotensin II, and reduction of the half-life of a vasodilatory substance called bradykinin. Individuals homozygous for this allele appear to have a worse prognosis for various cardiac and renal conditions. Meanwhile, possession of the I allele appears to correlate with increased performance in elite athletes, especially in endurance events such as long-distance runners, rowers and mountaineers. However, there is still some controversy about these findings and what can be concluded through them (Grossman, 2016).Another example worth mentioning, however, is the ACTN3 gene for which there is growing evidence that it has a strong influence on athletic performance, and apparently is involved in a type of evolution between speed and physical endurance (Yang, 2003).However, sometimes the immune system is required to participate in the combination process and biological changes with respect to

adaptation and resistance to viral loads. With new procedures in gene therapy, using intracines (intracellular chemokines), intracorporal (single chain intracellular antibodies) and ZFN (Zinc Finger Nuclei), orchestrating the functions of RNAs (messenger and transporter), preventing the expression of the CCR5 coreceptor in the membranes (Allers, 2011).

The maintenance of the human immunodeficiency virus occurs when the immune system is destroyed, when CD4 + T lymphocytes are destroyed, especially memory activated CD4 + lymphocytes. The entry of the virus into the CD4 + T lymphocyte depends on the interaction with the coreceptors, the most common being CCR5 and CXCR4 (Mehandru, 2004). Blocking the interaction of HIV with these co-receptors has been shown to inhibit virus replication in vitro in which homozygous cells presenting the genetic variant CCR5Δ32 and lacking functional CCR5 cell expression, being resistant (CCR5-HIV) infection (Sora, 2002). Allers et al. (Alvarnas, 2017) described the long-term follow-up of an HIV positive patient treated with allogeneic hematopoietic stem cell transplantation (HSCT) from a CCR5 Δ-32 / CCR5 Δ-32 donor. The patient in question remained without any evidence of HIV disease for 45 months of follow-up, even without the use of antiretroviral therapy. The cells of the immune system, the transplanted CD4 + T lymphocytes reached normal values in the peripheral blood, characterized by complete chimerism (100%), demonstrated absence of CCR5 expression.

In addition, Mehandru et al. (Badia, 2014) demonstrated by means of immunohistochemical techniques the presence of CD4 + CCR5 T lymphocytes in the intestinal mucosa, one of the main natural reservoirs of CD4 + T lymphocytes. This observation is fundamental to document the anti-HIV potential of HSCT, since the intestinal mucosa is also one of the main viral reservoirs, and the immunological reconstitution in this tissue is necessary for its eradication, a fact documented by the absence of viral copies in the intestinal tissue samples from the transplant.Sora et al. (Lopalco, 2010)suggest that allogeneic stem cell transplantation, combined with model chemotherapy, HAART, and with a greater control of graft-versus-host disease (GVDH), with several classes of drugs involved, such as corticosteroids, antibiotics, antifungals and immunosuppressants may be a therapeutic option for satisfactory results against HIV. This idea reinforces the importance of the development of gene therapy studies that aim to offer the HIV resistance to infection. The study published by Alvarnas et al. shows that about 10% of northern Europe has the mutant CCR5 Δ-32 gene, with an approximate index of 3% of homozygous individuals, although in the Asian and African continent this protection was not quantified by the low number of individuals presenting this polymorphism. In light of the advances made by advanced technology in the field of genetics, the CCR5Δ-32 variant can be employed in stem cell transplantation, transposing its resistance to HIV to other individuals. A patient in Berlin, Germany, was the recipient of stem cells from a homozygous donor for CCR5Δ-32, before the process his lymphatic system underwent irradiation, throughout the process he had a recurrence, soon after was submitted to a new infusion of the same previous grantor, after a certain period a broad analysis was performed in several organs and tissues of the patient, showing no evidence of DNA and RNA of the HIV virus, remaining without HAART, without any evidence after 8 years from the transplant. In the endless search for expansion of new techniques in engineering and gene therapy as opposed to the HIV virus, a new in vitro experiment using ZFN (Zinc Finger Nuclease) was used in human cells and mice to edit the CCR5 gene, aiming to get as close as possible to the 32bp deletion of CCR5Δ-32, maintaining the same polymorphism efficiency in designing HIV-resistant cells; reducing the off-target effects, without interfering with the CD4 + receptor and CXCR4 gene expression, resulting in an artificial mutant allele ZFNCCR5Δ32 / ZFNCCR5Δ32. Through the segmentation of the studies developed at the heart of CCR5 and its CCR5Δ32 mutation, a clinical study proposes the creation of the HIV vaccine using anti-CCR5 antibodies, where they recognize the N-terminal zone, dividing into extracellular loop (ECL-1) and other binding-only (ECL-2) antibodies, causing a permanent negative readjustment, severely competing with the glycoprotein 120 (gp120) of the HIV virus envelope, curbing the viral infection. With the improvement of this research, human monoclonal antibodies (PRO140 and HGS004), which are able to prevent viral infection and at the same time preserve the chemotactic activity of CCR5 have been elaborated.

Conclusion

In a complete aggregation of articles analyzed by this study, most of them have the CCR5 chemokine receptor searchlight, which is the main protagonist in the rise of HIV / AIDS infection. Based on these researches, we can verify that the procedures and methods for the eradication of HIV / AIDS are achieving successful results exhibiting real cases of patients who have reiterated the strength and robustness of their immune systems. It opens a perspective of healing and protection in the immunology conjuncture, in the development of new drugs, engineering and gene therapy, with the CCR5 Δ-32 polymorphism basilar.

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