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Genetic Diversity within Chemokine Receptor 5 (CCR5)

for Better Understanding of AIDS

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Abstract

The chemokine receptor 5 (CCR5) serves as a co-receptor for the human immunodeficiency virus-1 (HIV-1) that facilitates viral entry into cells. Individuals who are homozygous for a 32 bp deletion of the CCR5 gene are resistant to infection, while for heterozygote carriers their HIV disease progression is delayed. To understand the variable HIV-1 disease course that still exists among rare carriers of this deletion, studies have focused on polymorphisms of the CCR5 gene. Nine different CCR5 human haplotypes (HH) were defined as HHA, HHB, HHC, HHD, HHE, (HHF*1 and HHF*2), and (HHG*1 and HHG*2). Less is known about the effect of these polymorphisms during combined antiretroviral treatment (cART) as the influence of the CCR5 haplotypes on the treatment outcome was not studied extensively. We have reported four novel indels and two new polymorphisms from one ethnic adult Omani population in the 5'UTR of the CCR5 gene. Genetic diversity of the CCR5 haplotypes among acquired immunodeficiency syndrome (AIDS) patients receiving cART and healthy people is discussed. Our results demonstrated the importance of genetic diversity in the CCR5 gene and clearly indicate the importance of understanding the pattern of genetic diversity and its implications for better understanding AIDS.

Keywords: CCR5, genetic, diversity, polymorphism, AIDS, HIV-1, antiretroviral treatment

1. Introduction

Human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS) [1]. Two types of HIV exist: HIV-1 which is the most common virus worldwide and HIV-2 that is less common and mainly restricted to East Africa. HIV targets and destructs the CD4⁺ T-helper helper cells, one of the most important cells of the immune system. AIDS is a major global health emergency. Not all individuals infected with HIV-1 will progress at the same rate toward the terminal stages of the disease. It is well known that HIV-1-infected patients on combined antiretroviral therapy (cART) do not respond equally to treatment, despite proper compliance to therapy.

Accumulating evidence, over the years, strongly suggests the involvement of host genetic factors in the HIV-1 infection and rate of disease progression [2–4]. Therefore, intensive research efforts were directed toward defining the host genetic factors that may influence HIV-1 infection, virus transmission, and disease progression. Studies were focused on exploring the interaction between host genetic factors and the immunological and virological parameters [4, 5]. This will allow a better understanding of the immunopathogenesis of HIV-1 infection and disease outcome.

Candidate gene analysis approach was initially used to test for association of genetic variants with HIV-1 acquisition and disease rate. These variants were already known or suspected to influence HIV-1 infection and rate of disease progression. Studies suggested several important immune response genes to be associated with HIV-1 pathogenesis [6–8]. This includes genes that regulate HIV-1 recognition and entry such as chemokine co-receptors, human leukocyte antigens (HLA) type, T-cell receptors (TCRs), killer cell immunoglobulin-like receptors (KIRs), and toll like receptors (TLRs). These also include genes that are involved in immune cell trafficking such as chemokine ligands and adhesion molecules, genes implicated in signaling pathways and cytokines [9]. An important host factor found to be strongly associated with HIV-1 disease rate was the chemokine receptor 5 (CCR5), the major HIV-1 co-receptor. A deletion of 32 bases from the coding region of the CCR5 gene resulted in reduced expression of the CCR5 protein on the cell surface, rendering the cell completely resistant to HIV-1 infection among homozygous carriers of this deletion. Heterozygous carriers infected with HIV-1 were associated with delayed disease progression [10, 11]. A recent approach to identify host factors associated with AIDS progression is the genome-wide association studies (GWASs) [12]. This approach implies full scan of the human genome for additional factors without prior knowledge about their role in a particular disease.

A number of observational studies have found that immunological non-responders are at higher risk of disease progression and non-AIDS-related mortality than patients who had a complete response, raising a concern about the long-term effect of suboptimal immune response as previously reviewed in Ref. [13]. As a result, it is essential to investigate critically the factors that contribute to the increased risk of disease progression and predict immunologic non-response during long-term cART. A number of host factors were found to be associated with immunological failure (**Figure 1**). **Figure 1** shows a list of the most common factors known to affect immune recovery (i.e., CD4⁺ T-helper cell recovery).

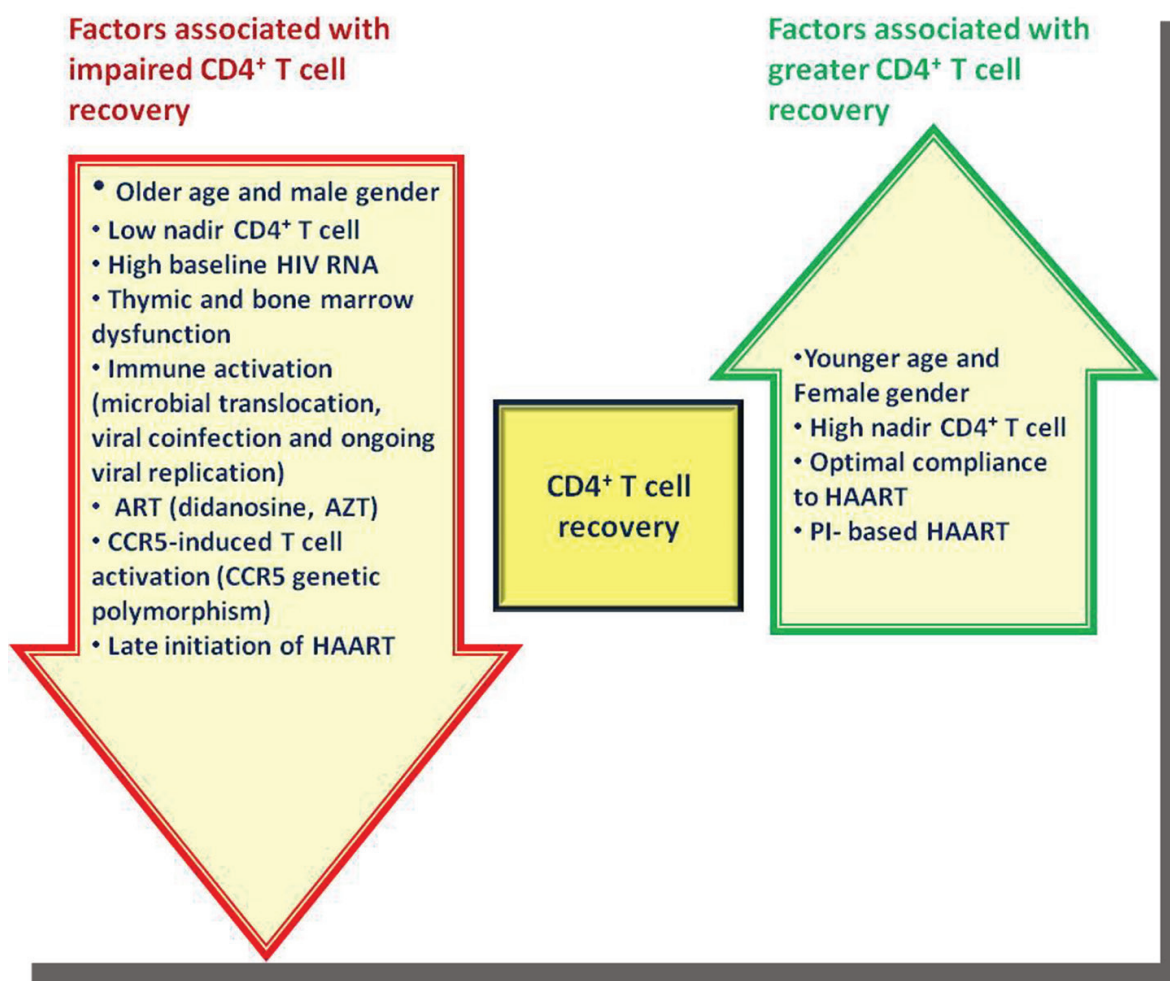


Figure 1. Factors affecting immune recovery among HIV-1-infected patients on cART. Courtesy of Pinzone et al. [14]. HAART, highly active antiretroviral therapy; ART, antiretroviral therapy.

2. The chemokine receptors

Chemokine receptors are transmembrane (TM) proteins that belong to a G protein-coupled receptors (GPCRs), which are classified into four distinct families—CXC, CC, CX3C, and XC—according to the structure of their natural ligands (**Figure 2a and b**) [15].

All GPCR share a common molecular structure, in which they have seven TM helices and transmit signals from extracellular ligands to intracellular biological pathways via heterotrimeric G proteins [16]. The structural regions required for ligand binding and receptor activation are defined for several chemokines. For example, in C-C chemokine receptor type 2 (CCR2) which is a protein expressed on human cells such as monocytes that is encoded by the CCR2 gene, the N-terminus domain is required for ligand binding, but it is not efficient for signal transduction. However, in CCR5 receptor, an additional region called the second extracellular loop is crucial for ligand binding and intracellular signaling. In the case of CX3C chemokine receptor 1 (CX3CR1), which is a protein expressed on human cells and encoded by the CX3CR1 gene, residues in the N-terminus and the third extracellular loop are required for ligand binding and intracellular signaling [17].

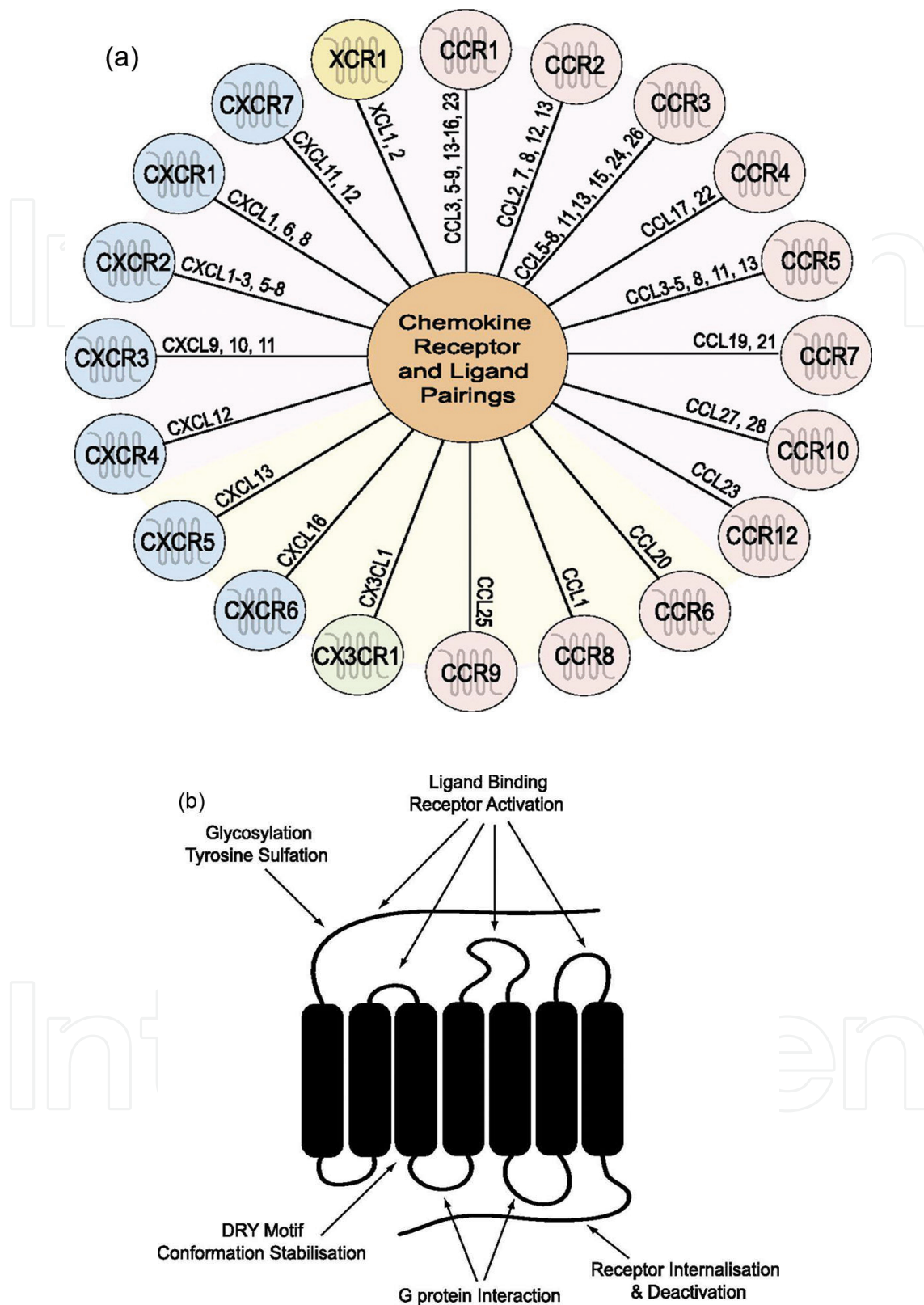


Figure 2. (a) CC chemokine receptor and ligand pairing. The known chemokine receptors belonging to each of the chemokine families—C, CC, CXC, and CX3C—are presented around the outer ring of the wheel, with their chemokine ligands shown along the wheel spokes. Courtesy of White et al. [17]. (b) Schematic presentation of the key functional regions of chemokine receptors. Studies have identified regions important for ligand binding, receptor activation, and internalization, although specific sequences involved in signaling differ between different chemokine receptors. Courtesy of White et al. [17].

Structurally, the GPCR can be divided into three main parts: (1) the extracellular region, consisting of the N-terminus and three extracellular loops (ECL1–ECL3); (2) the transmembrane (TM) region, composed of seven α -helices (TM1–TM7); and (3) the intracellular region, consisting of three intracellular loops (ICL1–ICL3), an intracellular amphipathic helix (H8), and the cellular C-terminus domain. The GPCRs possess a structural motif, which are critical for ligand-dependent signaling, desensitization, and receptor trafficking [18].

Another common feature of the GPCRs is the presence of aspartic acid, arginine and tyrosine (DRY) conserved motif at the cytoplasmic end of the third transmembrane domain, which has shown to be critical for signaling. The C-terminus of the GPCR receptor contains serine and threonine residues, which can be phosphorylated to induce recruitment of arrestin proteins. Beta (β) arrestin proteins have shown to be critical for receptor internalization and signal termination and to play an important role in the formation of a G protein-independent signaling complex pathway. A redundant role was played by the chemokine and their receptors, for instance, the selective activation of G protein versus β -arrestin-dependent signaling pathways may result in differential cellular responses. Moreover, the chemokine receptors can be regulated at the level of phosphorylation by the recruitment of different GPCR kinases, thus modulating the signaling complex cascade. For example, the CCR7 binds both CCL19 and CCL21 leading to different cellular responses [17].

2.1. Cell signaling and chemokine receptor functions

The network signal transduction through chemokine receptors is complex and leads to different functional consequences including homeostatic distribution of leukocytes and their mobilization from the bone marrow. In addition, chemokine receptors were found to be critical during inflammation, autoimmunity, lymphoid organogenesis, angiogenesis and immune regulation [19]. Growing evidence suggests synergism between chemokines in leukocyte migration through chemokine and/or receptor heterodimerization and further contributes to chemokine signaling.

This leads to enhancing the local leukocyte influx, thereby amplifying the outcome of inflammatory responses [20]. There is little information known about the signaling pathways for chemokine receptors because the activated pathways depend primarily on the specific type of the ligand and the receptor involved. A two-step model was proposed for chemokine receptor binding and activation, in which the core domain of the ligand is closely associated with the N-terminus and extracellular loops of the chemokine receptor. In the next step, the N-terminus domain of the ligand penetrates the helical bundle of the receptor [20].

2.2. The CCR5 receptor

The CCR5 is a pro-inflammatory receptor that binds to chemokine (C-C motif) ligand 3 (CCL3), CCL4, and CCL5, while CCL4 is known to be specific for CCR5 [16, 21]. CCR5 receptor was first identified in 1996 [22] using molecular cloning and localized the gene to chromosome 3p21 in which they suggested a potential role of this receptor in the granulocyte proliferation and differentiation. The CCR5 receptor is expressed on resting (memory/effector) T lymphocytes, monocytes, macrophages, and immature dendritic cells [23]. This receptor was the focus for an intensive research after being identified as a co-receptor for the R5

strain of HIV-1 [24, 25]. HIV strain that uses the **CCR5** as a co-receptor is called “CCR5 tropic” or “R5” tropic. The CCR5 receptor is made of 352 amino acid residues of a molecular mass of around 40.6 kDa. It shares around 71% sequence homology with C-C chemokine receptor type 2 (CCR2), which is a protein molecule found on human cells and encoded by the CCR2 gene, with most of the differences are located in the extracellular and the cytoplasmic domains. The CCR2 gene is located close to the CCR5 gene on chromosome 3p21.

3. The **CCR5** gene and HIV/AIDS

Researchers had a particular interest to some individuals who were able to remain uninfected with HIV-1 despite repeated exposure to the virus. Researchers were able to explain the cause of such phenomenon by the presence of molecular variants in the CCR5 gene that render the receptor inactive and further contribute to HIV-1 resistance [22, 26]. The best example, as mentioned above, is the deletion of the 32 base pairs in the second extracellular loop of CCR5 gene that results in the formation of a stop codon and the production of truncated protein [27]. The truncated protein lacks the HIV-1 interaction site, and its expression is reduced on the cell surface, which prevents the virus from infecting a target cell. Thus, homozygous carriers of this deletion are completely resistant to R5 strain of HIV-1, while heterozygous carriers exhibit slower progression to AIDS, higher CD4⁺ T-helper-cell counts, and lower mortality rates [10].

Since the role of CCR5 receptor is vital for the primary R5 HIV-1 strains that are present early during HIV-1 infection, this makes the CCR5 gene one of the central candidate host genetic factors that could explain the variable susceptibility to HIV-1 infection [22, 26]. The CCR5 Δ 32 is common in Caucasians, but it is almost rare among Asians and African populations [28, 29]. This clearly points out toward the importance of understanding the pattern of genetic diversity and its implications for better understanding AIDS.

3.1. Polymorphisms in the CCR5 gene and rate of AIDS progression

To understand the variable HIV-1 disease course that still exists among rare carriers of the CCR5 Δ 32, studies have focused on polymorphisms in the promoter region of the CCR5 gene [30, 31]. In addition to the CCR5 gene variations, a mutation at the CCR2 gene has shown to influence HIV-1 infection. Investigators have used evolutionary-based analysis to classify polymorphisms at the *cis*-regulatory region and the Δ 32 in the CCR5 gene and V64I mutation in the CCR2 gene into nine different CCR5 haplotypes [32]. The human haplotypes (HH) were defined as HHA, HHB, HHC, HHD, HHE, (HHF*1 and HHF*2), and (HHG*1 and HHG*2) (**Figure 3**) [32].

The CCR5 haplotypes may influence the HIV/AIDS disease course differentially according to the racial background of HIV-1-infected patients [32]. Some CCR5 haplotypes were shown to influence HIV-1 acquisition, early virus RNA concentration and subsequently disease progression in the absence of combination antiretroviral therapy [33], but in fact, less is known about the effect of these haplotypes during cART as the available information on the influence of the CCR5 haplotypes on AIDS treatment outcome is limited.

Human Haplogroup (HH)				CCR2	CCR5							ORF
					Promoter							
HHA				64V	A	G	G	T	C	A	C	Wt
	HHB			64V	A	T	G	T	C	A	C	Wt
		HHC		64V	A	T	G	T	C	G	C	Wt
		HHD		64V	A	T	G	T	T	A	C	Wt
	HHE			64V	A	G	A	C	C	A	C	Wt
		HHF*1		64V	A	G	A	C	C	A	T	Wt
			HHF*2	64I	A	G	A	C	C	A	T	Wt
		HHG*1		64V	G	G	A	C	C	A	C	Wt
			HHG*2	64V	G	G	A	C	C	A	C	Δ32
			SNP position	V64I	-2733	-2554	-2459	-2135	-2132	-2086	-1835	
			SNP db	rs1799864	rs2856758	rs2734648	rs1799987	rs1799988	rs41469351	rs1800023	rs1800024	rs333

Figure 3. The CCR2-CCR5 nucleotide variants and haplotypes. The main CCR2-CCR5 haplotypes are based on nine nucleotide variations including the V64I mutation in the CCR2 gene, the *cis*-regulatory region of the CCR5 promoter, and the Δ32 deletion in the ORF of the CCR5 gene. Linkage disequilibrium pattern between the above mentioned polymorphisms results in the generation of the CCR5 human haplogroup (HH) as shown in the figure. Nucleotide variants relative to their wild-type sequence are shown bracketed and in bold. ORF, open reading frame, and SNP, single nucleotide polymorphism.

We have previously reported the existence of four novel indels and two new polymorphisms from the Omani adult individuals [34]. The four new indels were detected out of 32 variable positions, -2973A/-, -2894A/-, -2827TA/-, and -2769T/-, and all were located in the 5'UTR of the CCR5 gene. The two new mutations, -2248G/A and +658A/G, were observed for the first time; the -2248G/A was detected in the Intron 1 region in one individual and +658A/G in the coding region of the CCR5 in another individual. *In silico* analysis showed that the novel variations in the 5'UTR could affect the transcription factor binding sites of the CCR5 gene. Moreover, the results demonstrated that the following four minor alleles were common: CCR5-2554 T and CCR5-2086G occurred at a frequency of 49 and 46%, respectively, and CCR5-2459A and CCR5-2135C both existed at a frequency of 36%. These alleles had moderate heterozygosity levels indicating that they were under balancing selection. However, the widely known allele, CCR5Δ32, was relatively rare in the Omani sample population. Eleven human haplogroups (HH) were constructed, four of which were common: HHC (46%), HHE (20%), HHA (14%), and HHF*2 (12%).

We also performed a linkage disequilibrium (LD) pattern to classify polymorphisms on the CCR5 gene. Eleven haplotypes were constructed; three of them were new: HHC*A, HHF*1A, and HHF*2A [35]. The results of both studies indicated that the one ethnic Omani population is genetically quite diverse when compared with other Asian populations such as Thais [36]. This information suggests that genetic markers can be used as predictors of the extent of HIV pathogenesis and immune recovery following treatment. This further indicates the importance of understanding the pattern of genetic diversity and its implications for a better understanding the human life.

Moreover, we have also investigated the possible correlation of the CCR5 haplotypes among Omani HIV-1-infected patients on cART with the average CD4⁺ T-cell count during a viremic period of 12 months before reaching the undetectable viral load level of <50 cells/μl. We have used the average CD4⁺ T-cell count as it provides a better understanding of the long-term effect

of *CCR5* haplotypes compared to the use of cross-sectional values [37, 38]. In addition, we have investigated the possible correlation of those haplotypes with the rate of CD4⁺ T-cell recovery over the first 18 months after achieving full viral suppression following the introduction of cART.

Our results showed that the common HHC haplotype was significantly associated with higher mean CD4⁺ T-cell counts among the Omani HIV-1-infected patients ($p = 0.024$). The effect of HHC was independent and remained significant even after adjusting for the remaining *CCR5* haplotypes as possible covariates ($p = 0.022$). The HHC haplotype was associated with delayed onset of AIDS (more than 10 years) in HIV-1-infected Japanese hemophiliacs [39]. The duration from the estimated time of HIV-1 infection to CD4⁺ T-cell decline to <200 cells/mm³ was analyzed among Thai injection drug users [36]. It was found that the individuals who possess the HHC haplotype have a slower decline in their CD4⁺ T-cell counts at the late stage (around 4 years after seroconversion) of the disease course [36]. Researchers studied the effect of *CCR5* haplotypes on the estimated time of infection to development of AIDS and time to death among 1151 HIV-1-infected patients that consisted of three ethnic groups, African-Americans, Caucasians, and Hispanics [32]. The HHC haplotype showed ethnic-specific characteristics in that it was associated with a delay in progression to AIDS and death among Caucasians and Hispanics, while it was associated with faster disease progression among African-Americans [32]. These investigators also found that there were differences in the effect of the same haplotype pairs among Caucasians and African-Americans. For example, the HHC/HHC and HHC/HHE haplotype pairs were associated with a delay in time to death in Caucasians but not among African-Americans [32]. The frequency of the HHC haplotype was higher in healthy individuals than in HIV-1-infected patients among Indians [40], suggesting a protective role of this particular haplotype. On the other hand, the investigations among Chinese patients failed to find any association between *CCR5* haplotypes and CD4⁺ T-cell counts [41]. However, in our studies, there is a significant association between HHC and CD4⁺ T-cell counts among the Omani ethnic population implying a possible protective role of HHC similar to Caucasians and Hispanics although the exact mechanism of this protective role is yet to be delineated.

Furthermore, we have studied the association of the average CD4⁺ T-cell count with immune recovery. The results showed that the immune responder (IR) group has a significantly higher level of average CD4⁺ T-cell count than the immune non-responder (INR) group during cART and before reaching undetectable viral load level ($p = 0.005$). In other words, individuals with a higher mean CD4⁺ T-cell count were able to better recover their CD4⁺ T-cell levels following cART compared with the individuals with a lower mean CD4⁺ T-cell count indicating that the level of average CD4⁺ T-cell count could be an indicator of determining the degree of immune recovery following successful cART, which suggests that the damage of the immune system during the viremic period will influence its capacity to recover upon treatment. These results are consistent with other findings [13, 42, 43] and support the assumption that the CD4⁺ T-cell level is an important factor that could predict immunological failure despite cART. This may suggest that in the INR group, the proliferation and the turnover of CD4⁺ T cells are impaired resulting in reduced production or increased destruction of CD4⁺ T cells.

It was noted that among the factors that could attribute to the observed phenomenon is the size of the thymus. It was found that HIV-1-infected patients with large thymus were able to better restore their CD4⁺ T-cell levels and have a broader immunological repertoire than

patients with smaller thymus. In addition, the positive association observed between the CD4⁺ T-cell counts and the immune recovery strengthens the classification method used for grouping the IR and INR in our studies.

To explain the variable HIV-1 disease course that still exists among rare carriers of the CCR5 Δ 32 such as Asians and African populations, studies have focused on polymorphisms in the promoter and/or coding region of the CCR5 gene [30]. Therefore, it was suggested that other polymorphisms in the CCR5 gene may influence the risk of HIV-1 transmission and disease progression, possibly by affecting the rate of receptor cell surface expression [30, 31, 43]. Many novel mutations were identified within the CCR5 gene coding region in Africans but not among Asian or Caucasian populations. In the Asian population, a single nucleotide deletion in the 893 position of the CCR5 gene coding region results in the lack of the entire C-terminal cytoplasmic tail of the CCR5 protein, thus reducing the expression levels of CCR5 receptors on CD4⁺ T cells. In addition, a rare mutation was found in the coding region of CCR5 gene, thymine to adenine at nucleotide position 303, leading to premature termination codon and reduced receptor expression. This mutation was associated with increased protection when combined with CCR5 Δ 32 [31].

Several single nucleotide polymorphisms (SNPs) have been defined in the CCR5 gene promoter region, the A2459G (rs1799987). Homozygous carriers of the mutant allele (-2459G) were found to progress slowly to AIDS more than those who carry the wild allele (-2459A) [30]. Another study reported a correlation between some promoter SNPs and AIDS; individuals lacking the -2459A and -2135C genotype may progress slowly toward AIDS/death [31].

A group of researchers identified single nucleotide polymorphisms (SNPs) in the *cis*-regulatory region of CCR5 gene at positions -2733, -2554, -2459, -2135, -2132, -1835, CCR5 Δ 32 - which were grouped into seven different haplotypes (A-G), which have been shown to affect the HIV-1 infection and progression to AIDS [32]. The frequency distribution of haplotypes was different among ethnic groups, in fact some haplotypes showed variable association to the disease status among different populations. For example, HHF*2 was linked to a delay in the progression to AIDS among African-Americans but not in Caucasians, while HHF*1 was associated with acceleration to AIDS among Caucasians, African-American, and Hispanics. HHG*2 was associated with delay in AIDS progression among Caucasians [32]. Understanding the pattern of genetic diversity is of great importance for understanding pathogenesis of many human disorders including AIDS. Another chemokine receptor, CCR2, is also found to affect HIV-1 disease progression rate. A valine to isoleucine amino acid substitution at position 64 of the CCR2 protein is associated with delayed HIV-1 disease progression. In addition, the CCR2V64I mutation is tightly linked to certain SNPs in the CCR5 *cis*-regulatory region [44].

To identify all the polymorphic sites that exist within the CCR5 gene as well as the CCR2V64I in adult individuals, we have examined the distribution of the detected variants from Omani adult individuals, and genomic DNA was amplified by polymerase chain reaction and sequenced to identify all the polymorphic sites that exist within a continuous region [of around 4.67 kb] of the CCR5 gene and to detect the known V64I mutation in the CCR2 gene. Out of 32 variable positions detected, four were new indels -2973A/-, -2894A/-, -2827TA/-,

and -2769T/-; all were located in the 5'UTR. Two new mutations were described for the first time: -2248G/A was detected in one subject in the Intron 1 region of the *CCR5* gene, whereas +658A/G was found in the coding region. These novel variations in the 5'UTR have shown to exhibit potential effects in the TF binding sites by *in silico* analysis that merit further investigation by experiments to validate our results. Moreover, we identified two novel haplotypes and eight known *CCR2-CCR5* haplotypes; those haplotypes were found to be at different frequency pattern compared to that documented worldwide. Our findings confirmed the wide spectrum of the genetic diversity found among populations of different ethnic groups within the *CCR5* gene region. This will allow us to better understand the role such individuals have in response to HIV-1 susceptibility and AIDS progression. There is indeed a need for studying and understanding genetic diversity in humans in order to better understand the complicated pathogenesis of HIV/AIDS.

The influence of HHA, HHC, HHD, and HHE haplotypes on *CCR5* receptor expression on B and T lymphocytes, NK cells, and monocytes among populations with either African or Caucasian ancestry in South Africa has been investigated [45]. In South African-Caucasians (SACs), the carriers of the HHC expressed *CCR5* receptors at significantly higher density on CD56⁺ NK cells and CD16⁺ CD56⁺ NK cell subset than South African-Africans (SAA) who do not carry this haplotype [46]. This may partly explain the protective role played by the HHC in Caucasians but not in Africans [47]. Likewise, such impact on the density of *CCR5* receptor expression may be the explanation of the protective role suggested in Omani patients carrying HHC. However, the experimental design of the current study was different from those of other studies in that the effects of the haplotypes were examined during the cART, whereas other studies were in the absence of the cART.

The results of our studies have shown that the HHC may play a protective role among Omani HIV-infected patients because of its association with a high average CD4⁺ T-cell count. Therefore, the mechanism of protection to understand the involvement of *CCR5* gene in AIDS progression among Omanis and other ethnic groups will be worth investigating.

4. Summary and future directions

Since HIV/AIDS is a major global concern, many governments implemented strategies and plans to control the spread of the disease and provide optimum antiretroviral treatment to AIDS patients. In this context, the literature review revealed that the genetic makeup of an individual is an important factor that may influence the acquisition of the HIV and the rate of HIV/AIDS progression. Several genes were found to be associated with HIV/AIDS, among which is the *CCR5* gene. It is apparent that the results were inconsistent across populations regarding the association of these genes with the rate of progression to AIDS. Additionally, the genetic component of an AIDS patient on cART, whose viral replication is fully suppressed, was found to affect the extent of immune recovery. Limited studies were conducted and their results were also inconsistent in the few ethnic groups. This is because the *CCR5* gene plays an important role in the signaling pathways that lead to the activation of T cells and T-cell survival and proliferation. Additionally, many factors may affect immune recovery for patients on cART [14].

Since the beginning of the AIDS pandemic and in the 1980s of the last century, scientists and clinicians were working with a disease that was not treatable at all, and the majority of patients died relatively quickly. In the 1990s of the last century and due to better recognition of how HIV spreads and to new drugs developed for treatments, AIDS became more treatable. The goal is now to go for a complete cure, in other words “complete viral eradication,” having the ability to remove the virus from the body or to suppress it to the point where it can no longer cause any damage to the host. This goal is reachable as the progress we are making against HIV/AIDS is much larger than in other comparable serious viral infections such as polio and smallpox [48, 49]. Currently, medications are much better than ever at treating AIDS patients, and our knowledge of how the immune system works against HIV/AIDS is improving.

Despite the heavy research to uncover the pathogenesis of HIV/AIDS, the whole picture of AIDS pathogenesis is not yet completely clear. During the infection with HIV, there is a known period of four to six weeks called the “window period” that we do not know much about. How exactly our immune system works during this critical “window period” is not completely understood. This was referred to as the “window of vulnerability.” This can be considered now as a “window of opportunity,” because in that very short period of time, there is a release of a huge amount of viruses and establishment of a latent HIV reservoir. It is in that short period of time our success or failure with vaccines as well as curing HIV/AIDS will rest. HIV reservoir is established literally within few days of acute infection. It has been shown that not only an HIV reservoir is formed early but also byproducts of CD4⁺ T-cell deaths increase significantly within days, and these cells are able to suppress the immune response to the virus. In fact, we have an interesting situation, an HIV reservoir that is almost immediately formed and products of cell death suppressing the immune response that is expected to prevent the formation of that reservoir. Future research should aim at reversing these processes. But we must take into consideration the importance of the existence of genetic diversity in the CCR5 gene, among other genes, and its importance for HIV/AIDS pathogenesis [50]. Genetic diversity is important for the protection of humans against certain pathogens such as HIV as discussed in this chapter.

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