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Review Article

CHEMOKINE RECEPTORS IN HIV INFECTION

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ABSTRACT

Chemokines and their receptors have been implicated as pivotal players in many pathological and physiological conditions including their role as coreceptors in the transmission of HIV. Horizontal and vertical transmission of HIV and further Infection require chemokine receptors for the entry into the target cells. The different chemokines receptors which are used by the viral variants as alternative coreceptors for HIV-1 entry are CCR5, CCR1, CCR2b, CCR3, CCR8, CX3CR1, CXCR4, CXCR6, CXCR7, FPRL1, GPR1, GPR15, APJ, STRL33 and D6. Every chemokine receptor has its own structural specificity and mechanism to bind with HIV. These receptors have their own specific binding ligands. CXC4, CCR5, CCR3, CCR6 and CCR7 are the major chemokines receptors which play a crucial role in the infection of HIV. In this review, we highlight the role of various chemokines receptors in the infection of HIV and the various aspects of future strategies to inhibit the HIV infection.

Keywords: Chemokine receptors, Chemokines, HIV.

INTRODUCTION

The infection of HIV- type I or II can occur by two ways in the human population one is vertical and the other is horizontal. Vertical transmission of HIV refers to the transmission of HIV infection from mother to child, either immediately before the birth of child or after the birth[1]. On the other hand horizontal transmission is the transmission of infection between members of the same species. In case of HIV infection, human immune deficiency virus requires chemokine receptors to get entry into the target cells. Chemokines are small soluble proteins of approximately 70 amino acid residues and molecular weight of 8- 10 kDa[2]. They act as potent chemo-attractants of a large variety of mononuclear cell types to the site of inflammation and secondary lymphoid organs by interacting with chemokine receptors[3]. These receptors are generally member of G protein-coupled receptor superfamily[4]. They possess seven trans membrane (TM) helices and transmit signals from extracellular ligands to intracellular biological pathways via hetero-trimeric G-proteins[5]. Chemokine receptors are also involved in the infection and pathogenesis of human immunodeficiency virus type 1 (HIV-1)[6]. Glycoproteins of HIV envelope play an essential role in the virus replication by mediating the fusion between viral and cellular membranes during the entry process. The envelope glycoproteins are synthesized as a polyprotein precursor that is cleaved by cellular proteases to the mature surface glycoprotein and the Trans-membrane glycoprotein[7]. During virus assembly, these protein complexes form heterotrimeric spikes onto the lipid bilayer of nascent virions. These spikes then initiate the infection process by binding receptor and co-receptors on the surface of target cells[8]. There are many types of chemokine receptors and co-receptors presents on the target cells of HIV virus[9, 10]. Specific properties of different chemokine receptors (CXC, CC etc.), and their role as a Coreceptors of HIV has been discussed in this article.

CXCR4

(CXCR-4) is a C-X-C chemokine receptor type 4 also known as fusin or CD184 (cluster of differentiation 184) is a protein in humans and encoded by the CXCR4 gene[11, 12]. Structural study reveals that CXCR4 contain extracellular and intracellular loops, seven TM helices, carboxyl (C)-terminus present (352 amino acid residues) and an amino (N)-terminus[13]. It has only one naturally occurring endogenous ligand known as SDF-1α also known as CXCL12 [14]. However, CXCR4 has an antagonistic ligand vMIP-II, encoded by the Kaposi's sarcoma-associated herpes virus[14, 15]. CXCR4 – SDF -1α interaction results in all essential physiological functions like immunomodulation, organogenesis, haematopoiesis and cerebellar neuron migration[16, 17]. Wu et al, 2010(11) characterized the CXCR4 interaction with HIV-1, Using High resolution crystal structures of CXCR4. They used natural ligands and de novo designed inhibitors for the study of binding sites[18, 19]. Their study demonstrated that some extracellular loops of CXCR4 act as co- receptor to enhance the interaction between HIV and CXCR4. These loops are named as the amino (N)-terminus, (ECL2) and (ECL3) extracellular loops[18, 19, 20]. Some multiple extracellular loops and TM domains of CXCR4 is also required in chemokine interactions and subsequent signalling. This separate site for binding and signalling revealed that there should be two binding sites[19, 20]. Wu et al again published the long-awaited crystal structure of CXCR4 and reported five independent crystal structures of CXCR4[21]. These structures are now revealing the new target sites for the ligands and new ways of drug designing . Their study revealed that the binding pocket of CXCR4 is larger, more open and located closer to the extracellular surface, and includes acidic Asp187, Glu288 and Asp97 which are important for SDF-1α binding[22]. Moreover, they observed that Lys1 is the most critical residue in SDF-1α for receptor activation. An another study conducted by Heveker N et. al. 1998 reported dynamic changes in the CXCR4 interactions with its natural ligand and HIV-1 gp120[22, 23] and based on their finding they hypothesised that this dynamism may explore new opportunities for drug discovery efforts to target specific functional states of the receptor.

CCR5

CCR5 is a C-C chemokine receptor type 5 encoded by the CCR5 gene in Human. It is a member of the beta chemokine receptors family of integral membrane proteins[24, 25]. The CCR5 protein has also recently been designated CD195 (signifying a cluster of differentiation of cell surface molecules present on white blood cells) CCR5 is made up of 352 amino acid residues[26]. It has many natural ligands including MIP-1α, MIP-1β, 'RANTES' protein and monocyte chemotactic protein (MCP). Out of them MIP-1β is known to be most specific for CCR5[27]. Like CXCR4, CCR5 is also involved in both physiological and pathological processes, including inflammation and haematopoiesis and signal transduction that has been proven by structural and mutation study[28]. Extracellular domains of CCR5 , the N-terminal domain and second ECL (ECL2) domain are involved in the HIV infection, along with some basic amino acids of binding sites and two hydrophobic amino acid consider to be effective in ligand binding[29, 30]. One more protein V3 loop also consider to the effective one as if V3 is mutated then HIV and CCR5 interaction reduced[31]. Although many viral variants can use alternative coreceptors for HIV-1 entry into transfected cell lines, including CCR1,CCR2b, CCR3, CCR8, CX3CR1, CXCR4, CXCR6,FPRL1 GPR1, GPR15, APJ, STRL33, and D6 the HIV entry into the host cell is mainly mediated by CCR5[32, 33]. The importance of the chemokine receptor CCR5 in the infection of HIV is also supported by the epidemiological study. It is reported that specific alleles in co-receptor genes (chemokines receptor gene) can modulate surface expression and profoundly influence HIV infection. The CCR5 allele (Δ32) encoding a 32-base pair deletion has been reported to reduce the progression of the virus. Homozygosity for

this allele confers strong resistance to HIV infection excluding some exceptional cases[34]. On the other hand, individuals with heterozygous gene of CCR5 allele (Δ32) do not protect from infection, but is associated with a slower progression of the disease [35, 36]. A study conducted by He, J. et al, 1997 identified novel CCR5 mutations in sooty manages that appear to promote the use of CXCR6, GPR15, and GPR1[37]. CCR5 is the most important corrector for M-tropic strains, which replicate both in monocyte-derived macrophages (MDM) and in microglia. These chemokine receptors mediate many type of infections[38]. A number of new experimental HIV drugs, called entry inhibitors, have been designed to interfere with the interaction between CCR5 and HIV, like PRO140 (Progenics), Vicriviroc (Schering Plough), Aplaviroc (GW-873140) (GlaxoSmithKline) and Maraviroc (UK-427857) (Pfizer).

CX3CR1

CX3CR1 chemokine receptor 1 is a C-X3-C type of receptor encoded by CX3CR1 gene. It is also known as V28 and GPR13. CX3CR1 are receptor for fractalkine, a Trans-membrane protein and chemokine which is secreted by neurons and involved in the adhesion and migration of leukocytes[39]. These receptors also work as Coreceptors for HIV-1. Fractalkine (CX3CL1) protects neurons from the neurotoxicity induced by the HIV-1 envelope protein gp120 but some variation in the gene lead to increased susceptibility to HIV-1 infection and rapid progression to AIDS[40].

CCR3

C-C chemokine receptor type 3 is a protein that in humans is encoded by the CCR3 gene [41]. CCR3 has also been currently designated CD193. The role of CCR3, another β-chemokine receptor, is very controversial. Several HIV isolated from the CNS use CCR3 to enter cells dually transfected with CCR3 and CD4 enter fatal microglia, which express CCR3 on their cell surface. However, studies that examined the inhibition of microglial infection by anti-CCR3 antibodies or the CCR3 ligand eotaxin have yielded conflicting results[42, 43].

CCR7

C-C chemokine receptor type 7 is a protein that in humans is encoded by the CCR7 gene [44]. CCR7 has also recently been designated CD197 (cluster of differentiation 197). Chemokine receptors CCR7 do not have direct role in the infection of HIV but they have considerable role in the maintenance of latency of HIV cell. In this way, they indirectly prolonged the HIV infection[45]. Long-lived latently infected resting memory CD4+ T-cells persist in patients of HIV thought to be the major barrier to curing HIV infection[46]. Given the low frequency of latently infected memory CD4+ T-cells in vivo, robust in vitro models of HIV latency in primary CD4+ T-cells are urgently needed to better understand the establishment and maintenance of latency as well as identify novel strategies to reverse latent infection[47]. Suha Saleh et al, 2007 have demonstrated that latent infection can be established in resting memory CD4+ T-cells in vitro following incubation with the chemokine's CCL19 and CCL21 (ligands for CCR7), CXCL9 and CXCL10 (ligands for CCR3) and CCL20 (ligand for CCR6)[48, 49]. These chemokines are important for T-cell migration and recirculation between blood and tissue, and they have proposed that the addition of chemokines invitro to resting CD4+ T-cells may model chemokine rich micro-environments such as lymphoid tissue, limited viral production and no T-cell activation. It therefore provides a tractable model to dissect the pathways of how latency is established and maintained in resting CD4+ T-cells[50]. According to the above experiment some chemokine receptors like CCR6 and CCR7 contribute to the indirect infection of HIV[51].

Role of CCR10 in combination with CCR3

C-C chemokine receptor type 10 is a protein that in humans is encoded by the CCR10 gene. CCR10 is the receptor for CCL27[52]. CCR10-CCL27 interactions are involved in T cell-mediated inflammation[53]. On the other hand C-C chemokine receptor type 3 is a protein which is encoded by the CCR3 gene in human[41]. CCR3 has also recently been designated CD193. The finding that CCR10 has some role in the infection of HIV became more bright when Wang W et al 2000, proved that CCR10 in combination with CCR3 help in making the vaccine against HIV[54]. Veronica Rain one et al 2004 reported that CCL28 (a ligand for CCR10) induces mucosal homing of HIV-1-Specific IgA-secreting plasma cells in Mice Immunized with HIV-1 Virus-Like Particles. In their study they found high IgA production[55]. Number of surface receptor proteins, including CCR3 and CCR10, which bound to specific chemokine characterized by IgA-secreting plasma cells (IgA-ASCs) when these chemokine receptor proteins bind to CCL28, a CC chemokine also known as mucosae-associated epithelial chemokine, or MEC[56, 57]. These interactions are involved in both migration and recruitment of IgA-ASCs into mucosal lamina propria[58]. These studies reveal some facts that CCR10 and CCR3 can also be used in HIV therapeutics.

CXCR7

CXCR7 chemokine receptor 7 is a C-X-C type of receptor. It is also known as RDC1, CMKOR1, and GPR159[59]. The gene encoding CXCR7 is located on chromosome 2 in human [60]. Its expression by trophoblasts and other placental cells have important implications for understanding their role in maternofetal HIV transmission[61]. A study conducted by a group (Tripathi et. al. 2008), they check the expression of CXCR7 in 45 different human placental tissues, out of which 20 were from early placental tissue. They revealed a greater expression of CXCR7 in term human placenta as compared to the early stage. At last they concluded that the precise role of CXCR7 in the human placenta needs to be determined and HIV vertical transmission is reported to occur mainly during the end stages of pregnancy[62]. CXCR7, have the same ligand (CXCL12) as CXCR4. This receptor work as the coreceptor for both HIV-1, HIV-II[63]. It has been also reported that CXCR7 is required for maturation of the B cells[64]. Above studies proven the significant role of CXCR7 in the transmission of HIV.

Some therapeutic development by modifying chemokine receptors

Some of the frequently used anti HIV drug are Stavudine (nucleotide reverse transcriptase inhibitors and used in the treatment of infection by retrovirus, primarily HIV)[65] and a series of novel 2-Phenyl-3-Substituted Quinazolin-4-(3H) one derivatives[66]. These drugs are not chemokine dependent but while designing drugs for HIV on the basis of chemokine receptors we mainly target the ligands to which the chemokine receptors bind. There are also some inhibitory ligands found in nature with the help of these inhibitory ligand infections of HIV can diminished considerably. One among these inhibitors is vMIP-II displays a broader spectrum of receptor activities than any mammalian chemokine, as it binds with high affinity to a number of both CXC and CC chemokine receptors, including CXCR4 and CCR5, and it inhibits cell entry of HIV-1 mediated by these receptors[67]. TAK-779, AD101 and SCH-C are some other inhibitors of CCR5. Synthetically and modularly modified-chemokines are now in process which has the altered binding sites for the receptors. In this way they disrupt virus binding and make viruses unable to enter in the cell[68]. Some CCR like chemokine receptors CCR10 and CCR3 are used to secret IgA as to cope up with the HIV infection. One more CCR5 blocker/antagonist found is GHS-R Blocker D-[Lys3] GHRP-6 (DLS) but the problem with this antagonist is that it can also inhibit other regulatory pathways[69]. There is a wide scope in finding the treatment based on chemokine receptor and inhibitors HIV.

Future Strategies

The review talks about the role of various chemokine receptors in the infection of HIV. These receptors act as a coreceptor and assist in the entry of HIV virus in the host cell and subsequent infection. The different type of chemokine receptors are structurally different and have their own specific binding domains and catalysing sites. Chemokine receptors study also facilitates the development of new therapeutic drugs. Understanding the genetics, structure, catalytic sites and elucidation of the molecular mechanisms triggered by the interaction of chemokines and their receptors may provide useful insights for future drug designing. In this regard, the discovery of various effective inhibitors against the chemokines could be helpful. The importance of the chemokine receptors in the infection of HIV is now supported by epidemiological data. At the co-receptor level, it

has been established that specific alleles in co -receptor genes modulate the surface expression of the chemokines receptors and profoundly influence HIV infection. Therefore, another approach could be focusing on the genetics of the chemokines receptors like exploring the role of various allelic variations and its effect on the susceptibility of a particular population for example one major co-receptor of the M-tropic coreceptors of HIV is CCR5. It is reported that if there occurs a mutation in the CCR5 gene because of the deletion of 32 base pair, the population having this mutated CCR5 gene show resistance to the HIV infection. However, the conflicting results exist about this and it is still debatable. But the finding that allelic variation in the chemokines receptor may change the progress of the disease is path breaking in the research of the HIV. The collection of the epidemiological status of the genes of various chemokines receptors in different continents would be very interesting in formulating the strategy to handle the infection of HIV for a particular population. To sum up a lot has been done and a lot needs to be done to address the challenge of infection of HIV and chemokines receptors would be instrumental in this endeavour.

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