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The role of polymorphisms in chemokines and chemokine receptors in the clinical course of HIV-1 infection

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ABSTRACT

The outcome of HIV-1 infection is highly variable: not all individuals exposed to HIV-1 will become infected, and among individuals who do become infected the time from infection to clinical AIDS is highly variable. This variability is thought to reflect the complex interactions between virus and host. An important role for host genetic factors in the pathogenesis of HIV-1 infection is increasingly being appreciated. Many novel genetic polymorphisms have been identified and analysed for their role in HIV-1 transmission and disease progression. Here an overview is provided of polymorphisms in chemokines and chemokine receptors that influence HIV-1 disease.

INTRODUCTION

The clinical course of HIV infection

HIV-1 infection is characterised by a gradual and progressive loss of $CD4^+$ T cells, ultimately leading to the acquired immunodeficiency syndrome (AIDS), which is characterised by opportunistic infections, neurological symptoms and malignancies. Among patients, the clinical course of HIV-1 infection is highly variable. Before antiretroviral therapy became available, the asymptomatic phase of infection could take only months (rapid progressors) or last for more than 15 years (long-term asymptomatics, LTA). Between these extremes, the median time from infection to AIDS diagnosis is eight to ten years.[1]

The course of HIV infection may be influenced by both viral and host factors. The host fights infection by generating HIV-specific cytotoxic T cells and antibodies. The error-prone nature of HIV-1 reverse transcriptase results in the generation of a spectrum of HIV-1 mutants in each replication cycle (viral quasi-species). The growth advantage of mutants with altered antigenic structures (escape mutants) allows the virus to escape from the suppressive action of the immune system. The variable nature of HIV-1 also results in the evolution of other biological characteristics, such as replicative capacity, cytopathicity and cellular tropism.

Though the significance of the humoral immune system to protect against AIDS remains controversial, cytotoxic CD8+ T cells have been shown to signifcantly influence HIV-1 disease progression. Depletion of CD8+ T cells in simian immunodeficiency virus (SIV)-infected macaques leads to a rapid increase in viral replication.[2] In humans, the presence of CTL has been associated with reduced viral load and a more benign disease course.[3-5]

The importance of the viral phenotype for HIV-1 pathogenesis is supported by multiple studies: experimental infection of macaques with late-stage SIV variants resulted in a more rapid disease progression than infection with early isolates;[6] extremely slow progression of disease was observed in haemophiliacs who were infected with an attenuated virus that lacked the regulatory viral gene nef[7]; and long-term nonprogressors more often harbour virus variants with slow *in vitro* replication kinetics.[8]

Another aspect of the HIV-1 phenotype is the so-called syncytium-inducing (SI) capacity. SI HIV-1 variants first got their name as they are able to infect and induce fusion of cells into multinucleate cells (syncytia) in T-cell lines, due to their ability to use chemokine receptor CXCR4 as a viral coreceptor (therefore SI HIV variants are also referred to as X4 HIV-1 variants).[9] Nonsyncytium-inducing (NSI)

HIV-1 variants are in general restricted to CCR5 usage (R5 HIV-1 variants). Whereas HIV-1 infection is in general established by a homogenous population of macrophage tropic NSI / R5 HIV-1 variants. SI / X4 HIV-1 variants may evolve from these R5 variants in approximately half of the HIV-1 infected patients. The emergence of these X4 variants in patients is associated with a more rapid loss of $CD4^+$ T cell numbers and a more rapid progression to AIDS.[10,11]

Chemokines, chemokine receptors and HIV-1

Chemokines are small, structurally-related molecules involved in chemotaxis of a large variety of cell types via interaction with G protein coupled 7-transmembrane spanning receptors. Chemokines play a role in a variety of biological processes, such as lymphocyte migration to sites of inflammation, migration through various lymphoid organs during lymphocyte development and in angiogenesis.[12-14] In 1996, chemokine receptors were identified as coreceptors for entry of HIV-1 (for references see *table 1*). Viral entry is a multistep mechanism, in which the envelope protein gp120 in succession binds to the CD4 molecule and a chemokine receptor. This results in a series of conformational changes, which eventually leads to fusion of the viral and cellular membrane. Several members of the chemokine receptor gene family have been identified as HIV-1 coreceptors (*table 1*). Of these, CCR5 and CXCR4 are thought to be the most relevant *in vivo*, whereas the *in vivo* role of the additional chemokine receptors remains to be established. Cellular tropism of HIV-1 variants is primarily determined by coreceptor expression on the cell surface and coreceptor preference of the virus. Thus, CCR5 expressing cells, such as macrophages and memory $CD4^+$ T cells, can be infected by R5 variants, whereas CXCR4 expressing cells, such as memory and naive $CD4^+$ T cells, can be infected by X4 variants.[15,16] Since naive cells are crucial in the process of T-cell renewal, the capacity of X4 HIV-1 variants to infect and eventually kill these cells may explain the more rapid $CD4^+$ T-cell decline associated with the presence of X4 HIV-1 variants. It should be noted that post-entry restrictions on HIV-1 replication may also influence tropism, as shown for macrophages and resting T cells, that may not efficiently support HIV-1 replication despite expression of the appropriate coreceptors.[17,18]

The natural ligands of the HIV-1 coreceptors, MIP1a, MIP1b, RANTES (ligands of CCR5) and SDF-1 (ligand of CXCR4), have been shown to inhibit virus replication *in vitro*[19-23] and enhanced *in vitro* chemokine production by patient peripheral blood mononuclear cells (PBMC) has been associated with slow disease progression.[24,25] Furthermore, expression levels of CCR5 have been shown to influence infectibility *in vitro*.[26,27] Therefore, it can be expected that genetic differences that influence the pattern and level of expression of chemokines and chemokine receptors may have a major impact on the course of HIV-1 disease.

Table 1

Chemokine receptors and structurally related molecules shown to mediate entry of HIV-1 into CD4+ cells

CHEMOKINE RECEPTOR FAMILY[a]	RECEPTOR	LIGAND	NEW NOMENCLATURE FOR LIGAND[b]	REFERENCE[c]
CC	CCR2	MCP1-4	CCL2, CCL8, CCL7, CCL13	105
	CCR3	Eotaxin, Eotaxin-2, RANTES, MIP1a	CCL11, CCL24, CCL5, CCL3	105,106
	CCR5	MIP 1a MIP 1b RANTES	CCL3, CCL4, CCL5	21,105-108
	CCR8	I-309	CCL1	109,110
	CCR9	TECK	CCL25	111
CXC	CXCR4	SDF-1	CXCL12	112
	CXCR6/BONZO/ STRL33[d]		CXCL16	113,114
CX3C	CX3CR1	Fractalkine	CX3CL1	109,115
Orphan	BOB/GPR15	Unknown		113,116
	GPR1	Unknown		116
	APJ	Unknown		111,117
	ChemR23	Unknown		118
Chemoattractant receptor	BLTR	LTB4		119
Virally encoded[e]	US28	Broad spectrum of CC Chemokines, fractalkine		109,120

[a]Chemokines can be divided into four families on the basis of the spacing between two N-terminal cysteines. Chemokine receptors are named according to the family of chemokines they bind. [b]A new nomenclature for chemokines based on chemokine family names, which consists of family name (C, CC, CXC, CX3C), L (for ligand) and the numbering of the respective gene, has recently been proposed.[13,121] [c]References for the papers first to describe the molecule as an HIV-1 coreceptor are cited. [d]Given the recent identification of a ligand and assignment of a systematic name for this molecule, alternative naming is also given. [e]This chemokine receptor is encoded by human cytomegalovirus.

POLYMORPHISMS IN CHEMOKINE RECEPTORS AND HIV-1 DISEASE PROGRESSION

CCR5 D32

Soon after the identification of chemokine receptors as the coreceptors for entry of HIV-1 into human $CD4^+$ T cells, individuals were identified who had frequently been exposed to HIV-1, and yet remained uninfected due to a homozygous genotype for an inactivating deletion of 32 base-pairs in the CCR5 gene.[28-30] This polymorphism in the CCR5 gene (CCR5 D32 leads to a premature frameshift and a nonfunctional protein that is not expressed on the cell surface. As with other polymorphisms, a large racial variation in the prevalence of the CCR5 D32 allele is observed. It is common among Caucasians, whereas it is virtually absent in African-Americans and Africans (*table 2*). The effects of CCR5 D32 on the course of HIV-1 disease have been widely studied, though primarily in cohorts of subtype B-infected homosexual men.[31-34] In these studies, heterozygosity for CCR5 D32 has been associated with a delayed progression to AIDS. In an international meta-analysis of individual patient data from ten well-characterised cohorts of seroconverters, a relative hazard of 0.74 for progression to AIDS was obtained for CCR5 D32 heterozygosity.[35] The mechanism of protection most likely involves a reduction of the number of CCR5 positive cells and hence the number of potential target cells for HIV-1, which may result in reduced virus replication already during primary infection and subsequently a lower viral set-point.[36,37]

In HIV-1-infected intravenous drug users, haemophiliacs and recipients of contaminated blood[28,38,39] no effect of CCR5 D32 on disease progression was observed, whereas a protective effect was observed among HIV-1-infected children.[40,41] It remains to be established whether this is due to study design or whether the effect of CCR5 D32 is indeed dependent on risk group and route of transmission.

CCR5 promoter

The CCR5 5'untranslated region (UTR) consists of three exons and two introns. In this region, 12 single nucleotide polymorphisms (SNPs) have been described,[42-45] which may, in part, explain differences in basal expression levels of CCR5 among individuals homozygous for the wild-type non-deleted CCR5 gene. To standardise the different numbering systems for the CCR5 promoter in literature, a numbering system was recently proposed in which the first nucleotide of the translation start site is designated as position 1, the nucleotide immediately upstream of this position as position -1, and so on.[46] In the paragraph below, we will use this numbering system and show the alternative nomenclature between brackets.

Among SNPs in the promoter region of CCR5, a high degree of linkage disequilibrium exists, allowing the identification of four common haplotypes (P1 to P4) and six rare haplotypes (P5 to P10), consisting of different combinations of 10 SNPs.[45] The P1 haplotype, including T-2135C (alternative nomenclature T627C, T59353C), was associated with a more rapid course of disease. SNP G-2459A (alternative nomenclature G59029A or G303A) was independently described to be associated with a more rapid disease course.[44] This SNP is in complete linkage disequilibrium with the T-2135C[47-49] and is now considered to be part of the P1 haplotype. The association of these SNPs with enhanced disease progression was observed in different risk groups, such as homosexuals, haemophiliacs and perinatally-infected children.[44,45,47-49] It is likely that these SNPs or linked mutations are involved in the regulation of transcription of CCR5, but results from reporter assays have been inconsistent thus far.[44,45]

CCR2 64I

A valine-to-isoleucine transition in the second transmembrane region of CCR2 (CCR2 64I) has been associated with a delayed progression to AIDS.[50] The protective effect of CCR2 64I is similar to the effect of CCR5 D32 (RH of 0.76 in meta-analysis of combined cohorts,[35] results from individual cohorts).[31,32,34] Though the effect of CCR2 64I on disease progression is obvious, the mechanism is still not understood. CCR2 is rarely used as a coreceptor and the mutated CCR2 molecule does not alter *in vitro* infectibility of cells,[51,52] therefore it is unlikely that the polymorphism directly influences infection. The mutation in CCR2 is in strong linkage disequilibrium with a single-nucleotide polymorphism in the promoter of the CCR5 gene, C-1835T (alternative nomenclature C927T or C59653T)[42,43] and may thus indirectly be involved in the regulation of expression of CCR5. However, neither basal expression levels of CCR5 nor transcription levels in primary lymphocytes were reduced in CCR2 64I heterozygotes.[51,52] An effect on CCR5 expression has been suggested by the finding that re-expression of CCR5 after internalisation by N-terminal modified RANTES was less rapid in two out of three CCR2 64I heterozygotes.[53] An alternative explanation for the effect of CCR2 64I was provided by Mellado *et al.*, who showed that CCR2 64I protein was able to form dimers with CXCR4 after sensitisation with the cognate chemokines, whereas the normal CCR2 protein was unable to do so.[54] This capacity may thus reduce the amount of CXCR4 available on the cell surface among CCR2 64I carriers. This, however, does not explain the finding that CCR2 64I already affects the viral load early in infection, when in general only NSI / R5 variants are present.[55]

CX3CR1 249I 280M

Although CX3CR1 is only used by a minority of HIV-1 variants as a coreceptor, an enhanced progression to AIDS was observed among patients homozygous for CX3CR1 variant V249I T280M. These two amino acid substitutions result in a reduced capacity to bind the cognate ligand

Table 2

Common polymorphisms described in chemokines and chemokine receptor genes, reported to significantly influence HIV-1 disease progression in prospective cohort studies, for details see text

GENE	POLYMORPHISM (NAME)	REFERENCES[a]	ALLELIC FREQUENCY[b]	EFFECT ON GENE PRODUCT	EFFECT ON HIV-1 DISEASE PROGRESSION	DISEASE MODIFYING GENOTYPE *VS* REFERENCE GROUP	REFERENCES
CCR5[c]	Deletion of 32 basepair (D32)	28-30	C: 0.08 A: 0.017	Defective protein, no expression on cell surface	Delayed, RH 0.76[d]	D32/+ *vs* +/+	31-34
CCR2	Val to Ile in first trans-membrane region (64I)	50	C: 0.098 A: 0.151 H: 0.172	Amino acid substitution	Delayed, RH 0.76[d]	64I/+ and 64I/64I *vs* +/+	31,32,34
CCR5	SNP in promoter region G-2459A[e,f]	44	C: 0.57 A: 0.43 H: 0.68	Enhanced promoter function[f]	More rapid, RH 1.74	A/A *vs* G/G	47-49
CCR5	10 haplotypes of 10 SNP in promoter region (P1 to P10)[f]	45	C: 0.560 A: 0.431g	Unknown[f]	More rapid, RH 1.53	P1/P1 *vs* all other genotypes	47-49
CX3CR1	Two amino acid substitutions (V249I T280M)	56	C: 0.135	Reduced ligand binding	Conflicting results	280 M/M *vs* T/T	56,57
SDF-1	SNP in 3' untranslated region (3'A)	62	C: 0.211 A: 0.057 H: 0.160	Unknown	Conflicting results, RH 0.99[d]	3A/3A *vs* +/+	42,62-64
RANTES	Two SNP in promoter region (C-28G, G-403A)[h,i]	58	C: 0.148h A: 0.357 H: 0.217	Increased promoter activity[58]	Delayed, RH 0.65[i]	II/I vs I/I[h]	
RANTES	Intron variant (In1.1C)[i,j]	61	n.a.[j]	Reduced promoter activity	More rapid[i]	n.a.[j]	

[a]Reference for the study in which the polymorphism was originally described. [b]Allelic frequencies of the polymorphisms may vary between different races. Here, allelic frequency of Caucasians (C), Hispanics (H) and African Americans (A) are shown, if available. [c]22 additional mutations leading to an amino acid substitution have been described in the coding region of CCR5.[46,122] Of these, only one allele was associated with reduced entry of HIV-1, and three with a limited ability to bind MIP1a.[122] Due to the low prevalence of the mutations, effects on disease progression can not be established in a cohort study. [d]Relative hazard as obtained in meta-analysis of individual cohorts.[35] [e]According to recently proposed nomenclature. [f]G-2459 is now considered a part of the P1 haplotype. As the study population in both studies is partially overlapping, the results obtained should not be considered confirmatory. [g]Allelic frequency of the disease modifying haplotype (P1) is shown. [h]Due to the linkage disequilibrium between these SNPs, three haplotypes were identified (haplotype I: -403G -28C, II: -403A -28C and III: -403A -28G). Prolonged survival was observed among individuals carrying haplotype I and II as compared with homozygotes for haplotype I. Allelic frequency for haplotype I is given. [i]A strong linkage disequilibrium between intron variant In1.1C and SNPs at position -28 -403 of the RANTES promoter is observed. In1.1C almost always occur in conjunction with -403A. Therefore, results from these survival studies should be considered as conflicting. [j]This study is not available in print yet, therefore, further details are missing.

fractalkine.[56] The effect on the course of HIV-1 infection could, however, not be confirmed in three US-based cohort studies.[57]

POLYMORPHISMS IN CHEMOKINES AND HIV-1 INFECTION

RANTES promoter

Beta-chemokines can block HIV-1 infection via CCR5 *in vitro*[19-21] and high production levels of these chemokines have been associated with less rapid disease course.[24,25] *In vitro* RANTES production levels can vary widely among PBMC from different individuals, which in part may be due to differences in the genetic make-up of the RANTES gene. Two SNPs were identified within the RANTES promoter region (C-28G and G-403A)[58-60] and recently a variant in intron 1 (In1.1C) was identified.[61] These variants are in strong linkage disequilibrium: almost all subjects who carry In1.1C also carry -403A, whereas -28G always occurs in combination with -403A / In1.1C. Both promoter SNPs display increased promoter activity,[58,60] whereas In1.1C is associated with a strong downregulation of promoter activity.[61] In a cohort of Caucasian homosexuals the -403A -28C haplotype was associated with a reduced progression of disease,[59] which could not be confirmed in an analysis of five US-based cohorts.[61] In the latter study, In1.1C was associated with more rapid disease progression in both Caucasians and African Americans.

SDF-1 3'A

Initially, a very strong protective effect was reported for homozygosity for a G-to-A mutation in the 3' untranslated region of the SDF-1 gene (SDF-1 3'A),[62] encoding the ligand for CXCR4. This effect could not be confirmed in other studies,[42,63-67] including an international meta-analysis of individual cohorts (RH=0.99).[35]

CHEMOKINE RECEPTOR POLYMORPHISMS AND THE ACQUISITION OF SI/X4 HIV-1 VARIANTS

The development of X4 / SI HIV-1 variants is a hallmark of disease progression, and their appearance has invariably been associated with a more rapid progression to AIDS.[10,11,68,69] It is still not understood why X4 variants develop in some patients and not in others. Several factors have been suggested to influence the development of X4 variants, including structural restrictions[70] and loss of fitness during the adaptive process of gp120,[71] levels of proteins that bind to CXCR4, such as SDF-1[23] and HIV-1 tat protein[72], and immune control.[73] Recently it was shown that host genetic factors may play a role in the appearance of X4 HIV-1 variants.

As compared with the CCR5 WT genotypic group, the acquisition of SI variants was delayed in the group of CCR5 D32 heterozygotes. An unexpected finding was the association of the CCR2 64I allele with an increased conversion rate toward X4 variants.[55,74,75] As this mutation is linked to the promoter mutation in CCR5, enhanced X4 conversion may be due to altered levels or patterns of CCR5 expression.

CHEMOKINE RECEPTOR POLYMORPHISMS AND HIV-1 TRANSMISSION

HIV-1 may be transmitted from mother to child, via sexual contact, needle sharing, or exposure to contaminated blood products. Exposure to HIV-1 does not invariably lead to persistent infection. A multitude of factors influence transmission rates, such as frequency and magnitude of exposure, inoculum size, disease stage, $CD4^+$ T cell numbers and immune response of the patient.[76-79] Early in infection, a homogenous population of mainly macrophage tropic, NSI / R5 virus variants can be found, suggesting a strong selection pressure with regard to virus phenotype in acute infection. Indeed, susceptibility of cells from the exposed individual to R5 HIV-1 variants has been correlated with transmission.[80,81] One of the most prominent determinants for transmission is the viral load in the donor, irrespective of whether it involves homosexual, heterosexual, parenteral or perinatal transmission.[40,81-85]

The role of host genetic factors in viral transmission is typically studied in a case-control setting, in which the prevalence of a genetic marker in a population of HIV-1-infected patients is compared with the prevalence of this marker in an HIV-1-negative control group or, more extremely, with a group of individuals who are known to have been exposed to HIV-1, yet remain uninfected (exposed uninfected). There has been considerable debate about the role of host genetic factors in protection against transmission of HIV-1. Part of these conflicting results may be due to differences in the composition of the study population and selection of the HIV-1-negative control group. Diverging results have indeed been reported upon selection of highly exposed uninfected individuals or nonexposed HIV-1-negative individuals as a control group.[62,86] Furthermore, confounding factors, such as viral load in donor, should preferentially be taken into account in transmission studies.

Considerable efforts have been undertaken to study the role of CCR5 D32 in transmission of HIV-1. Homozygosity for CCR5 D32 has been associated with protection from transmission in all risk groups studied.[39,87-90] This indicates an absolute requirement for CCR5 in the establishment of infection, irrespective of the route of entry. Despite the near complete resistance, the few case reports of infected CCR5 D32 homozygotes[91-95] and the identification of laboratory workers accidentally infected

with T cell line adapted, X4 restricted virus variants,[96] indicate that transmission via X4 variants can occur in selected cases. The role of CCR5 D32 heterozygosity in protection from transmission has been more controversial. Though protective effects of CCR5 D32 heterozygosity have been reported,[30,97] the majority of studies fail to show a protective effect of CCR5 D32 heterozygosity on transmission.[28,37,40,87,88,90,98-100]

Polymorphisms in RANTES (-G403A, -C28G, In1.1C), the ligand for CCR5, were shown to be associated with increased risk of homosexual transmission.[59,61] This fits the finding that $CD4^+$ T cells from exposed uninfected individuals express higher levels of MIP1a, MIP1b and RANTES upon *in vitro* stimulation.[20,101]

Kostrikis *et al.* reported a significant increase of HIV-1 transmission to African-American infants homozygous for a promoter allele CCR5 C-2132T (or CCR5 C59356T, C630T).[99] This mutation was rare in Caucasians and Hispanics, and a potential role for this allele could not be assessed in these children. John *et al.* showed that maternal SDF 3'A heterozygosity was associated with an increased risk in transmission, which was more pronounced when transmission occurred via breastfeeding.[102]

CONCLUDING REMARKS

Our insights into the role of host genetic factors in the course of HIV-1 infection are growing. However, it is important to note that the majority of genetic factors described so far only have a relatively mild influence on the course of disease and can only partly explain differences in disease course among patients. Of note, only a minority of long-term nonprogressing HIV-1-infected individuals carry known protective alleles and, conversely, the presence of a protective allele does not warrant a benign disease course. Furthermore, the majority of frequently exposed but uninfected individuals do not contain CCR5 D32 homozygous or other protective genotypes, and therefore other mechanisms, such as a potent CTL response or reduced infectibility of $CD4^+$ T-lymphocytes, may contribute to the resistance to infection in these individuals.[79,103,104] Without doubt, the identification of novel HIV-1 disease-modifying genetic factors will be ongoing in the coming years, yielding further insights into the complex interplay between virus and host and the relative role of host genetic factors therein. Besides expanding our understanding of the pathogenesis of HIV-1 infection, this will hopefully lead to the identification of critical targets for therapeutic interventions.

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Discussion following lecture by H. Schuitemaker

Hoepelman: The first studies with anti-CCR5 antibodies were performed in heavily pretreated AIDS patients. Surprisingly, a rapid decline in the viral load is seen in these patients. That decline persists at least 16 weeks. I would have expected there would have been a rapid shift of the virus, because many patients probably harbour R4 virus. Do you think this is due to short follow-up or is there another explanation?

Schuitemaker: When CCR5 is not properly functioning in the CCR5 D32 heterozygotes, we see a protective effect, even in individuals who have X4 viruses, so I guess you achieve benefits by blocking only the R5-using population. In really late-stage patients with very low CD4 counts, we sometimes see a natural infection which the X4 viruses do not survive, because at that time, X4 viruses mainly use naive T cells as their targets, whereas R5 viruses use memory cells and this leads to a depletion of naive T cells. So it might be by this shift in the predator-prey relation that at that time there are no longer any T cells that could serve as target cells.

Hoepelman: My second question concerns the prostitutes in Kenya who do not get infected. I thought this was due to homozygosity for the deletion, but you stated you do not see that in Africa. So what is the explanation?

Schuitemaker: These women are highly protected by cytotoxic T lymphocytes and it is assumed that when these women keep working, they are protected. There is continuous antigenic stimulation of their immune system. However, when they take a holiday, there is an increase in infection. It is completely opposite to what was expected.

De Marie: Persistent viraemia with a GB virus type C has been recently recognised as a protective factor, even in HIV patients treated with antiretroviral therapy. Did you study the presence of these viruses in relation to the CR5 gene?

Schuitemaker: We are going to do that. It is very difficult to set up a proper study, because the GBVC viraemia is normally transient, and only viraemia is associated with a protective effect.

De Groot: The disease course in perinatal infection is much more rapid with incubation time of about a year. Is there information on the expression of CCR5 on neonatal T cells?

Schuitemaker: I am not aware of those data. HIV infection being a viral disease, the loss of cells was thought to be a result of virus-mediated killing. The more recent idea is that it is chronic immune stimulation that consumes the T cells, rather than virus-mediated killing. All cells go through the process of becoming infected and dying a natural death from apoptosis. And since neonates respond more strongly to all kinds of infection, you can imagine that HIV infection may have a more dramatic course.

Verbrugh: Since AIDS is a relatively new disease, the R5 polymorphism was presumably there before the virus hit mankind and also the difference across the globe probably was there as far as the dissolution of this polymorphism is concerned. What would the role of this receptor have been in other types of disease?

Schuitemaker: When people ask me this question, I always say that CCR5 protects you from the negative effects of eating polar bears. I say this because in the northern regions like Scandinavia there is up to 40% of that genotype. SCCR5 is an activation marker and allows T cells to respond to inflammation and lead to immunopathology. For some infections it is not good to overreact. It is pure speculation, but having this polymorphism could be advantageous. It is of interest that individuals that are CCR5 D32 homozygous have no record of immune deficiency.

Kimman: Is CCR5 used as a receptor by other pathogens? I am thinking of endogenous retroviruses. Our genome harbours many retroviruses. Have they used CCR5?

Schuitemaker: Not that I am aware of.

Van Strijp: The finding of a coreceptor may turn the main receptor also into a coreceptor. Are there experiments with overexpressing one of these receptors, CD4 or CCR5, to see whether one of the receptors can do it on its own? Which is the most important one?

Schuitemaker: It is possible to change the chemokine receptor, but you need CD4 in addition. Therefore, CD4 is still assumed to be the main receptor. So in artificial systems you can use CCR5, but also CCR2 and CCR4 next to CD4, and it works. However, HIV-2 virus can become CD4-independent after passage, and also SIV, the related virus in macaques, is very frequently CD4-independent. It could very well be that the HIV was first using only chemokine receptors and, after introduction into humans, the virus adapted to using CD4 because of the proximity of CCR5 and CD4. High expression of the coreceptor does not change the susceptibility of the cell and that CD4 is always the limiting factor. That is also why macrophages are not susceptible to SI / X4 viruses, despite the presence of CXCR4 and CD4 on macrophages. When you upregulate CD4, these cells become susceptible to X4 viruses. So it seems that CD4 is the main receptor.

Kuijper: To give it a different perspective, the CCR5 D32 deletion seems also to be a susceptibility marker of asthma.[1] I also have a question: Is there a difference in proliferative potential between NSI and SI viruses? How easily do they disseminate?

Schuitemaker: Among individuals dissemination of NSI viruses is more efficient than of SI viruses. The viral load however is not very different between NSI and SI carriers, being slightly higher in SI individuals. The burst size of the viruses, however, is different and SI viruses may be able to kill cells earlier, thereby not allowing as much reproduction as NSI viruses do. This more or less compensates for the fact that SI viruses have more target cells, due to the availability of more CXCR4 CD4 positive cells than CD4 CCR5 positive cells.

Kuijpers: So you take away the disseminating potential of the NSI part? And this could perhaps explain the anti-CCR5 monoclonal effect?

Appelmelk: Where is the DC sign in your scheme with the coreceptors?

Schuitemaker: DC sign is only expressed on dendritic cells. It is still a matter of debate however whether DCs themselves really become infected via DC sign or whether this molecule only facilitates the infection of T lymphocytes. I know that people have found polymorphisms in DC sign, but considering the fact that I heard about this two years ago and that nothing has been published on a correlation between these polymorphisms and the clinical course, I assume that there are no correlations.

Appelmelk: What happens to the virus when it makes these new variants at a molecular level? Does it change its outside, maybe in the sugar chains? Because, as you know, GP120 uses a ligand to attach to the DC sign.

Schuitemaker: Looking at the envelope, the variable domain 3 (the loop that sticks out and is important for the interaction with the coreceptor) becomes more positively charged in SI viruses. There are two specific amino acid residues in the SI viruses at position 11 and 28. One or both are positively charged in SI viruses.

McAdam: You mentioned the differing use of receptors for HIV-2. Could that account for the slowness of its natural history and the low viral load?

Schuitemaker: HIV-2 is a very different story. Even when you provide an optimal situation, the virus still hardly grows, in contrast to HIV-1. I think something in the genome attenuates the virus and therefore it takes so long before the HIV-2 leads to disease. I think that it is not just due to coreceptor use.

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