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Host and Viral Determinants of CCR5 Usage in HIV Infection

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Human Immunodeficiency Virus (HIV) infections cause an incurable devastating immunodeficiency in infected hosts. Extensive research on the virus life cycle has lead to tremendous advances not only in understanding the biology of the virus but also development of novel therapeutics. One of the critical factors involved in HIV infection is the C-C Chemokine Receptor 5 (CCR5) that is utilized by the virus for gaining entry into the cells. Polymorphisms in the gene and promoter region of CCR5 have been associated with disease susceptibility as well as disease progression[1]. On the other hand the evolution of the virus throughout the course of the disease is also in many ways associated with CCR5 usage. How current advances in understanding the complex relationship between the virus and host factors like CCR5 can lead to better treatment strategies or disease outcome remains unknown.

HIV gains entry into cells by binding to a cell surface receptor (CD4) and a coreceptor (CCR5 or CXCR4) via the gp120 subunit of the Env glycoprotein [2]. Following this initial binding via the gp120 subunit, the gp41 subunit mediates the fusion of the cellular and viral membranes thereby permitting viral entry. Based on the coreceptor usage HIV viruses can be classified into CCR5 utilizing (R5 tropic) or CXCR4 utilizing (X4 tropic) or capable of utilizing either of the coreceptors (dual tropic) [3]. This tropism of HIV varies though out the course of infection with early viruses predominantly R5 tropic and emergence of X4 tropic viruses later during the course of the disease. The viral determinants of coreceptor usage are well characterized. Based on the amino acid sequence in the V3 loop of gp120 [4] coreceptor usage can now be predicted using numerous computer softwares like Geno2pheno, Wetcat, WebPSSM [5]. However these software are more sensitive at predicting HIV-1 subtype B tropism compared to other subtypes. Hence clinically the usage of a laboratory assay like the "Trophile" assay is considered the gold standard in determining coreceptor usage. The determination of virus tropism by this assay relies on cloning of the Env gene and determining coreceptor usage via infection of CCR5+ or CXCR4+ cells with viruses pseudo typed with the patient Env [6]. However this assay has its own limitations as well. Minor CXCR4 utilizing species can be overlooked by this assay. More recently some studies suggest that deep sequencing of the Env form patient derived cellular DNA or viral RNA maybe better predictive of minor CXCR4 utilizing quasispecies [7].

This information has become increasingly relevant owing to the development and clinical use of CCR5 inhibitors like Maraviroc (MVC). Before initiation of therapy the determination of virus tropism via clinically approved Trophile assay is being recommended. However recent studies suggest that deep sequencing of the V3 region can provide a more sensitive and accurate assay for determination virus tropism specially when a low frequency of non-R5 tropic viruses is present [8]. A more thorough analysis of minor non-R5 utilizing Envs maybe better predictive of successful therapy with MVC. The development of resistance against MVC is a limitation like any other anti-retroviral. Interestingly resistance to MVC occurs via two separate pathways. The virus either evolves a switch in the tropism to CXCR4 usage [9] or acquires specific mutations in the gp120 region that allow for use of MVC bound CCR5 [10]. In either case whether the parental virus genotype prior to MVC therapy or the host CCR5 promoter and gene polymorphism affect this phenomenon is not known. Hence understanding the host and viral genetics of CCR5 usage is an important factor not only in understanding the virus life cycle but also has implications for anti-retroviral therapy.

It is clear that the HIV Env glycoprotein is constantly evolving in HIV infected patients [1,11]. Amongst these evolutions the changes in the Env glycoprotein related to coreceptor usage are extensively studied and well established [11]. However the factors that influence this evolution of viruses remain largely unknown. It is known that R5 tropic viruses predominate during early infection with a switch to X4 usage late during the disease. However in 50% of the patient the virus does not undergo coreceptor switch and maintains R5 tropism [12]. What factors allow for or facilitate coreceptor switching are still unclear. Studies by various groups have shown that limiting amounts of CCR5 on the cell surface of CD4 cells may facilitate X4 switch. In fact, experimentally, culture of the virus in limiting amounts of CCR5 can induce coreceptor switch [13]. On the other hand suppression of X4 viruses by the immune system has been suggested as another mechanism behind emergence X4 viruses in the later stages of the disease when the immune system is compromised. Whether coreceptor switch is a cause or consequence of a failing immune system in HIV infections is again a question that remains unanswered. The evolution of virus towards X4 usage also varies by the subtype of the virus. Certain subtypes like subtype C HIV-1 virus largely maintain their R5 tropism throughout the disease [14,15]. On the other hand a 50% of subtype B viruses undergo coreceptor switch during late stages of disease [16]. With increasing spread of subtype C in different regions of the world the question arises as to what factors regulate coreceptor usage in different subtypes.

The earliest evidence of a role of CCR5 in HIV infection came from the observation that individuals homozygous for the CCR5Δ32 mutation (CCR5Δ32-/-), a deletion of 32 base pairs in the coding region of CCR5 [17] were resistant to HIV infection. The lack of a functional CCR5 on the cell surface was demonstrated to be the cause of this resistance. But more interestingly the CCR5Δ32 heterozygous (CCR5Δ32+/-) individuals have lower levels of CCR5 and show slower progression to AIDS [18]. The fact that CCR5Δ32+/- individuals are not resistant to infection but only to progression raises the question as to whether CCR5 levels influence HIV pathogenesis more than HIV infection per se. These suggestions are further supported by numerous promoter polymorphisms that tend to regulate the expression of CCR5 on the cell surface and have also been associated with HIV disease progression.

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How does CCR5 cell surface expression and HIV Env phenotype determine HIV disease outcome is a question that remains to be examined in detail. Recently we have demonstrated using cell lines with different levels of CCR5 that bystander apoptosis inducing activity of HIV Env glycoprotein is dependent on cell surface levels of CCR5 as well as Env fusogenic activity[19]. However the interplay between CCR5 levels seems to be more relevant to bystander apoptosis than HIV infection and replication. If this hypothesis were true then HIV infection with an R5 tropic virus in individuals with low levels of CCR5 would allow for virus replication in the absence of CD4 decline. Some of the long term non progressors in HIV may have delayed disease progression due to this phenomenon. In this scenario another factor to consider would be the evolution of virus to X4 usage. In individuals with CCR5 low phenotype like CCR5 Δ32+/- genotype, coreceptor switch maybe a prerequisite to progression to AIDS. Hence the slower disease progression rates maybe a consequence of slower evolution of virus to X4 phenotype. Whether this is a direct consequence of selective pressure on the virus for limiting amounts of CCR5 or due to immunological factors remains to be determined.

CCR5 protein is a key determinant of HIV pathogenesis and disease progression. The polymorphic nature of this gene and the constant evolution of HIV Env glycoprotein that binds CCR5 as a coreceptor suggest that this interaction is critical to understanding HIV biology. More importantly understanding the complex relationship between host and viral determinants of CCR5 usage in HIV infections could help predict disease progression and devise new strategies for therapeutic intervention.

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