HIV PATHOGENESIS-EMERGING CONCEPTS

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Abstract

CD4 receptor molecules on 'T' lymphocytes and macrophages have already been identified as the route of entry for HIV. However CCR5 and CXCR4 are identified only recently as the second receptors for HIV on macrophages and 'T' lymphocytes respectively. Presence of homozygous CCR5 Δ 32, a defective CCR5 gene leads to resistance to HIV infection in the risk groups. While heterozygous CCR5 Δ 32 leads to delay in the progress of HIV infection to AIDS.

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Since the beginning of the HIV pandemic, many a questions still remain unanswered. The most intriguing of them is susceptibility to HIV. Even in the same risk group, exposed to same risk factors only some of the individuals get the infection while others do not. Some of the siblings (about 20%) born from the same HIV infected mother develop AIDS whereas others escape. Another pertinent question is why some HIV infected people progress rather faster than the others towards AIDS? What protects the uninfected? What slows the progress of the HIV to AIDS? After years of research scientists have tried to find some of the answers to these questions.

Though possible HLA differences were postulated to be the cause of these differences [1], recent evidences suggest that the good fortune of some individuals, who are partly or fully resistant to HIV infection are due to possession of a particular variant of a gene involved in immunologic function. At present this gene and its variations are intensely studied for strategies to prevent and control HIV infection particularly to HIV-1.

Immediately after the discovery of the virus in 1984, at the National Cancer Institute, search for these factors were initiated. In a cohort study, groups of several hundred individuals at high risk of HIV infections-viz. homosexual men, IV drug abusers and hemophiliacs who had received contaminated blood products were monitored for years by physicians. The patients (with their consent) supplied blood, tissue samples and case reports to researchers for study of cell biology and DNA genetic testing. The cohorts

were divided into (a) those infected with HIV vs those who remained free of it after extensive exposure (b) infected patients who progressed to AIDS rapidly vs those who progressed to AIDS slowly, if at all (c) infected HIV, who developed a specific type of infection example, *Pneumocystis carinii* pneumonia vs those who did not. Their genotypes were studied [2].

An individual inherits two copies of all genes outside the sex chromosome (one copy from the mother and one copy from the father). The pair of alleles of a particular chromosomal locus or gene address constitute the genotype. One who inherits two identical alleles of a given gene is said to be a homozygote; one who inherits two distinct alleles is said to be a heterozygote. After more than a decade of relentless research for their differences in multiple centres of excellence, finally a ray of hope appeared in 1995 [3]. By 1990 it was well documented that HIV causes immunodeficiency mainly by depletion of white blood cells known as T lymphocytes that displayed a protein CD4 on their surface [4]. Many aspects of immune response against the virus are directed by T cells. Another immune cell, the macrophage also carry the CD4 receptor and are also infected by the HIV virus. As the macrophages are not destroyed by the virus, the infection persists for years. Thus the HIV virus has a cytolytic effect on the T cells but it has no such effect on the macrophages [5].

The glycoprotein gp120 of HIV virus attaches to CD4 receptor molecules of the cell to gain entry into them. Though CD4 receptor is essential, it is not sufficient by itself to allow the entry of HIV. The second

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receptor has been recently known as a chemokine receptor. Chemokines or chemoattractant cytokines, are short 10 kd amino acid chains which are responsible for luring immune cells to injured or diseased sites. The chemokines viz RANTES (Regulated upon activation normal T-cell expressed and secreted), MIP-1 α (Macrophage inflammatory protein), MIP-1 β , possibly interfere with HIV entry into immune cells by binding to and blocking some cell surface proteins that HIV requires for access to the interior [6]. These cell surface proteins are known as receptors and they physiologically mediate the chemotaxis of T-cells and phagocytic cells to areas of inflammation. Choe et al in 1996, discovered the second receptor on CD4 T cells called the chemokine receptor CXCR4. Simultaneously the second receptor on the macrophages was discovered it is called CCR5 [7]. CXCR4 is an α chemokine where the first two cysteine residues have an intervening amino acid, whereas CCR5 is a β chemokine where the first two cysteine residues do not have an intervening amino acid [8].

To keep the records of pathogenicity straight, the HIV virus initially infects macrophages by its gp 120 molecule by attaching to two receptors, i.e., CD4 and CCR5 (Fig-1). These are called the macrophagetropic strains or M-tropic strain or R5 strains. They are also known as transmitted strains [9]. Once inside the macrophages, it synthesizes large quantities of the virus. After years of infection the constantly mutating virus alters the gene for gp120 which changes its allegiance to CXCR4 instead of CCR5. Thus it becomes T lymphotropic as it gains entry via CD4 and CXCR4 receptor on its surface (Fig-2). These HIV strains are known as T-tropic strain or X4 strains. But here the disease takes a dramatic turn. The virus behaves here as cytolytic and kills the T lymphocytes after multiplying within it. The T lymphocyte count steadily dips

from 1000/cmm to <200/cmm when opportunistic infections set in and it becomes an AIDS defining condition [10]. However in another cohort study Winkler et al in National Cancer Institute, USA, found stromal derived factor (SDF-1) which is a principal ligand for CXCR4 has protective effect when its structural defective homozygous variant SDF1-3'A/3'A is present in some individuals. The protective effect against AIDS is twice as strong as that conferred by variants of CCR5 [11].

Liu and colleagues in July 1996 characterized the genetic sequence of CCR5 in both the groups of individuals in the cohort studies. It was found that the groups which were protected from HIV infection were having 32 nucleotides missing from the gene of CCR5 known as CCR5 Δ 32 gene. The 32 base pair deletion in the CCR5 gene correspond to the second intracellular loop of CCR5 and encodes a severely truncated molecule. They experimentally found that this CCR5 Δ 32 was producing a truncated CCR5 receptor protein which either fails to reach the cell surface or is so deformed that it cannot attach to HIV [12]. They found that the deletion mutant for the protection against HIV was highly significant statistically. Those individuals who are homogeneous for CCR5 Δ allele are resistant to HIV infection but those who are heterozygous may be infected with HIV, but progress slowly to AIDS, if at all and they have a lower level of viremia. In these cases the virus has 4-10 fold reduced ability to replicate [13]. Mishrahi in one study found that children with CCR5 Δ 32 heterozygosity are not protected against mother to infant transmission but, if, infected, there is a longer time before adverse clinical outcome develops than in children with wild type CCR5 genotype [14]. With increasing HIV exposure the prevalence of Δ 32/ Δ 32 CCR5 genotype increases. The wild type CCR5 and CCR5 Δ 32 alleles

Fig. 1 : Entry of HIV into macrophages and entry inhibition (M-Tropic Strain)

Fig. 2 : Entry of HIV into T lymphocytes and entry inhibition (T-Tropic Strains)

can be detected easily by polymerase chain reaction (PCR) technique using EcoR1 restriction enzyme digestion and running the digested DNA in agarose gel electrophoresis [15].

This recent knowledge has important bearing on the pathogenicity of HIV and potential for a possible therapeutic agent against CCR5-HIV-1 interaction.

On full analysis of the available data, it was found that Russians have the mutant allele in 13% of the population, Caucasian Americans have 11.1% for Caucasian European it is 10.0%, African American 1.7% and for Native American, African and Asian population it is 0% [16]. A study on the Indian population is yet to be done about this protective factor which limits HIV infections.

The final word about the protective factors against HIV has not yet been told as HIV infection has been reported in a person with hemophilia and several homosexual men with CCR5 Δ 32 homozygotes[8]. This only shows that research has to go on, for, the war on HIV seems to be endless.

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