ORIGINAL CONTRIBUTION

HIV-Disease and Host Allelic Polymorphism in Long-Term Non-Progressors

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Since its recognition in the early 1980's, Acquired Immunodeficiency Syndrome (AIDS) has become a pandemic, and in 1997 it was estimated that 30-40 million individuals worldwide are infected with the Human Immunodeficiency Virus (HIV). While it remains an incurable and potentially devastating infection, particularly in regions where modern health care is unavailable, recent years have seen striking advances in the understanding of AIDS pathology, development of diagnostic modalities, and rational design of new treatments. Recently it has been recognized that there exists a subset of individuals who, while infected with HIV, remain asymptomatic with regard to the classical manifestations of AIDS. These individuals have been called "long-term survivors" or "long-term non-progressors" (LTNPs). Similarly, there appears to exist a subset of exposed-uninfected individuals who, while exposed to virus multiple times, remain uninfected. This article reviews the current understanding of how these individuals remain resistant to HIV progression.

INTRODUCTION

Both long-term non-progressors and exposed-uninfected individuals have generated significant interest in the HIV/AIDS research community because their existence suggests the possibility of resistance to both HIV infection and disease progression. Whether there exists one unifying mechanism, or multiple mechanisms of resistance, the potential importance of knowledge gained from these groups has sparked a major research effort which over the past two years has yielded findings with wide-ranging implications for AIDS pathology and treatment. The goal of this paper is to discuss some of the molecular factors that are important in natural resistance to HIV. The primary focus will be on recent findings that certain host alleles may help determine the rate of progression to AIDS in some patients.

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A REVIEW OF HIV PATHOGENESIS

The purpose of this paper is not to provide a detailed analysis of AIDS pathology or the molecular virology of HIV. A basic review of the pathobiology and the clinical consequences of infection are, however, necessary as a basis for further discussion. The causative agent of AIDS is the Human Immunodeficiency Virus (HIV), with the most common strain world-wide being HIV-1 (1). HIV is classified in the human retrovirus family based on its structural characteristics and life-cycle (2). The mature viral genome consists of single stranded (+)-strand RNA. Infection at a cellular level requires that this RNA be reverse-transcribed by a virally encoded reverse transcriptase enzyme into a double-stranded DNA copy, which may then be integrated into the genome of a host cell. In this integrated state, the virus is called a provirus, and is considered to be latent. Upon excision of the viral genome, active replication and expression of viral proteins occurs, leading to propagation of the virus and death of the host cell. This process is complex and is influenced by both viral and host factors.

It is ultimately the nature of the interaction between any pathogen and its host which will characterize disease manifestation in the host. In the case of HIV, the primary target host cell is a subset of lymphocytes known as CD4+ (helper) T lymphocytes (3). It is the destruction of these cells, which are fundamental to every aspect of acquired immunity, that results in the devastating sequelae of HIV infection. The HIV surface envelope glycoprotein, gp120, uses the CD4 molecule as a receptor, allowing the virus to enter target cells and establish infection. As a result, other cells which express CD4, including certain subsets of macrophages, are also vulnerable (3). The primary immunopathogenic consequences of HIV infection include ablation of the CD4+ T cell population, destruction of the immune microenvironment required for generation of new immune cells, and a dysregulation of B-cells, which are the cells responsible for antibody production (3). It is a combination of these events, and a general dysregulation of immune function, which causes severe immunocompromise in HIV-positive individuals. AIDS is a syndrome defined by a set of characteristic opportunistic infections and neoplasms, resulting from compromised immunity. While the list of AIDS-related opportunistic illnesses is remarkably long, and changes over geographic regions and time, some common manifestations of AIDS include: *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, Kaposi's sarcoma, B-cell lymphoma, and various neurological syndromes (3). Individuals with intact immunity are generally able to eliminate these pathogens and prevent neoplasia, but in the absence of a functional immune system, they thrive unabated. It is these supervening illnesses which ultimately cause death in most patients with AIDS.

The normal clinical progression from HIV-infection to AIDS is never exactly the same in any two patients, but has well-defined general characteristics. The virus initially establishes infection in central lymphoid tissues such as spleen and lymph nodes, where it causes a radical depletion of immune cells. This initial phase occurs generally within the first few weeks of infection and may present with fever, chills, pharyngitis, skin rash, and various symptoms resembling other viral infections (3). HIV infection is sometimes misdiagnosed or missed completely due to the non-specific nature of these symptoms, which are collectively referred to as seroconversion sickness. Their appearance generally heralds the development of HIV-specific antibodies over subsequent weeks. For reasons which remain unclear, the virus then enters a clinically latent phase. During this time, CD4+ T cell counts may rise, but may never reach normal values. Early techniques to detect HIV replication, such as peripheral blood mononuclear cell (PBMC) culture, were relatively insensitive, leading to the mistaken assumption that the period of clinical latency was accompanied by true virologic latency. Since most antiviral drugs target viral replication, the latency hypothesis suggested that early treatment without high levels of replicating virus might not be effective. Subsequent studies, however, detected high level replication in lymphoid tissue, and documented the destruction of lymph node architecture (4). Since the development of more sensitive techniques such as quantitative reverse transcription-polymerase chain reaction (RT-PCR), it has been demonstrated that the virus replicates in t tissues and bloodstream from infection until death in mo individuals (5). The concept of set-point has become impo tant recently in assessment of disease state and prognosis (7 Based on a conceptual balance between constant viral rep cation and clearance by the immune system, set-point is measure of the quasi steady-state level of viremia which r flects this balance (8). Low set-point is generally thought be an indicator of good prognosis, while a high set-point h a negative correlation (7). The length of time required f sufficient immunocompromise to occur such that opportu istic infections can invade the body varies widely, and ma be influenced by many host and viral factors which will b discussed further. Opportunistic infections generally occ at a CD4+ T cell count below 150 cells/mL, and current re ommendations are to start drug therapy when the CD4+ cell count falls below 500 cells/mL, and when viral load higher than 10-20,000 copies/mL (5). The average length time from infection to death in North America is approx mately ten years (9). Recently, however, effective drug coc tails targeting various stages of the viral life cycle have yielde encouraging results. These drugs, known as Highly Activ Anti-Retroviral Therapies (HAARTs), hold significant hop of increased life expectancy for HIV-positive individuals (10

MECHANISMS OF RESISTANCE TO HIV

It has become clear that there exists a subset of HI positive individuals who remain asymptomatic for longer tha the normal period of disease progression (11). Originally, was thought that these individuals represented the high ex treme of a gaussian distribution of progression times within population. Research, however, has recently demonstrate that this is not the case, and suggests instead that these indi viduals share common features which may account for thei apparent protection from progression to AIDS. Another grou which suggests that natural resistance to HIV exists are thos individuals in high-risk cohorts who have been exposed t the virus, some repeatedly, yet have not been infected. Thes include individuals engaging in high-risk activity such as in travenous drug use, or unprotected sex with a known HIV positive person, as well as people transfused with HIV-posi tive blood (11). The identification of both long-term non progressors and exposed-uninfected individuals has caused much excitement within the AIDS research community. By studying people who appear to possess natural protection from HIV infection, investigators hope that deeper insight will be gained into mechanisms of pathogenesis, and that new thera peutic and vaccine strategies will be elucidated.

Several putative mechanisms have been postulated to explain HIV resistance. Virological studies have looked for attenuated HIV strains in long-term non-progressors, propos ing that defective viral replication, or attenuation of some other virulence factor, accounts for better prognosis among these patients (11). Such searches have proved fruitful in identify ing some virus strains that carry attenuating mutations (12). Other patients have been identified in which the integrated provirus appears unable to be excised from host cell genomic

DNA, although it remains unclear whether this is a result of viral or host factors (13). Despite these promising findings, it is unlikely that every long-term non-progressor is infected with an attenuated virus strain. This intuitive supposition has been confirmed (11). In addition, clinicians know well that two partners with the same strain may have widely divergent clinical courses. Thus, there must be host factors which predispose some of these individuals to a favorable outcome.

There are distinguishing immunological and serological features shared by some long-term non-progressors. The most consistent findings in these individuals are a low viral burden, as well as a strong CD8+ cytotoxic T-lymphocyte (CTL) anti-HIV response (14). Even in normal progressors, a strong CD8+ anti-HIV response correlates with a relatively good prognosis. This fits well with a general understanding that the immune system eliminates viral pathogens, and other infectious intracellular pathogens, largely by killing infected host cells via the cytotoxic activity of CD8+ CTL (4). In one study, PBMC's from long-term non-progressors were relatively resistant to infection with HIV-1 (14). This resistance, however, disappeared upon depletion of CD8+ cells, suggesting that in these patients resistance was not an intrinsic quality of the target CD4+ cells, but rather the result of a strong CD8+ T cell-mediated inhibitory response. Some studies show that exposed-uninfected individuals seem predisposed to mount particularly vigorous cellular responses, suggesting that an early powerful activation of CD8+ CTLs may result in protection from infection (15). Whether these individuals are genetically predisposed to have particularly potent cellular responses, or whether some epigenetic factor has shifted their immune profile, remains to be determined. It appears that humoral responses, including strong neutralizing antibody production, do not appear to be particularly protective (4). There is also no convincing evidence to date that any specific human leukocyte antigen (HLA) type confers longevity in HIV-infection, but conclusive studies of this possibility will be conceptually and logistically difficult to perform and interpret, owing to the enormous variation in HLA types within and between human populations.

It was recognized nearly a decade ago that gp120 binding to CD4 alone was not sufficient for cellular invasion by HIV, but that a coreceptor must exist which collaborates in this function (11). The search for coreceptors remained fruitless until a separate field of investigation came to maturity. It was with the discovery and description of chemokines and their receptors that several important steps were taken toward discovering HIV-1 coreceptors. Chemokines are a distinct set of secreted proteins, which are chemotactic for various cell types, but possess other cytokine-like properties, hence the name chemokine (16). This group of molecules is generally subdivided into two groups, the α (C-X-C) and β (C-C) chemokines, based on amino acid sequence at a conserved site. The chemokines bind to specific receptors on the surface of target cells to elicit a response. These receptors are G protein-coupled molecules which appear to play an important role in inflammation and immunity (16).

Concurrent with the search for HIV-1 coreceptors was the search for CD8+ T-cell-derived suppressive factors. It was recognised that CD8+ cells could limit viral spread not only through direct cell-mediated killing of infected cells, but also through secretion of some unknown inhibitor of viral replication in CD4+ T cells (17). Interestingly, it was also noted that CD8+ cells from long-term HIV survivors exhibited greater soluble suppressor activity than controls (18). In 1995, this suppressor activity was discovered to be mediated by three β-chemokines: RANTES (regulated-upon-activation, normal T expressed and secreted), macrophage inhibitory protein-1 alpha (MIP-1α), and MIP-1β (19). These molecules appeared to inhibit replication of M-tropic primary HIV-1 strains, a viral subset which predominates in early HIV infection, by blocking viral entry into cells, suggesting that the coreceptor of these strains might be a β-chemokine receptor. Five independent groups subsequently demonstrated that CCR5, a β-chemokine receptor which binds RANTES, MIP-1α, and MIP-1β, is used by M-tropic HIV-1 virus strains as a coreceptor for cell entry (11). Subsequently, much has been learned about the role of chemokines in HIV infection. The entry of M-tropic viruses requires the formation of a trimolecular complex between gp120, CD4 and CCR5; binding of gp120 to CD4 is thought to cause exposure of cryptic domains in gp120, allowing it to bind effectively to CCR5 (20). CD4-CCR5 interactions are blocked by neutralizing antibodies against gp120, and also by RANTES, MIP-1α, and MIP-1β, explaining their ability to inhibit viral entry into CD4+ cells (21). It should also be noted that CCR5 is not a universal coreceptor for all HIV-1 strain variants. It appears that CXCR-4, an α-chemokine receptor, serves as the main coreceptor for T-tropic viruses, a different viral subset which tends to predominate in late phases of the disease (22). There are also dual-tropic strains which use both coreceptors, as well as some which use other chemokine receptors (11).

It was a natural next step to question whether an allelic polymorphism or mutation in the CCR5 gene could account for viral resistance in long-term non-progressors and exposed-uninfected individuals. Previous studies had demonstrated that CD4+ T cells from a cohort of exposed-uninfected individuals were resistant to infection, and that this resistance was associated with RANTES, MIP-1α and MIP-1β activity (19). It was subsequently shown that two of these resistant individuals were homozygous for a mutant CCR5 allele (23). The identified mutation is a 32 base-pair (bp) deletion in the CCR5 gene, resulting in a truncated protein which is unable to carry out normal chemokine signaling activities, or to serve as a functional coreceptor for M-tropic HIV-1 strains (23). The deletion is thought to have arisen as a result of a recombination event involving a 10-bp direct repeat flanking the deleted region.

The functional implications of carrying the mutant allele, referred to by some as Δccr5, have been studied in large-scale genetic analyses of both normal populations and high-risk cohorts. In a study of 700 healthy Caucasian individuals, the allele frequencies were estimated to be 83% wild type homozygous (CCR5/CCR5), 16% heterozygous (CCR5/Δccr5) and 1% (Δccr5/Δccr5) homozygous (24). Furthermore, these values do not differ significantly from predicted Hardy-Weinberg frequencies, demonstrating that the mutant allele

does not affect fitness. While it was originally thought that the Δccr5 allele occurred only among people of European descent, it has recently been detected in South America, the Middle East and Indian subcontinent, but remains undetected in African or Japanese populations (25, 26). The main questions of interest have been whether bearing the Δccr5 mutation, in a heterozygous or homozygous state, confers protection from infection, and whether it delays progression of an established infection. It was hypothesized that if the Δccr5 mutation confers an advantage in terms of viral resistance, the frequency of homozygotes should be significantly lower in HIV-1 infected populations than in the general population; also, there should be a higher frequency of the Δccr5 mutation among exposed-uninfected individuals of high-risk cohorts. These hypotheses were both confirmed (24). Lower frequencies of the null allele among HIV-positive populations were found to be the result of fewer homozygotes and heterozygotes, suggesting that even one copy of the mutation confers some degree of protection. In heterozygotes, this may be due either to a relative decrease in the number of functional CCR5 receptors expressed, or to the mutant receptor acting as a dominant negative allele. One of the most striking findings in the initial studies was that Δccr5/Δccr5 homozygotes, who are essentially human knockouts for the CCR5 gene, were never found among HIV+ populations (24). This would strongly suggest that the null allele does in fact provide resistance to infection by primary HIV-1 virus strains. Recently, there have been a few isolated reported cases of HIV-positive Δccr5/Δccr5 homozygotes, demonstrating that the protection is not absolute or impenetrable (28).

The answer to the second question, whether inheriting Δccr5 results in a slowing of disease progression, has not been as clear. There is now, however, convincing evidence that heterozygosity for the Δccr5 allele does tend to promote long-term survival and a delayed progression to full blown AIDS when compared to wild-type homozygotes. In a study of 1955 individuals from high-risk HIV cohorts, groups who had been infected with HIV-1 for over 10 years without progression to AIDS had a significantly higher frequency of heterozygotes bearing the Δccr5 allele than rapid-progressor controls (24). Among some high-risk cohorts, Δccr5 heterozygotes were twice as frequent among long-term survivors, compared to rapid progressors. Epidemiological data from a recent publication involving the same cohorts also suggests that another chemokine receptor, CCR2 may be important in the rate of progression to AIDS (27). An identified mutation (CCR2-64I) in the gene which encodes the receptor has been identified in both Caucasians and African Americans. While conferring no immunity to infection, possessing even one copy of the mutation appears to be correlated with a 2-4 year increase in survival. This study, which involved 3003 patients, confirms earlier assertions that homozygosity for wild-type CCR2 and CCR5 is positively correlated with rapid progression to AIDS, while possession of a mutant allele for CCR2 or CCR5 demonstrates significant correlation with survival for 16 or more years, without progression to AIDS.

It is not a novel concept that bearing one potentially deleterious mutation could provide protection against another potentially more devastating disease. It has been known for many years that in the heterozygous state, the sickle-cell anemia mutation results in protection against malaria (29). Recently, it was also demonstrated that cells heterozygous for a mutant cystic fibrosis transmembrane conductance regulator (CFTR) allele, which in the homozygous configuration causes cystic fibrosis, are protected against infection by *Salmonella typhi*, the microbe which causes typhoid fever (30). It is now widely recognized that the presence of mutant chemokine receptor alleles in some individuals results in an HIV-1 resistant phenotype. It is important to note, however, that this cannot explain all exposed-uninfected individuals, and that other mechanisms are being explored. One particularly interesting puzzle is that of a cohort of prostitutes in the Gambia who, while exposed multiple times, have not been infected (15). This cannot be explained in terms of Δccr5-mediated protection, as this allele does not appear to be present in individuals of African descent. It is also unlikely that their non-infection is due to purely virological factors, such as a partially attenuated virus, as they have certainly been exposed to multiple virus strains. Thus, some other factor, such as predisposition toward a more appropriate anti-HIV immune response, may be responsible for their resistance to infection. In a recent paper, Cohen and Fauci also warn against the assumption that the Δccr5 mutation alone is responsible for long-term non-progression even in those who bear the null allele, since there is almost undoubtedly a strong immune component to maintaining a non-progressor state (6). They also suggest that the viral set-point, which may be influenced strongly by the Δccr5 allele, is probably the more relevant piece of clinical information for predicting the rate of disease progression.

While possession of the Δccr5 allele is not a universal mechanism of HIV-1 resistance, it is the first mechanistically feasible and therapeutically promising explanation for the existence of long-term non-progressors and exposed-uninfected individuals. There are, without a doubt, other mechanisms acting to limit virus replication and prevent destruction of CD4+ T cells which will be elucidated in coming years.

CONCLUSION

Research has shown that certain individuals may possess a genetic basis for protection against infection with HIV. The most convincing evidence has demonstrated that mutant chemokine receptors, which are unable to be used as co-receptors by the virus, can confer protection against viral invasion of target cells and subsequent establishment of systemic infection. Protection by this means, however, does not account for all naturally immune individuals, and so the search continues for other protective mechanisms. In the first decade of the epidemic, while many people were dying of AIDS, another population was "living with HIV". These included long-term survivors, who dealt with the difficulties of opportunistic infections and their therapies, as well as long-term non-progressors, many of whom even now remain in good health. With improvements in antiviral therapy, the unique

stresses and considerations of living with HIV will be seen in a larger percentage of patients. As their numbers grow, it will become increasingly important as clinicians, and as a society, to understand the difficulties individuals living with HIV face, and to thoughtfully develop the most supportive and effective ways of caring for them and sharing their lives.

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