J. Expt. & Clin Anat. 1(1): 30 – 33 (2002

JECA

HIV: The Roundtable Virus

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ABSTRACT

The paper concentrates information on the cell biology of the immunological crisis following the HIV infection, and on key aspects of the complex molecular biology of propagation of the virus in the organism, which explain why AIDS has no medical solution for now and in the foreseeable future. The enormity of the human tragedy is discussed in molecular terms all in effort to reiterate the importance of prevention programmes, education and counseling as the only effective methods of curbing the spread of the disease.

Key Words: HIV, quasispecies, retrovirus, reverse transcriptase, integrase, AIDS.

As the year 2001 draws to a close, over 40 million people face a future dominated by Acquired Immune Deficiency Syndrome, AIDS, a fatal disease unknown a few decades ago. With the HIV – positive population on the increase , and with over 5.3 million new infection cases in the year 2000 alone (WHO, 2000), the annual number of deaths from AIDS is expected to rise for many years to come. In sub-Sahara Africa where over 60% of the current global cases are reported (Piot et al., 1992), the epidemic is fast assuming the proportions of a terrible pandemic. This spells doom for humanity, made the more so by the fact that from the time of its first discovery in North America in 1981 till date, scientists have been trying to find a drug or vaccine for the disease but to no avail.

The ancestral form of the HIV occurs in a stable and non- fatal state in many animals ranging from sheep to monkeys (Hirsh et al., 1998). We do not know how and what species the ancestral virus mutated into its present lethal form, or in what way it was unleashed upon its first human victim. However, quite much is known about the mode of transmission, pathogenesis and clinical spectrum of the infection, including the cell and molecular biology of propagation of the HIV in the host organization. In this paper, we aim to demonstrate in molecular terms why medical solution to AIDS remains elusive and consequently, why preventive strategies continue to be only effective methods of curbing the spread of the disease.

Immunological Consideration

We live in a biological envelope dominated by microbes. In addition of these, microbes occur on the surface of our skin and in our body fluids and cavities. These microbes either of the environment or of the body flora, are kept at bay from penetrating the body tissues to cause disease conditions by the immune system. The immune system performs this protective function in two departments: innate immunity and acquired immunity. While innate immunity directs its action generally on disease causing agents, acquired immunity, so called because it is acquired in the course of historical development of the organism, is directed on specific pathogens or toxins. Much of the body immunity is due to acquired immunity. It is acquired immunity which is paralysed by the HIV (Cohen et al. 1994; Liblan & Witzburg, 1996: Vershigora, 1996)

Acquired immunity consists of two components: humoral immunity and cell-mediated immunity. While humoral immunity is achieved by formation of immunoglobulins against specific pathogens or toxins by the B- lymphocytes, cell – mediated immunity is achieved by the action of lymphocytes of the T- population which destroy specific pathogens or immunogens. The T – lymphocytes of the cell – mediated acquired immunity are divided into three

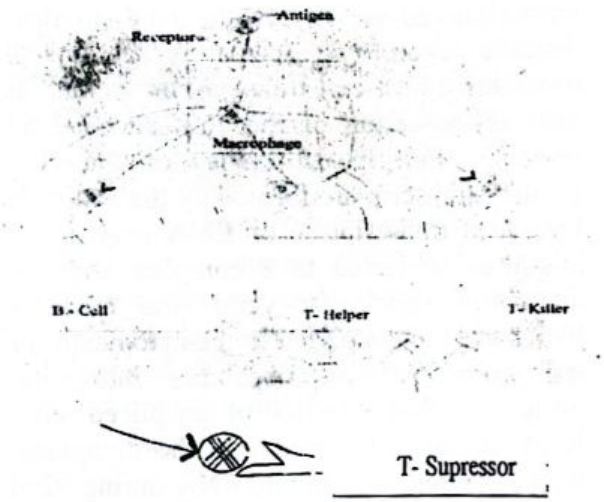

Fig. 1. Macrophage – Lymphocyte interaction in immune response.

sub-populations: the T – Killers, the T-helpers and the T-supressors. The T-killers are the main actors in cell – mediated acquired immunity.

Acquired immunity critically depends for its action on the cooperative interaction involving the tissue macrophages and the B and T-Lymphocytes. This interaction is presented in Fig. 1.

The invading pathogen is first phagocytized and partially digested by the macrophages, which then liberate and present the antigenic products of the digestion to the B – and T-lymphocytes by cell- to –cell contact. This presentation leads to activation of the specific lymphocyte clones. Apart from antigenic presentation, the macrophages elaborate the hormonoid, interleukin – 1, which promotes growth and proliferation of lymphocytes. The T- helper constitutes the coordinating centre of the macrophage – lymphocyte interaction. The T – helper performs this function by secreting lymphokines including interleukin – 2, -3, -4, -5, and –6, which enhance the activities, growth and proliferation of the other lymphocytes. This way, the B-lymphocytes are stimulated to produced copious quantities of antibodies, specific for the invading antigen; the T- Killer lymphocytes are stimulated to proliferate and produce Killer cell clones capable of destroying the particular antigen; the T- suppressor lymphocytes are stimulated to control and set the level of the immunological reaction according to the tide of the invading foreign agent. The T-helpers also produce interferon - $ as well as the hormonoid called the macrophage migration inhibiting factor (MMIF) which inhibits macrophage drift from the site of immunological aggression. By this cooperation, acquired immunity functions to generate the required titre of antibodies and the optimal quantity of T – Killer clones requires to ward off and completely eliminate any immunological threat (Ekpo & Ijeh, 2001; Vershigora, 1996; Guyton, 1996).

The tragedy with AIDS is that the HIV parasites the T – helper lymphocytes(Ekpo & Ijeh 2001; Vershigora 1996) thereby destroying the coordinating centre of the macrophage – lymphocytes interaction, consequently throwing the immune system into chaos. Humoral and cell – mediated immunity are paralyzed and the body becomes vulnerable to microbes and toxins including even those of the normal bosy microflora. Indeed, opportunistic infection is indicative of a progressive HIV disease (Cohen et al., 1994; WHO, 1994). The HIV also parasites the macrophages (Peter et al., 1992; WHO 1994) which are responsible for carrying the virus to the brain.

Molecular mechanism of the HIV infection

The HIV is a retrovirus. It belongs to the family Retroviridae, sub-family Lentivinae – so named because of the long incubation period between infection and over disease. The anatomical sketch of HIV – 1 together with aspects of the viral genome(Cohen et al. 1994; Essex et al., 1994) is presented in Fig. 2.

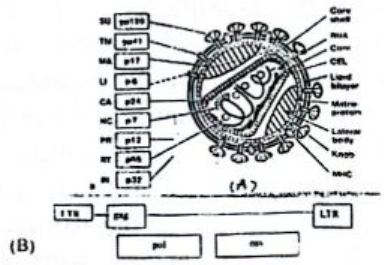

Fig 2 (A) The HIV – 1 Virion (Essex et al., 1994)
(B) The HIV Genome (Cohen et al., 1994)

The virus consists of a nucleoprotein core surrounded by a lipid bilayer of about 0.04 um thickness, containing viral surface (gp 120) and transmembrane (gp 41) proteins.

the lipid bilayer is of celluar origin, acquired during previous budding of the virus from the cell surface. Gp 120 contains viral determinants that bind to the host-cell surface receptor, and gp41 contains the transmembrane and cytoplasmic tail domains that anchor the envelope into the surface of the membrane. Gp 120 and gp 41 are products of the eny gene.

The nucleoprotein core of the virion comprises a diploid viral genomic RNA and associated tRNA molecules which prime DNA synthesis during reverse transcriptase production of the viral cDNA. The viral core also contains the mature protein products of the gag and pol genes: the matrix proteins (MA) which associate with the lipid bilayer, the capsid protein (CA) which forms the core, the nucleocapsid protein, (NC) which selectively binds the genomic RNA. MA, CA and NC are products of the gag gene. The mature pol proteins, which are the products of the pol gene, are protease (PR), reverse transcriptase (RT) and integrase (IN) The tat gene appears to play a role in the regulation of viral replication and in the pathogenesis of AIDS.

The scheme of propagation of the HIV in the infected T-helper cell is as presented in Fig. 3.

Propagation of the HIV in the Host Cell.

Infection starts with virus binding involving the viral gp 120 and the receptor on the surface of the T-helper cell (also called CD 4^+ Cell) (Homsy et al., 1989). Binding is followed by membrane fusion aided by gp41 and results in introduction of the viral core particle into the $CD4^+$ cell cytoplasm. This is followed by reverse transcription of the viral genome leading to the formation of he viral cDNA. The cDNA with associated protein factors including integrase, translocated into the nucleus for final incorporation into the chromosome of the T.helper cell. In the integrated cDNA form, the HIV is called a provirus. In the provirus condition the HIV is dormant. The transcriptional activity of the HIV provirus depends upon the regulatory action of constitutive host-cell transcription factors, as well as the action of the viral encoded tat protein. Full length copies of the viral primary transcrip are formed by the action of host- cell transcriptase or RNA polymerase and then subjected to a complex array of alternative splicing to yeild viral mRNAS which are then exported to the cytoplasm for translation by host ribosomes into viral proteins. Some copies of unspliced viral RNA are also exported into the cytoplasm for packahing as genomic RNA during viral assembly. The differential translation of viral mRNA species is controlled by the protein product of the viral rev gene. The viral mRNAs are usually polycystronic and their translation products are large – molecular weight proteins, which are cleaved into viral protein molecules by the action of protease, a product of the pol gene. Daughter viral particles are completely assembled at the inner cytoplasmic membrane, followed by budding and exodus from the cell. The life cycle becomes complete after protease within the virion carry out further post- synthetic modifications of products to transform the particles into mature infections virions (Cohen et al., 1994; Libman & Witzburg, 1996; Preston et al., 1988).

The HIV quasispecies

All living things posses the ability to reproduce themselves and to maintain their species and individual identities. This statement expresses the central Dogma of Biology which establishes the universal pathway of information flow in living systems according to the scheme.

DNA $\rightleftharpoons$ RNA $\longrightarrow$ PROTEIN

At the molecular heart of the above expression lies the DNA replication, controlled by the base-pairing rule and the 3^1 5^1 exounclease proofreading activity of the DNA polymerases which mediate the replication process. This guaranteed a stable and reliable transmission of information from parent to offspring from generation to generation in systems having the DNA as the main genetic material.

The foregoing is not true of the HIV or any other retroviruse in that matter. The

main enzyme that mediates the HIV propagation in the host, the reverse transcriptase, lacks the $3^{1}-5^{1}$ exonuclease, proofreading activity and consequently, mistakes made during synthesis of viral DNA from RNA go uncorrected. It is estimated that up to ten incorrect bases may be incorporated during each round of HIV replication (Preston et al., 1988; Roberts et al., 1988) Some of these mutations incorporated by the reverse transcriptase can lead not only to amino acid substitutions but also to frameshifting during translation of viral mRNAs into proteins. (Pathak & Temin 1990). Additional variation is introduced into the viral genome by recombination as the reverse transcriptase switches template between the two copackaged viral RNA molecules (Huw & Temin, 1990). The diverse viral strains generated by the action of reverse transcriptase are called quasispecies. Even within a sinlge organ such as the spleen, evidences of genomic heterogeneity in proviral copy number and sequence complexity abound (Delassus et al., 1992). In conditions of co-infection with other viruses, proteins belonging to other viruses can be sequestered to yield chimeric HIV strains during viral assembly. Viral variation is dynamic and quasispecies specutrum in the peripheral blood may change in as little as three months (Meyerhans et al., 1989). Thus, by reproducing myriads, the HIV poses a daunting challenge for the biological control of viral propagation and designing of effective therapeutic strategies against the pathogen.

Conclusion

The HIV, a virus of the scientific roundtable of our time, is a retrovirus of the lentiviral subfamily. Its propagation in the host proceeds without a proofreading mechanism, resulting in the production of diverse, constantly changing genomic variants or quasispecies. In a single infected individual, the sheer size of variant population can be on the order of 10^{7} —10^{11} forms (Essex et al., 1994). These variants can have altered cell – type tropism and resistance to drug, on can perhaps escape neutralization by the host immune system. The HIV is running an evolutionary course. This is the problem confronting modern medicine.

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