What host genetic factors have been demonstrated to influence the rate of progression to AIDS?

Introduction.

After the initial infection with HIV, the rate of progression varies depending on many factors such as genetic variations in the virus itself, susceptibility of the host, co-infections and the level of health care. Some people, referred to as Rapid Progressors, develop AIDS within 4 years of primo-infection, and can even die from AIDS during the first year after infection. Another group of individuals, often referred to as Long-Term Non-Progressors (LTNP), survive for many years without any visible signs of disease. And while many of these individuals are simply infected with an inefficiently replicating strains of virus, significant number of them owns their long-term wellbeing to their own genetic makeup that leads to the halting or significant delaying of the infection's progression. In this essay I will consider the host genetic factors that lead to both delayed and accelerated progression of HIV infection to AIDS.

Factors contributing to the rate of progression to AIDS in HIV infected individuals.

Long-Term Non-Progressors (LTNP) have attracted a very significant interest since the research into the reasons for their long-term survival can provide the ideas for treating other infected individuals or the clues for prevention of infection altogether. Some of them survive for more than 30 years without taking any anti-retroviral drugs. Some of these individuals have an exceptionally low level of virus in the blood that can be detected only by very sensitive techniques. The groups is called Elite Controllers. One in every 300 HIV-infected individuals demonstrate this ability to control the virus. Approximately 1% of infected individuals can be considered as Long-Term Non-Progressors (Walker, 2007).

Genetic variants influencing susceptibility to HIV-1 and limiting AIDS vary significantly. There are several ways how the LTNP effect can be achieved. More robust immune response or greater resistance can contribute to the longer survival of LTNPs.

Immune response.

Immune system always produces antibodies against HIV, but in most cases they are unable to stop the progression of infection. In case of many LTNPs, however, these antibodies seem to be able to keep infection in check. Their antibodies target some highly conservative regions of surface proteins gp120 and gp41 (Djordjevic et al., 2007).

In many cases when disease progresses very fast it was demonstrated that the individuals with the expansion of only a single subset of V-chains in CD8+ T-cells are unable to control infection and tend to have a very high viral load in 6-12 months after primo-infection (Pantaleo et al., 1997).

HLA system polymorphism

Strong cytotoxic T lymphocyte (CTL) response is one of the factors playing an important role in the infection control. Cytotoxic T lymphocytes become activated upon binding to antigenic peptides that are presented by human leukocyte antigens (HLA). This initiates the immune response. HLA polymorphism influences the response level and, as a result, influence the rate of the disease progression. Significant number of HLA antigens were reported to accelerate of delay the rate of progression (den Uyl et al., 2004).

HLA class I proteins bind to endogenous antigenic epitopes and present them to CD8+ cytotoxic T lymphocytes. HLA class II proteins present exogenous antigenic peptides to CD4+ T-helpers. Due to the polymorphism of HLA genes, many different peptides can be presented to immune system.

The polymorphism in HLA system, particularly in HLA class I locus, influence the progression of disease. Selective advantage against the disease is observed with increased heterozygosity at the HLA class I region. Heterozygotes are able to present a greater range of antigenic peptides to CTL thus resulting in a more protective immune response and delayed progression to AIDS (Singh et al., 2008).

Certain specific alleles have profound effect on the progress of infection. It was shown that HLA-B27 haplotype is strongly associated with LTNP group (den Uyl et al., 2004). HLA-B27 leads to the specific strong CTL response against Gag p24 epitope, which is a conservative HIV protein that does not mutate easily. Other haplotypes such as HLA B51 and HLA B57 are also associated with slower progression and favourable prognosis, presumably to the enhanced efficiency of antigenic peptides' presentation. Haplotypes HLA-A24, -A29, -B35, -C4, -DR1 and -DR3 were connected with rapid

progression of the disease (den Uyl et al., 2004) (Singh et al., 2008). The two locus haplotype B35 - Cw04 in a homozygous state increases susceptibility to infection and associated with rapid progression. The lack of these alleles, on the other hand, is associated with very slow progression of disease.

Killer immunoglobulin-like receptors (KIR) can also influence the disease progression. Allele KIR3DS1 in combination with HLA-Bw4 Ile 80 (the allele of HLA-B that encode molecule with isoleucine at position 80) provides a dual protection over HIV disease and is observed in LTNPs.

Cytokine receptors and ligands genes:

Chemokines, a family of small cytokines, are potent chemoattractors involved in immune response and produced by a number of cells including T-cells, macrophages and natural killer cells. In some cases the chemokine receptors serve as entry points for pathogen helping them to get into target cell and establish infection. Most of HIV strains use CCR5 receptors as entry portals to the CD4= T-cells.

Very significant number of LTNPs have a specific mutation in CCR5 receptor protein of CD4+ T-cells. CD4 is a primary receptor used by HIV-1 virus. Binding to CD4 is followed by the conformational changes in viral envelop that lead to interaction with one of two viral co-receptors - CCR5 or CXCR4. Thus, CCR5 is one of the co-receptors important for entering the T-helper cells by virus. The Δ32 version of CCR5 has a 32-bp deletion which results in non-functional receptor. This receptor is not recognised by virus and therefore prevents the virus from entering the cells (Lambotte et al, 2005) (Arenzana-Seisdedos and Parmentier, 2006). The CCR5-Δ32 allele is found in 5-14% of Europeans. Homozygosity provides very strong protection against HIV infection, while heterozygosity delays the progression to AIDS by approximately 2 years. It is possible that the higher frequency of this allele among Europeans is associated with the protection against smallpox, which this mutation seems to provide as well (Sabeti et al., 2005).

Other mutations of CCR5, most of which are very rare, can also influence the functionality or availability of the co-receptor for binding with HIV-1. These mutations can lead to the production of truncated proteins or affect the formation of disulfide bridges. Some mutations result in very low level of surface receptors (Lama and Planelles, 2007). On top of that, some mutations in the promoter region of CCR5 can alter the level of its expression. For example, CCR5P1 haplotype composed of 13 SNPs is

associated with faster progression to AIDS (Martin et al., 1998). Polymorphism in CCR5 regulatory 5' region is responsible for a number of haplotypes some of which are responsible for accelerated disease progression. For example, CCR5HHE is associated with increased likelyhood of development to AIDS in Caucasians and Thais (Kaur and Mehra, 2009) (Arenzana-Seisdedos and Parmentier, 2006).

Other chemokine receptors can work as HIV-1 co-receptor and provide some degree of protection against the progression of disease. For instance, the presence of CCR2-64I variant of CCR2, in which isoleucine at position 64 is substituted by valine, leads to a slower progression to AIDS (Smith et al., 1997).The I249-M280 haplotype of CX3CR1 receptor is associated with faster progression to AIDS (Faure et al., 2000) (Arenzana-Seisdedos and Parmentier, 2006).

Cytokine genes polymorphism.

The less studied area of research into the genetic factors affecting the HIV infection progression is the one dealing with the role of cytokine gene polymorphism. Cytokines are immunomodulatory molecules and obviously have a potential to influence significantly the outcome of disorders affecting the immune system. Genetic polymorphism in several pro-inflammatory and anti-inflammatory cytokines was studied recently (reviewed in Singh et al., 2008). It was demonstrated that a number of alleles are associated with decreased and increased rate of the disease progression. For example, over-representation of the IL1α-889T allele of pro-inflammatory cytokine IL1α is associated with accelerated progress of disease. IL1 α is known to enhance HIV-1 production through NF-κB mediated trans-activation of the viral long terminal repeat, elevated level of its production is observed in infected individuals. Another cytokine, γ-INF, plays important role in defence against viruses. 874T allele is associated with higher level of this cytokine's production and delayed onset of AIDS.

It was also shown that a number of other β-chemokines, natural ligands of CCR5, can influence the rate of disease progression. The CCR5 expression is upregulated by IL-2 and IL-10. The mutations in promoter region of chemokine RANTES (another ligand of CCR5), in particular, were shown to be able to either delay or accelerate AIDS, as described in the reviews of Kaur and Mehra (2009) and Lama and Planelles (2007). (These reviews also cover a significant number of other host genetic factors which influence the rate of progression but which roles are not yet confirmed and not well studied.) Both the availability of cytokine receptors on the surface of target cell and the level of their ligands and cytokines can significantly

influence the rate of infection's progression. Polymorphism in their genes can affect the level of their expression and modulate their molecular interactions.

The chemokines CCL3, CCL4, and CCL5 are natural ligands of CCR5 receptor capable to block the entry of HIV virus, thus having HIV-1 suppressive properties. CCL3 gene exists as a single copy in the genome, but the number of copies of highly homologous gene CCL3L1 varies among different individuals and populations. CCL3L1 is also a very potent ligand of CCR5 and therefore the variations in the number of its copies can be reflected in the level of CCL3L1 expression and may influence the entry of virus to the target cells (Kaur and Mehra, 2009). It's worth mentioning here that chimpanzees that are naturally resistant to HIV-1 have very high number of CCL3L1 copies (9 - 10).

Conclusion.

Interpersonal variability in the progression of HIV infection to AIDS can be caused by multiple genetic host factors, among other things. These factors can be involved in HIV-1 cell entry, immune recognition and antigen presentation. They include a number of chemokine receptors and ligands, HLA antigens, cytokines and other molecules. In-depth study of the phenomenon of slow progression to AIDS in a small percentage of HIV positive individuals, long-term non-progressors, has a potential to help in finding a suitable vaccine which is capable of preventing the infection or halting the disease progression. This research, however, relies on successful identification of long-term non-progressor, and this identification can be a formidable task since many HIV-positive individuals receive anti-retroviral treatment. As a result, it is often difficult to establish if the long-term survival of these individuals is due to their own genetic makeup, or due to the successful action of drugs in preventing the disease progression. Many of the contributing host genetic factors, including many of those mentioned in this essay, are still under investigation as potential causes of either fast development to AIDS or slower progression of infection.

Despite the difficulties faced by researchers working in this area, the studies of host genetic factors have already contributed to the improvement of diagnostic and therapeutic tools available to practitioners. The tests capable to identify the presence of the Δ32 version of CCR5 are now available, and their use help to provide a better treatment options for the carriers of this mutation. Also, a number of drugs called *entry blockers* are currently undergoing the clinical trials. These drugs work on the level of initial interaction between HIV-1 virus and co-receptors on the surface of

CD4+ T cell. Disrupting this interaction, they prevent the viral entry and thus limit and slow down the spread of infection.

References:

Arenzana-Seisdedos, F. and Parmentier, M. (2006) Genetics of resistance to HIV infection: role of co-receptors and co-receptor ligands. *Seminars in Immunology* **18**, 387-403.

den Uyl, D., van der Horst-Bruinsma, I.E. and van Agtmael, M. (2004) Progression of HIV to AIDS: a Protective Role for HLA-B27? *AIDS Reviews* **6**, 89-96.

Djordjevic, A., Veljkovic, M., Antoni, S., Sakarellos-Daitsiotis, M., Krikorian, D., Zevgiti, S., Dietrich, U., Veljkovic, N., Branch, D.R. (2007) The presence of antibodies recognizing a peptide derived from the second conserved region of HIV-1 gp120 correlates with non-progressive HIV infection. *Curr HIV Res.* **5**, 443-448.

Faure, S., Meyer, L., Costagliola, D., Vaneensberghe, C., Genin, E., Autran, B., Delfraissy, J.-F., McDermott, D.H., Murphy, P.M., Debré, P., Théodorou, I., and Christophe Combadière, C. (2000) Rapid Progression to AIDS in HIV^+ Individuals with a Structural Variant of the Chemokine Receptor CX_3CR1. *Science* **24**, 2274-2277.

Kaur, G. and Mehra, N. (2009) Genetic determinants of HIV-1 infection and progression to AIDS: susceptibility to HIV infection.*Tissue Antigens* **73**, 289-301.

Lama, J. and Planelles, V. (2007) Host factors influencing susceptibility to HIV infection and AIDS progression. *Retrovirology* **4**, 52.

Martin MP, Dean M, Smith MW, Winkler C, Gerrard B, Michael NL, Lee B, Doms RW, Margolick J, Buchbinder S, Goedert JJ, O'Brien TR, Hilgartner MW, Vlahov D, O'Brien SJ, Carrington M. (1998) Genetic acceleration of AIDS progression by a promoter variant of CCR5. *Science* **282**, 1907-1911.

Olivier Lambotte, Faroudy Boufassa, Yoann Madec, Ahn Nguyen, et al. (2005) HIV controllers: a homogeneous group of HIV-1-infected patients with spontaneous control of viral replication. *Clinical Infectious Diseases.* **41** (7), 1053.

Pantaleo, G.; *et al.* (1997). The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. *Proc. Natl. Acad. Sci. USA* **94**, 254–258.

Sabeti, P.C., Emily Walsh, Steve F. Schaffner, Patrick Varilly, Ben Fry, Holli B. Hutcheson, Mike Cullen, Tarjei S. Mikkelsen, Jessica Roy, Nick Patterson, Richard Cooper, David Reich, David Altshuler, Stephen O'Brien, Eric S. Lander (2005). The case for selection at CCR5-Delta32. *PLoS Biology* **3**, e378.

Singh, P., Kaur, G., Sharma, G. and Mehra, N.K. (2008) Immunogenetic basis of HIV-1 infection, transmission and disease progression. *Vaccine* **24,** 2966-2980.

Smith, M.W., Carrington, M., Winkler, C., Lomb, D., Dean, M., Huttley, G. and O'Brien, S. (1997) CCR2 chemokine receptor and AIDS progression. *Nature Medicine* **3**, 1052 - 1053.

Walker, B.D. (2007) Elite control of HIV Infection: implications for vaccines and treatment. *Top HIV Med.* **15,** 134-136.