Rapid Review #26: March 2010

Rapid Response Service

Elite Controllers for HIV

Key Questions

What literature exists about Elite Controllers and what are the main messages?

Key Take-Home Messages

- Elite control of HIV is very rare.
- There is no single mechanism to explain viral control in ECs that has been identified.
- Further study of how ECs control disease progression is crucial to the development of a viable vaccine against HIV.

The Issue and Why It's Important

Definition of an "Elite Controller":

The terms "elite controller" and "long-term non-progresser" are often used to describe people who do not progress to AIDS, despite having been infected by HIV, but these terms are not synonymous. Although both populations maintain high CD4+ and CD8+ T cell counts and strong immune responses, long-term non-progressers (LTNP) exhibit low detectable viral levels (< 5000 copies/mL), whereas elite controllers (EC) maintain "undetectable" viral levels (1). Although ECs are described as having undetectable viral levels, recent studies have used ultrasensitive tests to show that many ECs do exhibit very low viral levels (< 50 copies/mL) (2). Thus, ECs do not completely eradicate the virus, but rather, are able to control it. Viral replication continues to occur, in spite of very low viral loads (3;4). While LTNPs make up 1% of the total HIV population, the rate of occurrence of EC is much lower (1).

Why are Elite Controllers Important?

The study of elite control has become increasingly important in the search for a viable HIV vaccine. A vaccine that prevents infection by HIV is a long way off, but development of a preliminary vaccine that will prevent viral replication,

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EVIDENCE INTO ACTION

The OHTN Rapid Response Service offers HIV/AIDS programs and services in Ontario quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

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disease progression and further transmission may be possible as a large number of studies are looking at the phenomenon of natural viral suppression as a means of designing this kind of HIV vaccine (5). In order to do so, researchers have tried to determine what is different in this population.

What We Found

Background

CD4+ T cells

- key regulators of adaptive immune response
- provide help to other cells in the immune system, such as CD8+ T cell
- play a role in response to viruses
- HIV specifically targets these cells. Immune system collapses in patients with HIV because of a loss of these cells (6)

CD8+ T cells

- responsible for targeting and killing cells that are infected with HIV-1 (6)

Mechanisms for Viral Control

Early research suggested that ECs were infected with a weak or inactive HIV-1 virus; however, case studies have shown that many ECs have been infected by a "normal" virus. Thus, that ECs have been infected by a defective virus is not a sufficient explanation for viral control (6). However, the response by a person's immune system can affect the fitness of a virus. This phenomenon is often termed 'host response'. Although no single host response has been found to be present in all ECs, some host responses are over-represented in ECs (6). Many of these viral control mechanisms are unique to immune response to HIV and are not exhibited in the natural control of other viruses such as Hepatitis C or cytomegalovirus (7).

Researchers have been able to reach consensus about the likelihood of viral control mechanisms occurring early and rapidly in HIV infection and this control is less likely to occur at later stages of infection (6;8).

Although as a group, ECs generally show very little change in CD4+ counts over time but some ECs do exhibit a gradual decrease of CD4+ cell counts (9;10). There is also a great range of viral loads seen in these individuals over time. A cohort that compared the viral loads of ECs and people with HIV who were being treated by HAART found no significant difference between the two groups in terms of the number of people who maintained viral loads < 1 copy/mL; however, the EC group had greater viral load variability (11). Thus, researchers have concluded that there is no set point or steady state of viral load that ECs maintain, which may reflect an ongoing tug of war between the host and the virus (12).

Mechanisms that are currently thought to be important in the control of HIV in ECs are summarized below:

CD8+ T cells – CD8+ cells play a major role in control of viral replication. While studies have not shown any quantitative differences in CD8+ cells, different CD8+ cell responses have been observed in ECs. Specifically, EC CD8+ T cells exhibit a superior response as compared to people with progressive HIV (3;6;13;14). CD8+ T cells in ECs exhibit specific superior cellular functions, which may lead to more effective killing of HIV-infected cells (6;15). The HIV-specific CD8+ T cell responses in mucosal tissue are also much stronger in ECs (6;16).

*HLA-B*57 and HLA-B*27* – These alleles are over-represented among ECs, although there is no direct relationship with viral load (6;11).

HLA-C polymorphism – A single nucleotide polymorphism may cause changes in interactions between these molecules and natural killer (NK) cells, so that HIV-1 infected cells are killed more effectively (6;17).

IL-2 and IFN-γ – There have been conflicting conclusions about the role of CD4+ T cell secretion of IL-2 and IFN-γ in response to HIV-1 antigens. Further research is needed to determine the role of these secretions in elite control (6).

CD4+ T cells – CD4+ T cells in ECs can sometimes have a direct antiviral effect. In ECs, regulatory CD4+ T cells ("Tregs") play a role in the balance between non-specific immune activation and HIV-specific immunity (6).

There is considerable research on other possible mechanisms for viral control, such as enhanced APOBEC activity and titers of NAb; however, a recent review of the literature has shown that these mechanisms probably do not play a significant role in the control of HIV in ECs (6).

Case Studies

Case studies have provided further opportunities to try and understand how viral control works over time in this unique population. Clerc et al. describe a study of a 33 year old Swiss man who became infected through unprotected sexual intercourse while traveling in Nigeria. The man exhibited low viral levels due to low levels of HIV-1 replication, and thereby leading to limited stimulation of a full antibody response, as would be potentially seen in people with progressive HIV (18).

Rachinger et al studied super-infection of an EC in the Netherlands. According to their case study, the patient had unprotected sexual intercourse with a steady partner over 14 years without the partner ever becoming infected with HIV. However, the EC patient then had unprotected sex with a new partner and the original partner subsequently tested positive for HIV the following year. The researchers determined that the mechanisms that protect ECs from disease progression do not prevent against super-infection of HIV. In this case study, the EC patient had a spike in viral load after becoming super-infected that may have led to the increased risk of transmitting HIV to his original partner, who did in fact end up becoming infected with HIV (19).

Factors that May Affect Local Applicability

Many studies of elite control have taken place on macaques and other simians. For the purposes of this Rapid Response, study inclusion was limited to research that was done on humans at the expense of research that explores mechanisms for elite control in other species. Studies of long-term non-progressers were also excluded.

What We Did

To identify any systematic reviews we first conducted hand searches of the reviews and protocols from the HIV/AIDS Cochrane Review Group and searched www.health-evidence.ca (hand searched the 'acquired immunodeficiency syndrome', and 'HIV' categories). To locate additional reviews and primary literature we then searched Medline, Embase, PsychInfo, CINAHL, The Cochrane Library and DARE using combinations of relevant MeSH and text terms.

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For Medline, Embase and PsychInfo we used the following MeSH and text terms: 1) HIV Long-Term Survivors [MeSH term] and elite [text term]; 2) (Elite controller* or Elite suppressor*) [text terms] AND (HIV or Acquired Immunodeficiency Syndrome) [MeSH terms], 3) long-term non-progressor. For CINAHL we used the following search terms: 1) (Elite controller* or Elite suppressor*) AND HIV; 2) long-term non-progressors. For The Cochrane Library and DARE we searched using the term 'elite ontroller'