HIV vaccines: knowledge grows but progress is slow

Recent disappointments over the efficacy of antiretroviral drugs in patients with HIV infection have emphasised the need for effective HIV vaccines. However, progress in this area of research is proving frustratingly slow, with as many question being generated as are answered.

The key questions appear to be:[1]

- What are the correlates of protection from infection?
- How can the problem of viral variation be overcome?
- What is the best way to present antigens to the immune system, and what are the key viral antigens?

Other questions, equally important, address the ethical and social issues surrounding HIV vaccine trials.[2] A final dimension to the challenge is whether a comprehensive global HIV vaccination programme would be possible and affordable, if a vaccine becomes available.[3]

Prophylactic and therapeutic vaccines being developed

HIV vaccines are being developed for both prophylactic and therapeutic use. The concept of a prophylactic vaccine is a familiar one, whereby an immune response is stimulated enabling individuals to resist infection following exposure to wild type viruses.

A therapeutic vaccine is a less familiar approach. It has become apparent that the natural immune response is able to contain HIV infection for long periods before the patient develops symptoms.[4] Therapeutic vaccination aims to boost this natural immune response in HIV-infected individuals, and so delay progression to symptomatic disease.

Correlates of protection

The following may be correlates of protective immunity.[2]

- *Neutralising antibodies*, which 'neutralise' the pathogenicity of the virus by binding to it, preventing cells becoming infected, and speeding elimination.
- *Cytotoxic T cells (CD8$^+$ cells)*, which destroy HIV-infected cells.
- *Helper T cells (CD4$^+$ cells)*, of which there are 2 types. One promotes the activity of cytotoxic T cells and macrophages, while the other helps B cells to generate an antibody response.

It is not known which of these responses, if any, is the most important for protection against HIV.[5,6]

Vaccines in development

Traditional strategies for vaccine preparation include immunisation with either live attenuated viruses or whole inactivated viruses.[7,8]

However, because of the incurable nature of HIV infection, there are serious concerns over the potential pathogenicity of these types of vaccine. Live attenuated viruses may revert to wild type viruses by mutation, and incomplete inactivation poses a similar threat of introducing infection with killed vaccines.[8] Other disadvantages include a narrow spectrum of protection unless many strains of virus are included, and the possibility of causing lymphomas.[2,8]

Despite these potential disadvantages, both types of vaccine are in development. An attenuated vaccine with genetic deletions that impair viral replication seems to hold the most promise for a safe and effective vaccine.[9]

Inactivated virus vaccines produced encouraging results initially, but these have now been shown to be experimental artefacts.[8] Research continues, however, and whole inactivated viruses may be particularly useful as therapeutic vaccines.[8]

Harnessing biotechnology

Novel approaches to vaccine development, made possible by advances in biotechnology, concentrate on using various components of the virus to generate an immune response.

Vaccines based on recombinant envelope and core proteins, peptides and naked viral DNA have been developed, and incorporation of HIV genes into live vector viruses is another approach.[8]

A problem with vaccines based on either recombinant envelope glycoproteins (e.g. gp120, gp160) or peptides is that the immunity developed may have too narrow a spectrum of action. HIV can mutate rapidly, and immunological responses to the proteins used in the vaccine may not be triggered by alternative viral strains. Three groups of researchers have recently reported disappointing results demonstrating that blood from people who had received various vaccines could not neutralise HIV recently harvested from patients.[10]

Using core proteins, which are less variable than envelope proteins, or combining different antigenic peptides may improve protection.

Indeed, serum from animals immunised with a multicomponent synthetic peptide vaccine has been able to neutralise clinical isolates of HIV, an encouraging finding that has prompted phase 1 safety and immunogenicity trials with this vaccine.[11]

Incorporating HIV genes into live viruses appears to have the advantage of providing potent stimulation of cell-mediated immunity.[2,8] Disadvantages include poor stimulation of humoral immunity and concerns over the safety of the vectors.[2]

Injection of naked viral DNA may allow integration of the viral DNA into host cells, with resultant expression, production of viral proteins and stimulation of a cell-mediated immune response. This approach has shown promise in a mouse influenza model, but may also be subject to problems caused by the variability of HIV.[2]

Combinations of immunological techniques and/or the development of newer technologies such as gene therapy may be required for the production of a safe and effective HIV vaccine.

Until vaccine development is successful, behavioural methods of avoiding infection remain the only option for disease prevention.

References

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