
1. What cell receptor is required for infectivity of all strains of HIV virus?
CD4, found at high levels on T\(_H\), but is also found on macrophages and other cells.

2. What is the difference between M-tropic, T-tropic, and dual-tropic HIV strains?
- **M-tropic** – viruses only infect macrophages
- **T-tropic** – viruses only infect T-cells
- **Dual-tropic** – virus can infect both macrophages and T-cells.

3. What is the function of CCR-5 in normal healthy individuals?
Binds several cytokines related to macrophage function, e.g. macrophage inflammatory protein.

4. How does the mutant CCR-5 differ from the wild-type (Figure 1)? Do you expect the mutant protein to be functional? If so, does its loss of function lead to any defects in the immune system, based on this article.
- 32 basepair deletion.
- Frame shift causes non-functional protein (Fig 1)
- The deletion of this receptor doesn't have any noticeable effect based on the frequency of homozygous null alleles; an example of redundancy in cytokine receptors.

5. What experimental technique was used to identify the presence of the mutant allele in individuals (Figure 3)?
RFLP – restriction length polymorphism from PCR amplified region of chromosomal DNA.

6. Table I gives the number of mutant alleles found in seronegative and seropositive HIV patients. How does this data support the main conclusion of this paper?
All null alleles of ccr-5 were seronegative, i.e. there were no nulls that were infected.
This strongly suggests that if an individual has two copies of \(\Delta\)ccr-5 they can't become infected with HIV, at least the M-tropic virus which is considered to be more infectious than the T-tropic virus.
Heterozygotes seem to be partially protected as the frequency of seronegative individuals is higher than seropositive (0.162 versus 0.108).
B. Genetic Immunodeficiencies.
There are two types of individuals with SCID (severe combined immunodeficiencies):
   i) Lacking both B and T cells (B\(^{-}\)T\(^{-}\))
   ii) Lacking only T cells (B\(^{+}\)T\(^{-}\))
   List as many genetic deficiencies that you can think of that could cause the above two types of SCID. The more correct deficiencies you list, the more points you get!

**B\(^{-}\)T\(^{-}\) SCID:**
Two key checkpoints in B and T development are generation of the receptor chains. If the cell cannot make a functional receptor chain it dies. The key enzymes involved in generation of the receptor are:
Rag1/Rag2 – responsible for recombination
Additional Deficiencies (Discussed in class):
   Adenosine deaminase and purine nucleoside phosphorylase are also required to supply a large amount of nucleobases during this process, if these are defective there are no B or T cells).

**B\(^{+}\)T\(^{-}\) SCID**
You need to think of processes that only affect T-cell development. The additional checkpoints here are interaction with self-MHC and signaling from that interaction. This would not be possible if CD4 and CD8, or CD3 were missing (If just CD4 was missing, T\(_{C}\) cells would be generated. If just CD8 was missing T\(_{H}\) cells would be generated.
Additional Deficiencies (Discussed in class):
   IL-2 is needed during T-cell development, if chains of the receptor are missing (e.g. gamma) or the signaling kinase (JAK-3), no T-cells develop.

If you are interested in a few more genes, try looking at this review article: The Journal of Clinical Investigation, [http://www.jci.org](http://www.jci.org), Volume 114 Number 10 November 2004

C. Solutions will be posted later.