Strategy to Overcome Cross-Pairing in TCR Gene Therapy

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The major immune response that is known to help keep HIV under control in infected persons is a type of cell that kills infected cells, the cytotoxic T lymphocyte (CTL). CTLs work by binding pieces of HIV-1 proteins that come to the cell surface, called epitopes. This binding is specific for the sequence of the epitope, and causes a signal within the CTL triggering it to kill the bound cell. The T cell receptor (TCR) on a CTL is the sensor and trigger that mediates this binding and sends the signal.

CTL responses against HIV vary in their efficacy, and many people lack effective CTLs. A developing strategy to address this problem is to deliver the genes for effective TCRs into existing CTLs in infected people so that those CTLs are now reprogrammed to recognize HIV-1-infected cells via the new TCRs. A major problem is that each TCR is made of paired a/ß chains. Normally a CTL has one of each, and so there is only one pairing. However, once the genes for another TCR are delivered to a CTL, there are two of each, and there are four pairings. This is a hindrance because the desired TCR is only a quarter of the TCRs being produced in the CTL, and also a danger because the new cross-pairings have unknown properties, and could cause autoimmune disease.

Besides the typical a/ß CTLs, there is a rare type of CTL that has TCRs comprised of paired ?/d chains. For both types of TCRs, the binding of epitope occurs through the "variable regions" of the chains, while the pairing and signaling occurs through the "constant regions." Notably, the a/ß and ?/d constant regions appear to work in exactly the same way. Thus in theory they could be interchangeable. However, it has been shown that they do not cross-pair.

We propose to make hybrid a/ß TCRs against HIV that have had their constant regions swapped with ?/d constant regions. We believe these would work like the original a/ß TCRs, but when put into a CTL would not cross-pair with the original TCR in the CTL. This will be done by genetic engineering, and the new chimeric TCRs will be tested for their functionality against HIV-1. To test how they might work for gene therapy, they will be put into mice with human immune systems, which are then challenged with HIV-1 infection.

If this works, it would be a unique solution to the problem of TCR cross-pairing during TCR gene therapy. This would improve both the efficiency and safety of this approach, with important ramifications for TCR gene therapy not only for HIV, but for other viruses and cancers.