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Engineered T lymphocytes – powerful killers ▼

The immune system has evolved to fight against pathogens and it is against its nature to destroy the self, even when the self becomes a threat to the survival of the whole organism. Moreover, cells that undergo malignant transformation do their best to prevent themselves from being recognized and destroyed. The term immunotherapy refers to the group of strategies that increase the ability of the immune system to recognize and destroy transformed cells. In a recent review in *Drug Discovery Today*, Whelan *et al.* [1] describe several humoral- and cellular-activating immunotherapy strategies that are under clinical investigation, together with an assessment of their results. These strategies are based on the idea that tumor antigens must be presented to the immune system in such a way that the immune system no longer tolerates self antigens, allowing cytotoxic T lymphocytes (CTLs) to be induced. CTLs are able to recognize and lyse specific target cells. Tumor antigens can be presented as naked DNA, peptides, proteins or whole tumor cells. Powerful antigen-presenting cells such as dendritic cells can be loaded with tumor antigen *ex vivo* and injected back into patients to ensure optimal processing and presentation of antigenic peptide. In general, these strategies depend on the activation of CTLs *in vivo*. Some of these strategies have encouraging results but many problems still need to be overcome.

A different approach that was not covered by Whelan *et al.* [1] involves *ex vivo* genetic manipulation of CTLs to alter their specificity and activation requirements. This is achieved by introducing a receptor that recognizes a tumor antigen linked to an intracellular domain that drives activation. Recent studies using this technique have shown that systemic B-cell lymphoma and colon carcinoma were eradicated *in vivo* [2,3]. The important lesson that stems from these studies is that we can control the survival and activity of the $CD8^+$ T lymphocytes to exploit their killing potential. This strategy has the advantage of being human leukocyte antigen-independent (the target of CD8 is the tumor antigen, independent of processing and association to class I molecules), but it is limited to tumor antigens that are expressed at the plasma membrane.

In conclusion, we are learning to control delivery of tumor antigens and to prepare effective and long-lasting CTLs. Our continuing progress in understanding the mode of function of the immune system should help us to find the best way to combine different approaches to obtain clinically relevant results.

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