Artificial antigen-presenting cells: a natural approach to chronic viral infection?

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‘Artificial antigen-presenting cells would save a considerable amount of time and can even be tuned for optimal CTL expansion with the addition of appropriate costimulatory molecules.’

The aim of any immunotherapeutic treatment is to minimize nonspecific toxicity, thus utilizing the body's own mechanisms to target and kill abnormal cells. This has the potential to treat any disease that is characterized by a specific antigen expression. Adoptive transfer of *in vitro*-expanded antigen-specific cytotoxic T cells (CTLs) is a promising new form of this approach, with enormous potential to treat a wide range of malignancies and chronic viral infections.

CTLs are CD8⁺ and this molecule can recognize specific antigen peptide bound to human leukocyte antigen class I (HLA I), in both virally infected cells and cells undergoing cellular transformation (including virally induced). Many tumor antigens are self-antigens and thereby protected by tolerance mechanisms, but CTLs generated *in vitro* are not subject to such mechanisms and can thus be armed against tumor cells. For example, treatment with leukemia reactive CTLs has been shown to drive chronic myeloid leukemia into complete remission in one patient [1], and Epstein–Barr Virus (EBV)-infected dendritic cells (DCs) have been shown to activate a CTL response in Hodgkin's lymphoma that can promote complete remission in others [2]. Another potential use for CTL infusion could be for treating cytomegalovirus (CMV) reactivation, a serious complication for patients undergoing bone marrow transplantation [3].

Classically, CTLs are generated via co-culture with antigen-pulsed DCs. The disadvantages of these expensive methods to expand CTLs are due to the lengthy *in vitro* work required to prepare host antigen-presenting cells (APCs), capable of activating and expanding CTLs, which are difficult to culture and require large quantities of blood in order to isolate enough cells [4]. In addition, it is

susceptible to contamination and the natural variability of APCs isolated by this method means that preparation of a custom-made enriched culture of an antigen-specific CTLs can take months.

An alternative approach is to create an artificial APC (aAPC) that can present antigenic peptides on their HLA class I molecules thus leading to expansion of their own CTLs. This would save a considerable amount of time and can even be tuned for optimal CTL expansion with the addition of appropriate costimulatory molecules [5].

Approaches to date have included B cells coated with antibody-targeted HLA class I/peptide [6,7], dyanal beads coated with recombinant immunoglobulin (Ig)-HLA fusion proteins [8] and microspheres coated with HLA I complexes [9,10]. Potential advantages of recombinant HLA-based systems include simplicity of complex construction, ability to adhere to GMP standards, stability in storage and ease of administration. Additionally, they should allow expansion of T cells recognizing clinically important non-immunodominant epitopes; expansion of these cells can be difficult with DC-based systems as the immunodominant CTLs rapidly kill the APCs, thereby limiting their expansion [11]. In addition to coating cells with MHC I, cell lines have also been transformed with lentiviral vectors to express HLA I (these aAPCs still have to be pulsed with antigenic peptide like traditional DCs, but have been shown to be more efficient at activating CTLs with 85.5 versus 66.5% activated CTLs with aAPC and DCs respectively achieved after 5 days coculture [5]).

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Using HLA-peptide complexes to coat cells achieves a greater frequency of antigen-specific HLAs and thus a greater ability to stimulate antigen-specific CTLs. As well as activating CTLs, this technology has the potential to stimulate populations of antigen-specific CD4⁺ helper T cells via the construction of an HLA II-peptide monomer [12]. This enables the double adoptive

transfer of antigen specific CD4⁺ and CD8⁺ positive cells that could not only target malignant or virally infected cells, but then maintain the response via the help provided by the CD4⁺ T cells [13]. Focusing and amplifying the body's natural response to abnormal cells in this way has the potential to be the most effective and safe treatment for these life-threatening diseases. Of course, such an approach offers the potential to eradicate the latent reservoir of HIV.

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