Chapter 38

Design and Testing of Peptide-Based Cytotoxic T-Cell-Mediated Immunotherapeutics to Treat Infectious Diseases and Cancer

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1. BACKGROUND

1.1. The Role of Cytotoxic T Cells in the Control and Elimination of Infectious Diseases and Cancer

Cytotoxic T lymphocytes (CTLs) have been implicated in the control and elimination of various viral and bacterial infections, tumors, and some parasitic diseases. CTLs that are characterized by the presence of the CD8 antigen generally recognize peptide fragments derived from intracellular processing of various antigens in the form of a complex with MHC class I molecules expressed on the cell surface (Germain and Margulies, 1993). This recognition may result in the lysis of the cell bearing the MHC–peptide antigen complex in an antigen-specific, MHC-restricted manner (Germain and Margulies, 1993). In addition, CTLs also generate a number of different lymphokines including gamma interferon (IFN-γ) and tumor necrosis factor (TNF), which are either directly cytolitic, regulate viral
replication, or function to amplify the ongoing immune response (van der Bruggen and Van den Eynde, 1992; Jassoy et al., 1993; Rosenberg et al., 1988).

The importance of CTLs in recovery from viral infection has been demonstrated both in animal models and in natural infections in humans (Rouse et al., 1988). This type of response is critical for the establishment of protective immunity. Classic adoptive transfer or immunodepletion experiments in murine systems have shown that CTLs are critical for protection against lethal challenges with lymphocytic choriomeningitis virus (LCMV) (Byrne and Oldstone, 1984; Zinkernagel and Doherty, 1979), influenza virus (Yap et al., 1978; Lukacher et al., 1984), herpes simplex virus (HSV) (Sethi et al., 1983), and murine cytomegalovirus (CMV) (Reddehase et al., 1985). Adoptive transfer of CD8+ CTLs into either virus-infected mice or normal mice prior to viral challenge resulted in reversal of disease progression, clearance of the virus, and decreased mortality. In addition, sustained memory was established, resulting in protection from subsequent challenge with virus. Depletion of CD8+ T cells prior to viral challenge generally resulted in increased viremia, acceleration of disease progression, and increased mortality. In humans, the presence of virus-specific CTLs is associated with protective immunity and resolution of infections caused by influenza virus (McMichael et al., 1983) and CMV (Quinnan et al., 1982). Virus-specific, MHC class I-restricted, CD8+ CTL responses have also been demonstrated in natural infection with HIV-1 (Walker et al., 1987, 1988; Johnson et al., 1991, 1992, 1993; Koenig et al., 1988; Nixon et al., 1988), HSV (Yasukawa et al., 1989; Tigges et al., 1993), hepatitis C virus (HCV) (Koziel et al., 1992, 1993), and hepatitis B virus (HBV) (Bertoletti et al., 1991, 1993; Missale et al., 1993; Nayersina et al., 1993).

CTLs have also been implicated in the elimination of tumors and prevention of recurring metastases. Original studies were performed in well-defined murine tumor model systems in which adoptive transfer of tumor-specific CTLs resulted in the eradication of experimentally induced tumors (Metief, 1992; Greenberg, 1991; Urban and Schreiber, 1992). It is now generally accepted that some human tumors express specific tumor-associated antigens (TAAs) which may be recognized by CTLs and may potentially be utilized in vaccination protocols (Urban and Schreiber, 1992). In general, identifying human tumor CTL epitopes is accomplished by analyzing tumor-infiltrating lymphocytes (TILs) or peripheral blood mononuclear cells (PBMCs) that are isolated from cancer patients with tumors (van der Bruggen et al., 1991; Jerome et al., 1991; Muul et al., 1987; Anichini et al., 1989; Vose and Bonnard, 1982), by vaccination studies in mice (Skipper and Stauss, 1993; Feltkamp et al., 1993; Chen et al., 1991, 1992), or by examining in vitro induction of CTLs by peptides (Stauss et al., 1992; Houbiers et al., 1993). In humans, few TAAs have been characterized in terms of the presence of CTL epitopes. Potential CTL targets include gene products of oncogenic viruses, mutated oncogenes or suppressor genes, chromosomal translocations, and abnormally expressed or glycosylated self proteins, or overexpressed developmental proteins (Urban and Schreiber, 1992).

Since most tumor cells are weak immunogens, new strategies to enhance the cellular immune response to tumor-specific antigens are being investigated. These strategies include treatment of tumor-bearing hosts with lymphokines such as IL-2, IL-7, IFN-γ, and TNF (Lanzavecchia, 1993). Another strategy to augment tumor immunogenicity is the introduction of costimulatory signals into the tumor cells which may be critical for T-cell activation. Future therapies that may be efficacious in the treatment of a wide variety of