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ROLE OF CD4$^+$ CYTOTOXIC T LYMPHOCYTE (CTL) IN IMMUNOLOGICAL HOMEOSTASIS

Yasuhiro YASUTOMI

Department of Bioregulation,
Mie University School of Medicine,
Tsu, Mie, 514 Japan

Cytotoxic T lymphocytes (CTL) have been shown in a number of infectious and neoplastic disease to prevent the progress of disease. Antigen specific T cell responses alone have been shown to confer protection against various types of disease. Cytotoxic activity is generally a property of CD8$^+$ class I-restricted T cells, while CD4$^+$ class II-restricted T cells function principally by secretion of lymphokines. However, CD4$^+$ T cells with cytotoxic activity have been documented in several murine and human systems (1, 2). The ability to derive primary in vitro cultures of CD4$^+$ CTL and the demonstration of CD4$^+$ CTL in certain disease states, either together with CD8$^+$ CTL or as the predominant population, has led to renewed interest in understanding their role in normal immune responses and their mechanism of killing.

Although antigen recognition mechanisms of CD8$^+$ CTL are well characterized, CD4$^+$ CTL are unknown. Because antigenic target peptide of CD4$^+$ CTL associated with MHC has not been reported in any infectious and neoplastic disease. We found two antigenic target peptides of CD4$^+$ CTL in Friend virus (F-MuLV)-induced tumor (FBL-3) immune mouse by employing CD4$^+$ CTL clone cells. One is F-MuLV env 122–141 (fn: DEPLTSLTPRCNTAWNR LKL) restricted with I-Ab and the other is F-MuLV env 462–479 (i: HPPSYVYSQFEKSYRHKR) restricted with I-Eb. These antigenic peptide were effective to protect against infection of Friend virus. Substitution with alanine of each residue of antigenic peptides demonstrated that peptide fn has three TCR-contact residues (128L, 129T, 133N) and two MHC-anchoring residues (131R, 134T). Peptide i has also three TCR-contact and two MHC-anchoring residues. Interestingly, these CD4$^+$ CTL clone cells lysed the target cell labeled with Molony virus peptide of the same position to Friend virus but not homologous sequence peptide of endogenous virus.

Two major mechanisms have been shown to be responsible for virtually all T cell-mediated cytotoxic activity observed in short term in vitro assay. The first involves the regulated and polarized secretion of lytic granules, containing perforin and granzymes, upon contact of a T cell with a target (3). The second mechanism involves the interaction of membrane-bound Fas ligand on the T cell with the Fas molecule on the surface of the target cell (4). Recently, mechanisms of target cell

lysis by $CD4^+$ CTL have been shown to be dependent on Fas mediated apoptosis (5). Our study showed that established Friend virus specific-$CD4^+$ CTL clone cells lysed target cells by both perforin and Fas-Fas ligand systems.

In the present study suggested that T cell mediated immune responses by CTL may be involved not only MHC class I-restricted $CD8^+$ CTL but also MHC class II-restricted $CD4^+$ CTL.

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