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Identification of MHC class II-restricted tumor antigens and intracellular delivery of antigenic peptides into dendritic cells

Rongfu Wang

Baylor College of Medicine, Houston, TX

Abstract

Increasing evidence from both human and animal studies indicates that CD4+ T cells play a central role in orchestrating the host immune response against cancer and other diseases (1). While a number of MHC class I-restricted tumor antigens have been identified, relatively little is known about MHC class II-restricted tumor antigens recognized by CD4+ T cells. Recently, we developed a genetic targeting expression (GTE) approach to identifying such MHC class II tumor antigens by screening an invariant chain (Ii)-cDNA fusion library (2). These studies have revealed several mutated or fusion proteins that serve as MHC class II-restricted tumor antigens (2, 3, 4). The second approach, also called "Reverse Immunology", is to identify CD4+ T-cell epitopes from a given candidate antigen. We have used this method to identify several T-cell epitopes from NY-ESO-1, a potentially important tumor antigen, by the combined use of DR4-transgenic mice and an *in vitro* stimulation with peptides predicted by a computer-assisted DR4-binding algorithm (5, 6). Meanwhile, in collaboration with Dr. Old and his colleagues we are currently working on identification of CD4+ T-cell epitopes derived from breast, colon and prostate cancer antigens that are originally identified by SEREX (7). I will summarize the current status of MHC class II-restricted tumor antigens as well as their potential biological relevance to tumor development and metastasis.

To develop effective cancer vaccines, tumor immunologists have used dendritic cells pulsed with antigenic peptides as promising cancer vaccines. However, human clinical trials conducted at multiple institutions have not yet realized this promise (8). We recently developed a novel strategy to enhance antitumor immunity by intracellular delivery of antigenic peptides into dendritic cells. Vaccination of mice with DCs intracellularly loaded with peptides showed a complete protective immunity against subsequent tumor challenge and potent therapeutic effects on tumor growth, while peptide-pulsed DCs failed to elicit antitumor immunity (9, 10). Enhanced antitumor immunity induced by intracellularly loaded peptide-DCs requires the participation of both CD4+ and CD8+ T-cell responses. Hence, the combined use of MHC class I and II restricted antigenic peptides and an effective delivery system may lead to developing potent cancer vaccines for the treatment of patients with cancer.

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