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ORIGINAL ARTICLE

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Costimulation of T-cell-mediated tumor immunity

Work conducted in the 1950s and 1960s has demonstrated that many experimentally induced, and some spontaneous, mouse tumors express tumor-specific transplantation antigens against which an immune response can be induced that leads to tumor destruction in vivo (for a review, see [13]). The immune response was found to be primarily mediated by lymphocytes [14], although the role of antibodies must not be discounted. Immune T-lymphocytes, including both $CD8^+$ cells with cytolytic T-cell (CTL) activity in vitro and $CD4^+$ T-helper cells, are the most important mediators of the immune response [12, 25].

Work done in the late 1960s has provided some of the first evidence that human neoplasms can also be recognized by the immune system [14], and evidence suggested that some of the antigenic targets of the immune response were oncofetal [16]. However, it was not until the past few years that precise information regarding some of these targets became available [3]. Antigens encoded by viral genes such as the E6 and E7 genes of human papillomavirus (HPV) 16 [1, 5, 6, 26] are of particular interest, as are antigens encoded by oncogenes [4, 15].

The reason why an antigenic neoplasm can develop in an immunocompetent host remained unknown for many years. This situation was resolved by the demonstration that T-cell activation in response to an antigen needs a second signal and that the key second signal is mediated via an interaction between the CD28/CTLA.4 receptors on T-lymphocytes and their ligand, B7, on antigen-presenting cells [22]. Most tumors lack B7 [7, 8] and, hence, present their antigens in a way likely to be ignored by the immune system, sometimes even leading to anergy. By transfecting the B7-l gene into tumor cells expressing the HPV-16-encoded E6 or E7 genes, Chen et al. [7] made them rejectable by immunocompetent syngeneic mice. Tumor rejection was caused by an immune response induced by the B7-transfected tumor cells and was primarily mediated by $CD8^+$ T-lymphocytes with CTL activity. Immunization with $B7^+$ tumor cells caused B7-negative wild-type cells expressing the same tumor antigen also to be rejected. This work has since been confirmed and extended by other investigators and has recently been reviewed [17].

A second ligand for CD28/CTLA.4, B7-2, has been identified more recently [20]. Transfection of the B7-2 gene into tumors gives results similar to those obtained by transfecting B7-1 [30]. No further improvment in tumor immunogenicity was detected by combining B7-1 with B7-2.

Transfection of either B7-1 or B7-2 into tumors that are immunogenic, i.e., that can immunize a syngeneic host such that it becomes capable of rejecting a small transplant of cells from the same neoplasm, vastly increases the level of immunogenicity against transplanted, wild-type tumor cells. In contrast, such transfection does not bestow immunogenicity on nonimmunogenic tumors [9]. However, we have recently demonstrated [21] that transfection of either B7-1 or B7-2 in combination with a second costimulatory molecule, CD48, which is the ligand for CD2, bestows immunogenicity upon two previously nonimmunogenic mouse tumors, sarcoma Ag104 and melanoma K1735. Tumor-specific CTLs against Ag104 could be generated and used in adoptive transfer experiments to prevent death of mice from lung metastases established by intravenous injection of wild-type cells.

A large number of tumor antigens have been identified [4, 13, 18, 23, 24, 28, 29]. Although most are differentiation antigens, which may not always be immunogenic in the native host, there is no lack of molecules that are associated with human neoplasms and are likely to induce an immune response in humans. Recent studies performed in a mouse model system have shown that even the long-transplanted EL4 lymphoma, which has a low, albeit detectable, immunogenicity when studied using classic approaches in syngeneic mice, can, after transfection with the B7-1 gene, induce a CTL response that recognizes at least six

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different antigenic peptides [19]. In contrast, wild-type EL4 cells induce only a weak CTL response to only one or two peptide fractions.

The identification of many potential antigenic targets for an immune response, as well as the elucidation of the role of costimulation via second signals, has increased the probability that active immunization against cancer antigens will prove to be therapeutically useful in humans. However, there are at least two important problems to overcome. First, many tumors are deficient in the mechanisms needed for antigen processing, transport, and presentation by multiple histocompatibility complex molecules [2, 11]. Although this deficiency is often quantitative rather than qualititative and affects the ability of tumors to induce an immune response more than the ability to serve as its target [17], it remains one of the greatest obstacles to the therapeutic use of active immunization to tumor antigens. Another problem is likely to be the local down-regulation of T-cell responses at the tumor site, a phenomenon that may be related to decreased expression of certain T-cell signal molecules at that site [10, 27]. We are hopeful that the mechanisms responsible for this down-regulation will be identified and approaches to overcome its impact developed.

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