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Review

Immunology and immunotherapy of neuroblastoma

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ABSTRACT

Purpose: This review demonstrates the importance of immunobiology and immunotherapy research for understanding and treating neuroblastoma.
Principal results: The first suggestions of immune system–neuroblastoma interactions came from in vitro experiments showing that lymphocytes from patients were cytotoxic for their own tumor cells and from evaluations of tumors from patients that showed infiltrations of immune system cells. With the development of monoclonal antibody (mAb) technology, a number of mAbs were generated against neuroblastoma cells lines and were used to define tumor associated antigens. Disialoganglioside (GD2) is one such antigen that is highly expressed by virtually all neuroblastoma cells and so is a useful target for both identification and treatment of tumor cells with mAbs. Preclinical research using in vitro and transplantable tumor models of neuroblastoma has demonstrated that cytotoxic T lymphocytes (CTLs) can specifically recognize and kill tumor cells as a result of vaccination or of genetic engineering that endows them with chimeric antigen receptors. However, CTL based clinical trials have not progressed beyond pilot and phase I studies. In contrast, anti-GD2 mAbs have been extensively studied and modified in pre-clinical experiments and have progressed from phase I through phase III clinical trials. Thus, the one proven beneficial immunotherapy for patients with high-risk neuroblastoma uses a chimeric anti-GD2 mAb combined with IL-2 and GM-CSF to treat patients after they have received intensive cyto-reductive chemotherapy, irradiation, and surgery. Ongoing pre-clinical and clinical research emphasizes vaccine, adoptive cell therapy, and mAb strategies. Recently it was shown that the neuroblastoma microenvironment is immunosuppressive and tumor growth promoting, and strategies to overcome this are being developed to enhance anti-tumor immunotherapy.
Conclusions: Our understanding of the immunobiology of neuroblastoma has increased immensely over the past 40 years, and clinical translation has shown that mAb based immunotherapy can contribute to improving treatment for high-risk patients. Continued immunobiology and pre-clinical therapeutic research will be translated into even more effective immunotherapeutic strategies that will be integrated with new cytotoxic drug and irradiation therapies to improve survival and quality of life for patients with high-risk neuroblastoma.

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1. Introduction

Neuroblastoma is the most common extracranial solid tumor of childhood, and 45% of patients have high-risk tumors, nearly all of which are metastatic (stage 4) when diagnosed [1–4]. Although outcome has steadily improved over the past 20 years, event-free survival (EFS) is still only 45% for patients with high-risk, metastatic disease [5–7]. This review will focus on this group of patients since those with low- and intermediate-risk disease are currently effectively treated with surgery alone or surgery and modest-dose chemotherapy and so are not likely to receive immunotherapy in the future.

Initial evidence suggesting immune responses to neuroblastoma was provided in 1968 when blood leukocytes, which were 50–70% lymphocytes, from nine children with neuroblastoma were reported to inhibit colony formation by neuroblastoma cells that had been cultured for 10–30 days prior to testing [8]. These lymphocytes inhibited colony formation by both autologous and allogeneic neuroblastoma cells but did not affect growth of fibroblasts from the same donors. Plasma from these patients also was reported to

Abbreviations: mAb, monoclonal antibody; CTL, cytotoxic T lymphocyte; GD2, disialoganglioside; EFS, event-free survival; NKT, Vα24-invariant (type I) natural killer T cell; NK cell, natural killer cell; ADCC, antibody dependent cellular cytotoxicity; AHSCT, autologous hematopoietic stem cell transplantation; TAM, tumor associated macrophage; Tregs, T regulatory cells.

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inhibit tumor cell colony formation in the presence of complement [8]. In this same time, primary tumors were reported to contain leukocytes [9,10], and some localized and metastatic neuroblastomas were reported to regress spontaneously [11–13]. Together, these studies supported the hypothesis that the immune system could develop an anti-neuroblastoma response. However, the technology available at the time was not sufficient to define the cellular or molecular basis for the observations, and so definitive conclusions could not be reached.

Current "standard" therapy for high-risk patients, given in sequence, consists of (1) intensive induction chemotherapy and surgery; (2) myeloablative consolidation chemotherapy, autologous hematopoietic progenitor cell transplantation, and local irradiation; (3) 13-cis-retinoic acid (cisRA) combined with IL-2, GM-CSF, and anti-disialoganglioside (GD2) mAb ch14.18, which targets tumor cells [6,7]. Although EFS was improved by adding ch14.18, IL-2 and GM-CSF immunotherapy to cisRA, approximately 40% of patients still relapse during or after this therapy [7]. Development of new and more effective immunotherapy strategies for treating minimal residual disease and possibly for treating clinically measurable disease will be based upon improved understanding of interactions between tumor cells and the immune system and upon maximizing anti-tumor cell immune responses while minimizing or blocking pro-tumor and immunosuppressive immune responses.

This paper will review anti-tumor and pro-tumor (Yin and Yang) functions of the immune system in the context of neuroblastoma. The development and implementation of clinical immunotherapy with mAb ch14.18 has been successful as demonstrated in a phase III randomized study [7]. However, anti-neuroblastoma T cell therapy trials, including those testing vaccines and adoptive cell therapy, are in early development and not yet proven to be beneficial. Pro-tumor functions (Yang) of the immune system in the tumor microenvironment and their negative impact upon immunotherapy of neuroblastoma are just beginning to be recognized, and further improvement of immunotherapy will need to address the tumor microenvironment.

2. Cytotoxic T lymphocytes

The discovery that human cytotoxic T lymphocytes (CTLs) recognize a peptide presented by MHC class I molecules on autologous melanoma cells [14–16] opened the way for defining T cell targets on tumor cells. The peptide recognized in these experiments was derived from a protein encoded by the melanoma antigen-1 gene (MAGE-1, which was subsequently renamed MAGEA1). This gene, which is expressed by cancer cells and but not by normal cells with the exception of testis, was found to be a member of a large multi-gene family that has been termed the cancer/testis antigen family [16–18]. Neuroblastoma cell lines and tumors express MAGE-1/MAGEA1, MAGE-3/MAGEA3, MAGE-6/MAGEA6, and NY-ESO-1/CTAG1B [19–22]. Although these genes are expressed by human neuroblastoma cells, natural immune responses to their peptides have not been reported, and clinical vaccine trials have not been performed. There is one report that CTLs against peptides from MAGEA1, MAGEA3, and CTAG1B can be generated in vitro using T cells from normal donors and that these CTLs are cytotoxic against HLA class I compatible human neuroblastoma cells [23].

Clinical and pre-clinical studies have identified peptides from survivin, which is an inhibitor of apoptosis protein, as targets for CTLs. Survivin is expressed by many malignancies, including neuroblastoma [24,25]. In a study of nine patients with high-risk neuroblastoma, T cells specific for survivin were detected in blood at diagnosis by tetramer analysis, and circulating survivin-specific CTLs, after stimulation with survivin in vitro, were cytotoxic for autologous and HLA-compatible neuroblastoma cells. However, by immunohistochemistry, tumor-infiltrating T cells were few or absent in 26 of 26 tumors [25]. Survivin specific CTLs from patients have been induced in vitro by monocyte-derived dendritic cells transfected with neuroblastoma cell line mRNA [26]. Using a syngeneic mouse neuroblastoma model, protective tumor immunity that at least in part was due to CTLs that recognized survivin peptides was induced by immunization with Neuro-2A cells transfected with IL-21 [27]. With the NXS2 murine neuroblastoma model, oral vaccination with a survivin DNA minigene was associated with increased target cell lysis, increased presence of CD8(+) T-cells at the primary tumor site, and enhanced production of pro-inflammatory cytokines. Therapeutic vaccination led to complete neuroblastoma eradication in over 50% of immunized mice and surviving mice showed an over 80% reduction in primary tumor growth upon re-challenge [28].

Pre-clinical studies have demonstrated that tyrosine hydroxylase and MYCN proteins, which are relatively specific for neuroblastoma cells compared to normal cells, include peptides that can be targets for CTL. Vaccination of mice with tyrosine hydroxylase DNA minigenes can induce CTLs, eradicate established primary NXS2 neuroblastoma tumors, and inhibit spontaneous metastases without induction of autoimmunity [29,30]. MYCN derived peptides have been reported to generate MHC class I restricted human CTL in vitro that lyse MYCN amplified human neuroblastoma cells [31].

Pre-clinical and clinical immunotherapy studies have used neuroblastoma cells that have been transduced with cytokine genes to provide multi-antigen vaccines without identifying the specific target antigens. Murine Neuro-2A neuroblastoma cells that were transfected with IL-2 were less tumorigenic than unmodified parent cells, induced protective immunity against parent cells, and prolonged survival of mice with established Neuro-2A tumors. These functions were dependent upon CD8+ T cells [32]. The Neuro-2A model also was used to demonstrate that transfection of tumor cells with GM-CSF and IFNγ genes significantly improved their ability to induce protective immunity against liver tumors [33].

Early phase clinical trials have used cytokine transfected autologous or allogeneic neuroblastoma cells for immunization. IL-2 transfected autologous neuroblastoma cells induced antitumor immune responses in patients with neuroblastoma manifested by IgG antitumor antibody and increased CTL killing of autologous tumor cells. Clinically, five of 10 patients had tumor responses (one complete and one partial response and three stable disease), and four of these five were shown to have coexisting antitumor cytotoxic activity [34]. In a second study, 12 patients were immunized with an IL-2 transfected allogeneic neuroblastoma cell line, and although none showed any increase in direct cytotoxicity against the immunizing cell line, one had a partial response, 7 had stable disease, and 4 had progressive disease [35]. Another phase I study used the same allogeneic neuroblastoma cell line transfected to secrete both IL-2 and lymphotactin/XCL1, a chemokine for T cells. Among 21 patients with relapsed or refractory neuroblastoma, the vaccine increased CD4+ T cells, NK cells, eosinophils, and serum IL-5. Six patients had increased NK cytolytic activity, and 15 made IgG antibodies that bound to the immunizing cell line. Measurable tumor responses included complete remission in two patients and partial response in one patient [36]. In a phase I study, seven patients received lymphotactin/XCL1 and IL-2-secreting autologous neuroblastoma cells, and this was associated with increased tumor recognition as measured by enzyme-linked immunosorbent spot (ELISPOT) assays (two patients had IFNγ and three had IL-5 responses). Clinical responses did not occur [37]. In the most recent study, 13 patients who were presumed to have minimal residual disease (8 in first remission and 5 after treatment for recurrent NB) received an autologous neuroblastoma cell-IL-2 vaccine. ELISPOT

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