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REVIEW

Targets for active immunotherapy against pediatric solid tumors

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Abstract The potential role of antibodies and T lymphocytes in the eradication of cancer has been demonstrated in numerous animal models and clinical trials. In the last decennia new strategies have been developed for the use of tumor-specific T cells and antibodies in cancer therapy. Effective anti-tumor immunotherapy requires the identification of suitable target antigens. The expression of tumor-specific antigens has been extensively studied for most types of adult tumors. Pediatric patients should be excellent candidates for immunotherapy since their immune system is more potent and flexible as compared to that of adults. So far, these patients do not benefit enough from the progresses in cancer immunotherapy, and one of the reasons is the paucity of tumor-specific antigens identified on pediatric tumors. In this review we discuss the current status of cancer immunotherapy in children, focusing on the identification of tumor-specific antigens on pediatric solid tumors.

Keywords Antigen · Cancer · Immunotherapy · Pediatrics

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Introduction

Despite major advances in the treatment of childhood malignancies, cancer remains in the developed world the second most common cause of death for children >1 year of age [76]. Children and adolescents with primary multifocal, refractory, or relapsed malignant solid tumors still have a poor prognosis. Moreover, most cancer therapies are associated with significant toxicity leading to long-term morbidity and an increased second malignancy rate [75, 135]. Therefore, new treatment strategies are warranted. One of them is immunotherapy, in which the patient's own immune system is mobilized to fight the cancer in a specific way, thereby causing only mild toxicity [101].

The immune system can reject tumors

Early studies in mice showed that the immune system can recognize and reject tumors [39]. Numerous mouse tumor models have been developed to identify which part of the immune system is responsible for the eradication of tumors. These studies indicate that both $CD8^+$ and $CD4^+$ T cells play a critical role in tumor rejection or in inhibition of tumor growth [13]. The cytolytic activity of $CD8^+$ T cells exerts a direct anti-tumor effect [66]. $CD4^+$ T cells participate through the activation and maintenance of $CD8^+$ T cells and the recruitment of inflammatory cells such as macrophages, granulocytes, natural killer (NK) cells, and B cells [24, 47, 51, 93, 131].

Tumor-infiltrating immune cells have frequently been observed in a wide variety of pediatric tumors [103, 125]. Tumor infiltration of lymphocytes is generally associated with a more favorable prognosis and occasionally tumor regression [34, 119]. Another element is the observation

that immunosuppressed patients, such as graft recipients, are at higher risk to develop cancer [36, 89]. Initial studies have consistently shown a role of the immune system in the prevention of virally induced cancers in adults such as Kaposi's sarcoma (linked with human herpes virus 8), cervix carcinoma (human papilloma virus), and hepatocellular carcinoma (hepatitis B and C) [96] but also in children with certain lymphomas (induced by the Epstein-Barr virus) [42, 114]. These data suggest that the immune system plays an important role in preventing or controlling malignancy in both adults and children. In spite of the blood-brain-barrier and lack of conventional lymphatics in the brain, there is accumulating evidence that even brain tumors can cause immune activation [10, 72, 99].

Immunotherapy strategies in pediatric cancer patients

Immunotherapy can be defined as any approach that seeks to mobilize or manipulate the immune system of a patient for therapeutic benefit (Fig. 1) [61, 116]. Clinical experience of immunotherapy in the pediatric oncological setting has been gained in treating hematologic malignancies with allogeneic bone marrow transplantations and infusions of donor lymphocytes to generate graft versus leukemia responses [98]. Other clinical trials for pediatric patients have involved general immunostimulation with cytokines such as IL-2, TNF-α, and IFN-α, as adjuvant therapies to eradicate minimal residual disease [62, 112, 123, 133]. Immunotherapeutic therapies targeting identified tumor-associated antigens are discussed in the following.

Antibodies

The identification of tumor-specific cell-surface molecules opened the possibility for antibody-mediated passive immunotherapy. Antibodies (Ab) against tumor-associated antigens can induce complement dependent cytotoxicity (CDC) and Ab-dependent cell-mediated cytotoxicity (ADCC) [70]. Promising pediatric clinical phase I trials have been described using monoclonal Ab against gangliosides, which are highly expressed in neuroblastoma and osteosarcoma [40, 87, 88, 128]. Tumor-specific Ab

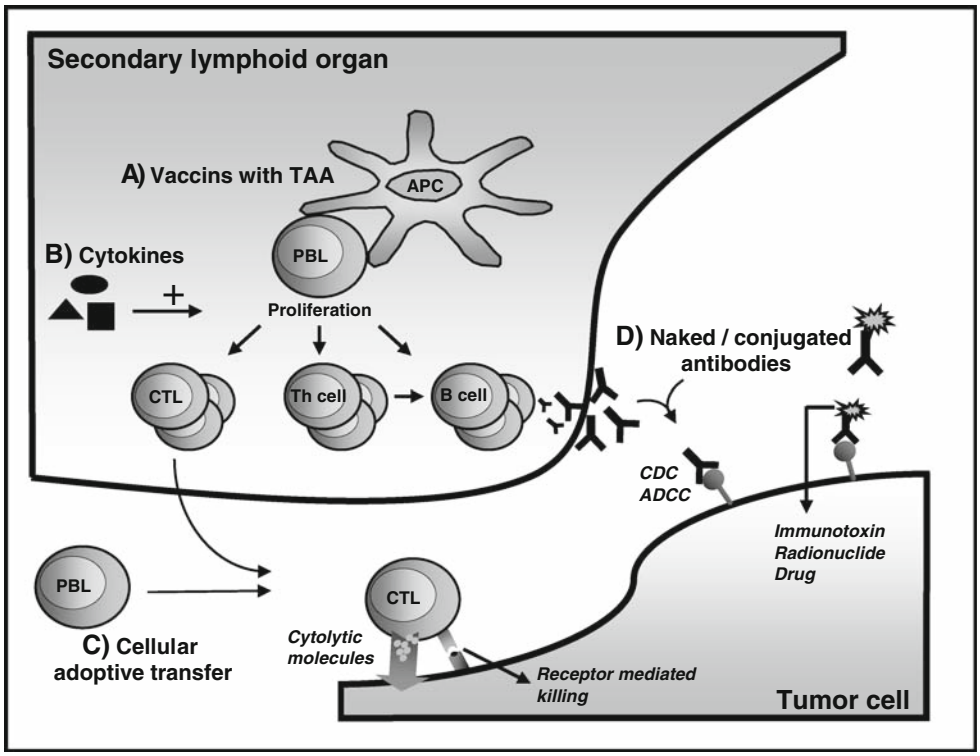

Fig. 1 Immunotherapeutic strategies applied in pediatric clinical trials. *A* Administration of tumor antigens either directly into the body or loaded onto APC. The TAAs are presented by the APC to lymphocytes in secondary lymphoid organs to initiate a tumor-specific immune response. *B* Non-specific stimulation of the immune response by cytokines, for example IL-2, TNF-α and IFN-α and GM-CSF which induces T cell proliferation. *C* Adoptive transfer of donor lymphocytes or natural killer cells for complete eradication of leukemic cells following allogeneic transplantation. *D* Monoclonal antibodies (mAb) that bind specifically to cancer cells can induce an immune response. Alternatively, mAb can be modified for targeted delivery of a toxin, radioisotope, cytokine, or other active conjugate. *TAA* tumor-associated antigens, *APC* antigen-presenting cell, *PBL* peripheral blood lymphocyte, *CDC* complement dependent cytotoxicity, *ADCC* antibody dependent cell-mediated cytotoxicity

conjugated to toxins are under investigation as targeted drug-vehicles for embryonal tumors [86, 105].

Adoptive cellular immunotherapy

Reconstituting or increasing cellular immunity can be achieved through the infusion of tumor-specific T cells. Autologous $CD4^+$ or $CD8^+$ T cells can be manipulated ex vivo in various ways to obtain high numbers of clinical grade tumor-specific T cells [23]. The therapeutic effect of infused tumor-specific T cells depends on the viability of the cells, their homing to the tumor, and their ability to kill within the tumor microenvironment.

Another aspect is the renewed appreciation of the role of the innate immune system. Immune-mediated tumor lysis is the result of a combined action of adaptive and innate immunity, in which NK cells are important effector cells. NK cell activation is regulated by a balance between signals mediated through activating receptors such as NKG2D and inhibitory receptors such as killer immunoglobulin-like receptors (KIRs). Upon cellular transformation in tumor cells, MHC class I ligands for inhibitory receptors are often downregulated and ligands for activating NK cell receptors are upregulated on the tumor cell. Together, these events can shift the balance toward NK-mediated tumor-cell killing [78]. Next to the direct cytotoxic effect on tumor cells, NK cells produce type I interferons that create a proinflammatory tumor microenvironment [106, 113]. Clinical studies on adoptive transfer of NK cells in adults have shown that NK cells can have a role in the treatment of selected malignancies [84]. Adoptive transfer of NK cells in pediatric patients with leukemia is feasible [68]. Ongoing clinical studies further investigate NK cell-mediated immunotherapy for pediatric patients with leukemia or neuroblastoma (http://www.clinicaltrials.gov).

In vivo induction of tumor-specific lymphocytes

The advantage of active immunization over adoptive transfer is the possibility of inducing memory T cells that can control tumor relapse [37]. On the basis of the successes of attenuated pathogen vaccines and owing to the initial lack of defined tumor antigens, the first active immunizations were carried out with whole tumor cells that were previously irradiated or otherwise inactivated [134]. In children, most of the clinical experience using whole tumor cell vaccines is obtained with neuroblastoma patients. In these trials, the neuroblastoma cells are (gene-) modified to express various co-stimulatory molecules or cytokines to increase their immunogenicity [9, 16, 107].

When tumor-associated antigens are identified, therapeutic vaccination can involve the administration of the antigen either as a whole recombinant protein or as antigenic peptides presented by HLA class I or class II molecules. One clinical trial reports on using chimeric antigenic peptides encoded by translocated genes expressed in Ewing's sarcoma and rhabdomyosarcoma [26]. Another strategy is the administration of autologous antigen-presenting cells, such as dendritic cells, loaded with defined tumor antigens or with tumor cell lysates. We reported that clinical grade dendritic cells can be cultured from blood monocytes of pediatric cancer patients [55]. Others have reported that such dendritic cells can induce tumor-specific T cells that can cause regression of high-risk malignancies in pediatric patients [19, 29, 30, 43].

Advances in gene transfer technology have added new possibilities to optimize vaccine preparation [74, 94]. These include transferring genes encoding pro-inflammatory proteins to tumor cells and transferring tumor antigen-encoding genes into professional antigen-presenting cells. Tumor cells can be engineered to express MHC class I and class II, costimulatory molecules, or cytokines, and used as vaccines. Several gene therapy applications to induce antitumor immunity have been reported for pediatric cancer patients in preliminary phase I studies [9].

Current research also focuses on vaccinating directly with antigen-encoding DNA. Studies in animal models have demonstrated the feasibility of utilizing DNA vaccines to elicit protective cellular and humoral antitumor immune responses [95]. In humans, DNA vaccines are being tested in phase I to III clinical trials for cervical cancer, melanoma, renal cell carcinoma, and prostate cancer [80]. Preliminary results confirm the safety and immunogenicity of these vaccines. DNA vaccinations have not been studied in pediatric patients. However, first steps are being taken with murine studies showing that DNA-vaccination is potentially effective to treat neuroblastoma and prevent neuroblastoma metastases [79, 97].

Tumor-associated antigens

One of the reasons for the paucity of clinical trials of therapeutic anti-cancer vaccination in children is the lack of information about the expression of tumor-specific antigens on many pediatric tumors. In the second part of this review we will summarize the current data on the expression of tumor antigens recognized by T cells on a selection of the most common solid pediatric tumors.

Tumor antigens that can be recognized by T lymphocytes are complexes of HLA class I or class II molecules presenting small antigenic peptides. The antigens can be classified into four major groups, based on the pattern of expression of the genes encoding the antigenic peptide [14, 90].

Antigens resulting from mutations or translocations

These antigens are encoded by genes that are mutated in tumor cells as compared to the normal cells of the patient; the antigens can therefore be considered strictly tumor-specific. The mutations can be point mutations, or translocations, in genes that are expressed ubiquitously. The mutation affects a coding region of the gene, and antigenic peptides contain mutated residues or straddle the junction of chimeric proteins encoded by translocated genes.

Antigens encoded by cancer-germline genes

Cancer-germline genes are expressed in different types of human tumors. They are not expressed in normal tissues with the exception of male germline cells which do not express HLA molecules and therefore cannot present antigenic peptides to T cells [115]. For this reason the antigens encoded by cancer-germline genes are strictly tumor-specific.

Differentiation antigens

Differentiation antigens are encoded by lineage-specific genes that are expressed in tumor cells as well as in the normal cells from which the tumor arises. The natural tolerance to these antigens is not complete, and the induction of an immune response against differentiation antigens is possible [35].

Antigens encoded by genes that are overexpressed in tumors

This last group of tumor antigens is encoded by genes that are overexpressed in tumors as compared to normal tissues. Some oncogenes are expressed in normal tissues at a low level and overexpressed in several tumors [17, 38]. Since both differentiation antigens and overexpressed antigens are expressed in normal tissues, autoimmunity can be a side effect when these antigens are used as immunotherapeutic target.

T cell defined antigens in pediatric solid tumors

For usefulness in immunotherapy, an antigen has to meet two important criteria. It has to be expressed by the tumor of the patient, and it has to be immunogenic. These criteria can be tested with gene/protein expression and lymphocyte recognition/tumor lysis assays (Fig. 2). For an effective cellular immune response, the tumor-specific antigen must be processed into peptides and presented on HLA molecules. Many tumor-associated antigens and epitopes have been described that are recognized by $CD4^+$ and/or $CD8^+$ T cells. Detailed lists of antigen-encoding genes and of epitopes can be found at http://www.cancerimmunity.org.

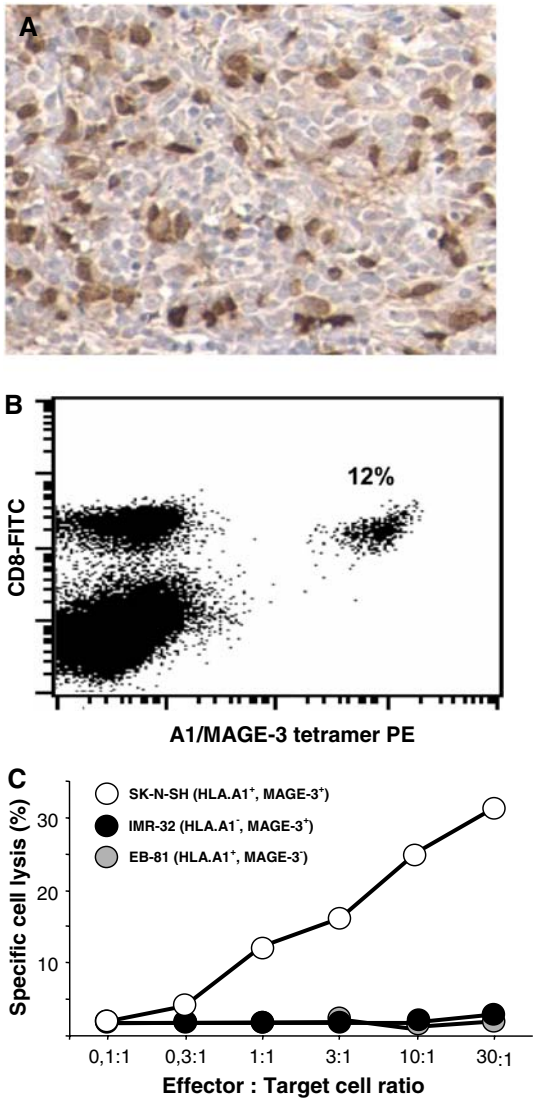

Fig. 2 In vitro assays to assess target suitability. **a** Immunohistochemistry of MAGE-1 expression in a neuroblastoma tumor (antibody MA454) demonstrates the heterogeneous expression of MAGE-1 in this tumor sample. **b** Visualization of MAGE-3 specific $CD8^+$ cells using labeled CD8-Ab and A1/MAGE-3-tetramers. Dot plot of peripheral blood mononuclear cells from a patient who received a vaccine containing MAGE-3.A1 peptides. Twelve percent of the $CD8^+$ cells are tetramer-positive after 2 weeks of in vitro re-stimulation with the MAGE-3.A1 peptide (EVDPIGHLY) [63]. **c** Chromium release assay using cytotoxic T lymphocyte clone EH-1 B2.C10, which recognizes peptide MAGE-$3^{168-176}$ presented by HLA-A1 molecules. Lysis was tested after 4 h at 37°C, as previously described [12]. Only the HLA-$A1^+$, MAGE-3^+ SK-N-SH neuroblastoma cell line (*white dots*) is efficiently lysed by the CTL clone. Cell lines that are either HLA-A1 negative (IMR-32, *black dots*) or do not express gene MAGE-3 (EB81-EBV-B, *gray dots*) are not lysed

Tables 1 and 2 summarize T cell defined antigens on a selection of the most important pediatric solid tumors. The

Table 1 T cell defined antigens in extra-cranial pediatric solid tumors

Antigen (refs)	Neuroblastoma (%)	Rhabdomyosarc. (%)	Osteosarc. (%)	Ewing's sarc. (%)
Antigens from fusion proteins:				
PAX3/FKHR [67]	0	60[a]	0	0
EWS/FLI 1 [31]	0	0	0	85
Cancer-germline genes:	82	9–16	ND	100
GAGE [20, 27]				
MAGE-1 [25, 27, 52, 54, 117, 118]	18–60	25–38	55–88	0
MAGE-2 [21, 27, 54, 118]	60–61	33–51	55–78	0
MAGE-3 [25, 27, 52, 117, 118]	33–76	35–42	52–100	28
NY-ESO-1 [54, 104, 117]	36–82	25	88	0
Overexpressed antigens:				
HER-2 [3, 41, 49, 83, 124, 139]	14	11	0–44	0
MYCN [33, 46, 130]	20–25	43–60[a]	ND	ND
P53 [3, 6, 28, 91, 121, 124, 126]	84	19–67	14–27	11–43
Survivin [1, 53, 122]	47–54	ND	58	ND

The percentages indicate the proportion of tumors expressing the gene, tested with RT-PCR or IHC

GAGE G antigen, *HER-2* human epidermal receptor 2, *MAGE* melanoma-associated antigen, *ND* not determined, *NY-ESO-1* New York esophagous 1, *P53* protein 53, *WT-1* Wilms' tumor 1 gene

[a] Expression in alveolar rhabdomyosarcoma; no expression of MYCN in embryonal rhabdomyosarcoma

Table 2 T cell defined antigens in pediatric brain tumors

Antigen (refs)	Low grade astrocytoma (%)	High grade astrocytoma (%)	Ependymoma (%)	Medulloblastoma (%)
Cancer-germline genes:				
GAGE [110]	ND	11	43	13
MAGE-1 [11, 22, 57, 102, 110]	0–33	0–100	0	9–13
MAGE-2 [57, 110]	12–18	10–11	57	18–60
MAGE-3 [22, 57, 108, 110]	18–35	20–33	0–33	13–18
NY-ESO-1 [57, 108]	0–14	0–10	ND	9
Overexpressed antigens:				
HER-2 [44, 45, 77, 111]	0–77	5–93	83	38–86
IL-13R [59, 65]	79	100	67	67–100
MYCN [2, 8, 50, 71]	ND	43	ND	5–21
P53 [58, 69, 73, 85, 132]	8–72	52–63	28–48	17–27
Survivin [60, 64, 92, 109]	37–64	80–92	100	100
WT-1 [32]	40	56	56	39
Differentiation antigens:				
Tyrosinase [22]	67	38	50	ND
Gp100 [22, 77]	33	38–47	50	ND

The percentages indicate the proportion of tumors expressing the gene, tested with RT-PCR or IHC

GAGE G antigen, *gp100* glycoprotein 100, *HER-2* human epidermal receptor 2, *IL* interleukin, *MAGE* melanoma-associated antigen, *ND* not determined, *NY-ESO-1* New York esophagous 1, *P53* protein 53, *WT-1* Wilms' tumor 1 gene

antigens are categorized according to the four groups mentioned in the previous paragraph. To produce a clinically relevant list, we have included only antigens of which (1) peptides recognized by T cells are identified, (2) the HLA presenting molecule is identified, (3) evidence exists that the peptide is processed and presented by tumor cells, and (4) a certain level of tumor- or tissue-specificity is reported. Virus-encoded and artificially modified epitopes are excluded from this list. Antigens of solid tumors outside the central nervous system are shown in Table 1, and those of brain tumors in Table 2. The percentages indicate the proportions of tumors expressing the gene, tested with RT-PCR or immunohistochemistry. Original papers are only referred to if expression has been investigated in at

least ten histologically similar tumors, with no restriction as to the year of publication.

All tumors reviewed here, except neuroblastoma, also occur in adults. Most papers about antigen expression do not report whether tumor samples are derived from adults or children. Only a few papers specifically report on antigen expression in pediatric tumors [44, 54, 57, 65, 73, 85, 92]. It is important to note that the expression of a given antigen in tumors of adult patients does not guarantee that this antigen is also expressed in the tumor of that same subtype from a pediatric patient. We and others observed significant age-related differences in the expression of tumor antigens in glioblastoma samples [57, 92, 100, 120]. For some antigens we noticed important differences in the expressions reported by different groups. They can be due to the sensitivity/specificity of the techniques used (microarray, RT-PCR and immunohistochemistry), to different antibodies or primer-pairs for the same antigen, and to differently chosen cut-off points.

Which antigens to choose for pediatric clinical trials?

Table 1 and 2 list T cell defined antigens expressed on pediatric tumors that can be used as immune target in clinical trials. So far, these antigens have primarily been used in clinical trials in adult patients with the exception of clinical trials in pediatric patients targeting the following antigens: PAX3/FKHR and EWS/FLI1 [26, 82], WT-1 (ongoing clinical trial, http://www.clinicaltrials.gov) and MAGE-A1 (Jacobs et al., manuscript in preparation). Choosing the best antigen in a specific immunotherapy trial depends on the individual needs for that study such as the immunogenicity of the antigen, the level of antigen expression by the tumors, the tumor-specificity of the antigen, the availability of clinical grade antigenic products, and the HLA-type of the included patients.

Mutated tumor antigens are attractive antigens for cancer immunotherapy because of their strict tumor-specificity and because of their potential resistance to immunoselection when the mutated gene product plays an important role in the oncogenic process. One drawback is that most point mutations, in contrast to chromosomal translocations, are not shared by tumors from different patients. Examples of chimeric proteins in the pediatric setting are the PAX3-FKHR, EWS-FLI 1, TEL-AML1, and BCR-ABL fusion proteins seen in alveolar rhabdomyosarcoma, Ewing's sarcoma, acute lymphatic leukemia, and chronic myeloid leukemia, respectively [18, 81, 129, 137]. For all four fusion proteins several MHC class I and class II chimeric peptides have been described that induce specific T cells and can be considered for immunotherapy [82, 136–138].

The other genetic mechanism responsible for tumor-specificity of antigens is the aberrant expression in tumor cells of genes that are silent in normal cells. When the antigens are encoded by genes that are expressed in many different tumors they are called 'shared tumor-specific antigens'. Most of the shared tumor-specific antigens are encoded by cancer-germline genes. Cancer-germline genes such as MAGE, GAGE, or LAGE/NY-ESO-1, are expressed in different types of pediatric tumors (Tables 1, 2). Numerous peptides, binding to different HLA class I and HLA class II molecules have been identified [15]. Because of their tumor-specificity and immunogenic potential, antigens encoded by cancer-germline genes have been one of the main components of antitumor vaccines tested in the clinic during the last decade [115].

Approximately 20% of all identified tumor antigens are encoded by genes that are overexpressed in cancer cells as compared to normal cells. Overexpression in this context means more antigenic peptides presented on MHC molecules at the cell surface, explaining the tumor-specificity of the T lymphocytes. As shown in Tables 1 and 2, many of the identified antigens in pediatric solid tumors are classified as overexpressed antigens. HER-2, WT-1, and MYCN are the most interesting candidates for immunotherapy since these genes are involved in cell proliferation and their overexpression plays a direct functional role in tumor progression. This role in oncogenesis implies that it is more difficult for the tumor to escape immune attack through downregulation of antigen expression. The absence of autoimmune tissue damage in cancer patients with HER-2, WT-1, or MYCN specific CTLs suggests that these antigens can be safely used as immunotherapeutic target [5, 7, 48].

With the observation that tumor-specific CTL clones derived from melanoma patients could also recognize normal melanocytes it became obvious that natural tolerance to differentiation antigens was incomplete [4]. Gp100 and tyrosinase are the only differentiation antigens expressed in pediatric tumors for which T cell specific peptides are identified (Table 2). Autoimmunity can be a side effect when differentiation antigens are used for vaccination. Since gp100 and tyrosinase are expressed in normal melanocytes, it is possible that pediatric patients will develop vitiligo when these antigens are used in a vaccine [56, 127].

For safety concern, the target antigens used in pediatric clinical trials should be strictly tumor-specific. If such an antigen is not available, the normal tissue expressing the antigen must be dispensable, to avoid serious autoimmune toxicity. Finally, it is probably preferable to use combinations of antigens to decrease the probability of in vivo selection of antigen-negative tumor cells.

Conclusion

Immunotherapy against cancer is a field of growing interest. Most therapies are still experimental and focus on adult patients. However, the first immunotherapeutic trials for pediatric cancer patients have been published, and more are ongoing. These novel trials aim at stimulating both humoral and cellular anti-tumor immune responses. The identification of many tumor-associated antigens, including for most pediatric solid tumor types, should facilitate this clinical endeavor.

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