Considerations for the Development of Innovative Therapies Against Aggressive Neuroblastoma: Immunotherapy and Twist1 Targeting

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Abstract

Neuroblastoma (NB) is one of the major challenges of pediatric oncology with a 5-year survival rate of less than 40% despite intense therapy. The aggressiveness of the disease has been recently correlated to the degree of myeloid cells infiltrating the tumor. Together with the tumor cells and immunosuppressive cytokines (e.g., IL-10 and TGF-β), these cells hamper the generation of an efficient antitumor immune response and, therefore, favor tumor growth and metastasis. Novel therapeutic approaches are designed to target immune cells instead of cancer cells. To improve their efficacy, recent cancer immunotherapy strategies have focused on the depletion, blockade, or reprogramming of these tolerogenic immune effectors. Therefore, the principal clinical challenge is currently to identify therapeutic strategies which could overcome the primary and secondary resistances to these cancer immunotherapies. In this review, we discuss the dialogue of immune microenvironment of neuroblastoma and the immunotherapeutic strategies to cure neuroblastoma.

Keywords: immunotherapy, immune checkpoint modulators, microenvironment, inflammation, TWIST1

1. Introduction

Our immune system is continuously monitoring our tissues and recognizes the abnormal cancer cells to kill them. The immune cells originate from hematopoietic stem cells inside the bone marrow that give birth to two different lineages: the myeloid and lymphoid progenitor cells. The different populations derived from myeloid progenitor cells are monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, dendritic cells (DC), and megakaryocytes.
(or platelets). The population driven from lymphoid progenitor cells is T and B lymphocytes, natural killer (NK) cells, and other innate lymphoid cells. These different populations are the principal actors of innate and adaptive immune system. The innate immunity populations include the natural killer cells, granulocytic cells, such as neutrophil, and antigen presenting cells (APC), such as DC and macrophages. These cells provide the first line of self-defense against foreign pathogens as well as cellular damages and cancers. The innate immune response is very rapid but has no antigen specificity and immunological memory. In contrast to the innate immune response, adaptive immune responses are highly specific to the particular antigen and provide a long-lasting protection through induction of memory. The two populations of adaptive immunity are T lymphocyte populations (T helper and cytotoxic T cells) and B lymphocytes (plasma cells which are capable to secrete the antibodies).

The fact that tumors arise from self-tissues expressing antigens which induced immune tolerance implies the lack of immunogenicity and lack of immune control of the tumor. Latter based on different studies, the concept of immune editing emerged [1]. This process contains three phases: elimination, equilibrium, and escape. Elimination is the classical concept of immune surveillance, whereas the Darwinian natural selection of tumor variant developing the mutations which make them resistant to immune attacks occurs in the equilibrium phase. This process can lead to immune escape of immune resistant tumor variants and the formation of clinically apparent tumors [2]. It is now accepted that the immune system has a primary role in the prevention of tumors.

In high-risk neuroblastoma (HRNB), amplification of MYCN oncogene leads to an important oncogenic stress that normally drives to the induction of a program allowing the elimination of proliferating cells by cell death, apoptosis, or replicative senescence.

Usually, apoptotic or necrotic bodies are uptaken by antigen presenting cells (APC) allowing their elimination by the immune system leading to an adaptive immune response. Therefore, immune editing is a crucial step in tumor development. However, neuroblastoma (NB) is a pediatric tumor and from an immunological point of view, children age clearly determines the status and capacities of an adaptive immune response. Children less than 1 year of age with immature immune system, with innate cells preferentially, have better prognosis than children more than 1 year of age with a more mature immune system. These paradoxical observations reflect the functional duality of immune system harboring both the antitumoral and protumoral abilities.

Interestingly, metastatic tumors diagnosed in children at age ≥18 months had higher expression of inflammation-related genes than those in patients diagnosed at age <18 months. These data suggest that these inflammatory cells in the tumor microenvironment may contribute to the clinical metastatic neuroblastoma phenotype and reveal a novel rational for immunotherapy of neuroblastoma (NB) [3].

2. Immunotherapy of neuroblastoma

Checkpoint inhibitors, such as ipilimumab (anti-CTLA4) or pembrolizumab (anti-PD1), demonstrated spectacular benefit in some adult cancers, but lack of activity in pediatric cancers,
likely due to the rarity of neoantigens [4]. Neoantigens are uniquely present on the tumor and not expressed by normal tissue, in contrast to different molecules overexpressed on tumors that are also present on normal prenatal or postnatal tissues, which induce immune tolerance. In fact, many adult tumors arise in response to environmentally mediated genotoxic damage and bear large numbers of mutations. In contrast, pediatric tumors typically display few mutations but mostly translocations or gene amplifications. In NB, MYCN amplification, activating mutations, or rearrangements of ALK (observed in 8–10% of sporadic tumors) preexist in prenatal tissues and might be responsible for immune tolerance [5]. Therefore, NB (and others pediatric cancers) can be compared with resistant to immune checkpoint inhibitors in adult cancers and need to be treated as such. First, while pediatric tumors demonstrate low mutation burdens at diagnosis, increases in mutation frequency can be enhanced after exposure to chemotherapy or radiotherapy [6, 7]. In addition to increase neoantigens, radiation may increase immune response to checkpoint blockade as localized radiation along with checkpoint blockade resulted in an abscopal effect with regression of metastatic lesions outside of the radiation field [8]. Using agents that induce tumor cell death or tissue differentiation might lead to release or expression of new tumor-associated antigens (TAA) or differentiation antigens. Therefore, combining checkpoint inhibitors with agents that augment innate and/or adaptive immunity could provide effective antitumor responses in children despite low inherent immunogenicity [9].

Synthetic immunotherapies, such as monoclonal antibodies (Mabs) and chimeric antigen receptor (CAR) T cells, harbor such characteristics. This is probably one reason of their impressive effects against childhood cancers in general. The only clinically available mAbs in neuroblastoma cells is dinutuximab, a chimeric, human-murine, anti-disialoganglioside GD2 overexpressed on NB tumors. Dinutuximab was approved in combination with granulocyte/monocyte-colony stimulating factor (GM-CSF), aldesleukin (interleukin-2 [IL-2]), and isotretinoin (13-cis-retinoic acid [RA]) for maintenance treatment of patients with high-risk neuroblastoma who respond at least to first-line multimodality therapy [10]. In phase III trials, dinutuximab increased 2-year event-free survival (EFS) and overall survival (OS) compared to standard treatment. It was shown that major mechanism of action of dinutuximab passes though the induction of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) leading to tumor cells lysis and TAA release [11]. Therefore, combination of dinutuximab with immune checkpoint inhibitors, such as anti-PD1/PDL1 Mabs, might increase effective adaptive antitumor immune response leading to better survival. Since serious adverse reactions have been reported with the dinutuximab-containing regimen, with infusion reactions and neuropathy prompting the Food and Drug Agency (FDA) to issue boxed warnings, this combination could be a very promising issue.

Another promising way to stimulate immune system consists in the development of bispecific antibody targeting GD2 and CD3 expressed on T cells. The idea to bridge activated T cells (ATC) to GD2-positive neuroblastomas provides preclinical rationale for immunotherapy using this bispecific antibody in children with neuroblastoma [12].

Another novel approach recently developed to improve the current anti-GD2 immunotherapy is based on NK cell stimulation using Toll-like receptor (TLR) activated plasmacytoid dendritic cells (pDCs). NK activation by pDCs led to a NK-cell phenotype characterized by increased surface expression of tumor necrosis factor-related apoptosis-inducing ligand
(TRAIL), CD69 on CD56dim cytotoxic cells, and strong interferon-γ production. These data suggest that children with HRNB may benefit from NK-cell stimulation by activated pDCs to increase NK-cell lytic functions against NB cells [13].

In fact, NK cells impact on the normal immune surveillance of HRNB. Quantification of serum concentration of soluble B7-H6, ligand of NKp30 activation molecule, correlated with the downregulation of NKp30, bone marrow metastasis, and chemoresistance [14]. Thus, interaction between NKp30 and B7-H6 may contribute to neuroblastoma immunosurveillance and both NKp30 expression on circulating NK cells and the serum concentration of soluble B7-H6 may represent biomarkers for risk stratification [14].

Although adoptive transfer of T cells expressing chimeric antigen receptors (CARs) targeting hematopoietic lineage demonstrated impressive response in chemorefractory pediatric patients, in solid tumors, lack of efficacy seems multifactorial and includes the suppressive tumor microenvironment [15, 16].

Pule et al. reported partial response in patients with refractory neuroblastoma using first-generation GD2-CAR (e.g., TCR zeta signaling endodomains without additional costimulation) incorporating the scFv shared with dinutuximab [17]. Efforts to add both CD28 and OX40 as costimulatory domains were disappointing with no improved objective response [18].

CD171 (L1-CAM) is another abundant cell surface molecule expressed on neuroblastomas, which is detectable at the diagnosis and relapse time independently on patient clinical risk. The CE7R CAR targeting CD171 demonstrated activation of tumor cell lysis and Th1 cytokine production [19, 20]. Infusion of autologous CD8(+) cytolytic T lymphocyte clones coexpressing CE7R and the selection suicide expression enzyme HyTK in children with recurrent/refractory neuroblastoma was the first-in-humans pilot study that set the stage for clinical trials employing adoptive transfer in the context of minimal residual disease. No overt toxicities to tissues known to express L1-cell adhesion molecule (e.g., central nervous system, adrenal medulla, and sympathetic ganglia) were observed.

Finally, a large panel of primarily resected neuroblastoma samples demonstrated expression of the cancer-testis antigen (NY-ESO-1) in 23% of the samples. NY-ESO-1 is expressed by many solid tumors and has limited expression by mature somatic tissues, making it a highly attractive target for tumor immunotherapy. Transgenic TCR (tTCRs combined with HLA-A2+ neuroblastoma cell lines) targeting NY-ESO-1 has been shown to slow the progression of both local and disseminated disease, and significantly enhanced animal survival providing rational for therapeutic option for patients with neuroblastoma [21].

Again, as proposed for therapeutic Mabs, the combination of CAR T cells with immune checkpoint modulators could bring a profit in terms of antitumoral response and remain to be evaluated.

Recent studies have shown that MYCN nonamplified metastatic neuroblastomas have higher infiltration of Tumor Associated Macrophages (TAM) myeloid CD163+ cells than locoregional tumors. Macrophage-colony stimulating factor (M-CSF) or colony stimulating factor (CSF-1) is known to be essential for the differentiation and survival of these myeloid cells [22]. It is
associated with poor survival in various human cancer and CSF-1R (CSF-1 receptor) targeting strategies have been explored [23]. In NB, it has been shown that CSF-1R+ myeloid cells predict poor survival in patients and, as a consequence, combining CSF-1R inhibitor (BLZ945) with PD-1/PD-L1 blocking agents induce robust antitumor effects against established aggressive tumors in the TH-MYCN murine neuroblastoma model [24].

Cytokine-induced killer (CIK) cells, immune effector cells that have the properties of T lymphocyte and NK cells, capable to recognize malignant cells in the absence of Major Histocompatibility Complex (MHC), also have provided encouraging results in clinical studies. IL-15-activated CIK cells have revealed synergistic antitumor effects in combination with standard therapy and higher toxicity in comparison with IL-2-stimulated NK cells [25].

3. New prospects in immunotherapy

A very promising therapy currently in development in adult cancer consists in the combination of oncolytic viruses (OVs) with immune checkpoint inhibitors. Oncolytic viruses can infect cancer cells and induce cell death to produce the new viruses. Some oncolytic viruses, such as parvovirus, reovirus, Newcastle disease virus (NDV), mumps virus, or Moloney leukemia virus, have natural preference to replicate into cancer cells leading to the destruction of the cells [26]. Viruses such as measles virus, adenovirus, vesicular stomatitis virus (VSV), vaccinia virus (VV), and herpes simplex virus (HSV) can be engineered to confer them cancer specificity [26]. Some were engineered to directly target unique cell surface receptors expressed by cancer cells such as adenovirus to target CAR [27] and measles virus to express a single-chain antibody that recognizes carcinoembryonic antigen (CEA) [28]. Others are deficient viruses like E1B mutant adenovirus which preferentially replicate in p53 inactivated cells [29].

There are already two engineered OVs approved in clinic in adults: E1B-deleted adenovirus and talimogene laherparepvec virus (T-VEC). T-VEC is based on herpes simplex virus type 1 deleted for ICP 34.5 gene (neurovirulence factor), ICP47 (block antigen presentation in HSV infected cell), overexpressed US11 (viral RNA binding proteins), and inserted for GM-SCF [30]. T-VEC is approved by the FDA for the treatment of melanoma [31]. Others are under active development.

Most oncolytic viruses can induce cancer cell death and directly eliminate tumor cells but they also initiate systemic immune responses through different mechanisms such as inducing an immunogenic cell death, releasing danger-associated molecular patterns (DAMPs) and tumor-associated antigens (TAA) from virus-infected cells. They also release viral pathogen-associated molecular patterns (PAMPs) contributing APCs maturation that conduct the activation of antigen-specific CD4+ and CD8+ T cell responses. Once activated, CD8+ T cells become cytotoxic effector cells that traffic to tumor sites, where they mediate antitumor immunity upon antigen recognition [32]. Combining checkpoint inhibitors to virotherapies might ultimately prove beneficial for neuroblastoma resistance to immune checkpoint blockade antibody therapy.
4. Twist1 targeted therapy

In correlation with MYCN amplification (NMA), we previously reported that TWIST1 was constantly overexpressed in neuroblastoma with NMA and highlighted in vivo cooperation between TWIST1 and MYCN for primary cells transformation through inhibition of apoptosis and differentiation [33]. Based on different clinical data tumor sets, we demonstrated that TWIST1 overexpression was associated not only with NMA but also with MYCN or MYC overexpression and highlighted TWIST1 as a direct MYC transcriptional target [34].

We previously showed that inhibition of TWIST1 expression restores the apoptotic properties of NB cells overexpressing MYCN [33]. Based on the observation that stage 4S NB with higher levels of N-Myc proteins are more prone to spontaneous regression by apoptosis [35] or neuronal differentiation [36], it has been speculated that MYCN not only mediates malignant progression, but is also involved in spontaneous regression in favorable NB [37]. We, and others, have demonstrated that inhibition of MYCN leads to MYC upregulation [38]. For all these reasons, both MYC family members have to be simultaneously targeted. Restoration of MYCN or MYC proapoptotic properties though TWIST1 inhibition is, therefore, a promising concept.

In many other tumor types, Twist1 has been associated to Epithelial–Mesenchymal Transition (EMT) and cancer stem cell phenotype (CSC) [39]. There are different drugs currently in development targeting the cancer stem cells associated with Twist1 deregulation. Some show promising results from preclinical trials like Salinomycin able to effectively eliminate CSCs and to induce partial clinical regression of heavily pretreated and therapy-resistant cancers [40, 41].

5. TWIST1, MYC, and immune system

Recent papers suggest that oncogenes playing key role in transformation might also play a role in protumoral microenvironment properties [42]. This is true for TWIST1 since its overexpression was reported correlated with increased vascularization in breast carcinoma [43]. In fact, Twist1 does not directly induce vEGF production by tumor cells but rather chemokines like CCL2 that are attractive for vEGF-producer macrophages. Their homing in tumor microenvironment site and production of vEGF contribute to metastasis [42]. In aggressive NMA neuroblastoma, it was shown that TAMs are correlated to bad prognosis [10]. Macrophages are key players in maintaining the tissue homeostasis, shaping adaptive immune response, inflammation, and tissue repair [44]. In response to signals from the microenvironment, macrophages are polarized into distinct phenotypic subtypes, referred as proinflammatory macrophages M1 and anti-inflammatory M2 subtype [45]. Macrophages that reside within a tumor, often referred as TAMs, display M2-like phenotypes with immunosuppression regulatory functions to support tumor development [46]. Interestingly, it was shown that Twist1 inhibition in tumor cells lead to TAM decrease and vascularization regression. Once more, Twist1 was shown to directly produce immunosuppressive cytokines attracting immunosuppressive Gr1+CD11b+ myeloid-derived suppressive cells (MDSC) in tumor microenvironment that can be reversible after Twist1 inhibition [47]. Therefore, the role of inflammatory cells
in tumor microenvironment may contribute to the clinical metastatic neuroblastoma phenotype, improve prognostication, and reveal novel ratio for immunotherapy of neuroblastoma. Interestingly, MYCN has also been recently revealed as the most highly upregulated gene in macrophages upon the treatment of immune suppressive soluble factors that are released from apoptotic cells [48]. Once more, it was shown that inhibition of MYC in macrophages attenuates the protumor function of TAM and suppresses tumor growth [49].

These studies implicate MYC and MYCN as a key player in regulating macrophage functions and suggest that MYC inactivation may suppress tumor growth in a cancer cell-extrinsic manner. Therefore, MYC and MYCN may not only regulate proliferation but also exert immune modulatory functions in macrophages, therefore, on immunosuppressive microenvironment.

Therefore, strategies aiming to inactivate Twist1 and/or Myc proteins might be of interest both on tumor cells survival capacities but mostly in reprogramming the tolerogenic immune effectors within the microenvironment.

For example, Twist1 inhibition might lead from one hand, by inducing tumor cell death or tissue differentiation, to release of tumor-associated antigens or differentiation antigens, and on the other hand, to reprogramming of inflammatory myeloid cells within tumoral microenvironment. Combination of both events might contribute to efficient destruction of tumors by reactivation of immune system leading to an efficient antitumoral adaptive immune response. Combination with immune checkpoint inhibitors needs to be further analyzed.

6. Conclusion

Despite recent advancement in the understanding of molecular pathways that drive the development of neuroblastoma, insights have not fundamentally changed the therapeutic approach, which still consist in nonspecific, cytotoxic chemotherapy. Chemoresistant and relapse make that neuroblastoma always represents 15% of all pediatric cancer deaths. Innovative treatment approaches are, therefore, needed. Intense efforts are underway to enhance the effectiveness of immunotherapies through combination with agents designed to selectively attack the tumor cells and amplify immune responses.

Based upon the results with dinutuximab, immunotherapy has already demonstrated impressive benefit to children with neuroblastoma. Checkpoint inhibitors administered alone or in combination have not yet been studied in childhood cancer, although they will not be sufficient as single agents. CART cells have shown unprecedented results in pediatric hematological cancer but showed limited efficacy in solid tumors to date.

The ultimate goal would rather be to deliver a specific innovative tumor destruction system permitting the release of TAA, and local induction of inflammation, in order to provide immune priming and amplification of the immune response after combination with immune checkpoint modulators. Therefore, strategies that target both tumor cells and microenvironment are focusing interest.
In the race of improving immunotherapy for pediatric cancer, oncolytic viruses might find a very important issue. OVs have many features that make them advantageous for cancer immunotherapy: (1) there is a very low probability for the generation of resistance to virus (not seen so far), because OVs often target multiple oncogenic pathways and induce cytotoxicity in different ways, (2) they are nonpathogenic, replicate, and destroy cancer cells, (3) virus dose in the tumor increases with time due to in situ virus amplification, which is opposite to classical drug pharmacokinetics that decreases with time, and (4) OVs can be manipulated to include safety features such as drug and immune sensitivity allowing to control them [50]. Intratumoral delivery of the OVs can be a good strategy to minimize the sequestration of the virus in the spleen and liver as well as antiviral response [26].

Targeting oncogenes that control both tumor cells survival and proliferation and immunosuppressive microenvironment might also bring new hope in the treatment of HNRB. Twist1 and MYC might be suitable for that purpose. Since Twist1 expression is restricted to tumor cells, it represents a very interesting target. Efforts to develop specific drugs or inactivation system remain to be done, even some are promising [41].

In fact, the take home message would be to target the microenvironment rather than the tumor. Few killing of tumor cells, allowing release of specific TAA, could be sufficient to induce a massive antitumoral immune response when done in combination with reprogrammation of the immunosuppressive inflammatory microenvironment into an antitumoral inflammatory microenvironment. Many believe that combining different approaches will ultimately induce the broadest and most effective immune response to cure HNRB.

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