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Review Article

Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy

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ABSTRACT

Primary immunodeficiency disorders (PIDs) convey increased susceptibility to infections and sometimes to malignancies, particularly lymphomas. Such cancer development can be contributed by immune impairments resulting in weakened immunological surveillance against (pre)malignant cells and oncogenic viruses. Molecular defects in PID-patients are therefore being clarified, identifying new targets for innovative immunotherapy. Particularly pediatric cancers are being scrutinized, where over one-third of cancer-related deaths are accounted for by leukemia and lymphomas. Here we review how immunopathogenic mechanisms of several PIDs might associate with lymphoma development. We furthermore delineate existing immunotherapy strategies in adults for potential therapeutic application in childhood leukemia and lymphomas.

Contents

1. Introduction

First proposed over 50 years ago, the tumor immunosurveillance hypothesis set forth the idea that components of the immune system, later recognized to be cytotoxic immune cells and natural IgM antibodies, can eliminate transformed cells at a very early stage [1,2]. In immunocompetent individuals such immunosurveillance should provide a substantial fitness barrier for neoplastic cells to gain a foothold and develop into disease. However, in immunocompromised individuals it is likely that tumor immunosurveillance would be impaired, resulting in increased risk of developing all types of malignancies.

Already in 1973, an international registry-based study of renal-transplant recipients revealed that organ transplantation accompanied with immunosuppression therapy is associated with a higher risk of developing cancer, primarily lymphoid in origin [3]. Also, HIV patients suffering from acquired immunodeficiency syndrome present an elevated

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incidence of various cancers, most notably including Epstein-Barr virus (EBV) induced lymphomas [4], providing further support that genetic defects that affect immune function may also predispose for cancer development.

The application of gene sequencing approaches in previously genetically undiagnosed PID-patients now makes immune pathway analysis possible [5–7]. Indeed, congenital primary immunodeficiency disorders (PIDs) have been reported as associated with increased risk of malignancy onset early in life [8–11]. Data from the international Immunodeficiency Cancer Registry shows that nearly 60% of all reported malignancies in PID are lymphomas, 85% of which non-Hodgkin lymphomas (NHLs) [8,11,12]. Here we set out to clarify how individual PID-disorders can contribute to the development of cancers of lymphoid origin. We highlight recent developments in immunotherapy for hematologic malignancies in adults for possible applications in pediatric PID-patients.

2. Impairment of immune surveillance as contributor to cancer development

Typically surfacing during early childhood, PIDs are monogenetic diseases that are characterized by dysfunction of one or more components of the immune system. Patients suffering from PIDs may present with abnormally high rates of infection, often with opportunistic pathogens, autoimmunity, or childhood cancer. With the establishment of PID registries worldwide, it has become increasingly clear that PIDs form a spectrum of disorders with more than 130 phenotypically distinct diseases and over 200 related genetic defects affecting various aspects of the immune system [13].

While impaired tumor immunosurveillance certainly contributes to the high rate of malignancies in PIDs, this alone does not suffice to explain this relationship. After all, highly immunogenic cancers such as melanoma and renal cell carcinoma, are only marginally more prevalent among PID-patients compared to otherwise healthy individuals [14]. Instead, cell-intrinsic processes appear particularly relevant in the connection between PIDs and malignancies [15]. A genetic defect that affects immune function can also directly add to oncogenesis. Perhaps the clearest example of this is the PID Ataxia–Telangiectasia in which the machinery for double-stranded DNA break repair is affected. This machinery is critical for 'variable diversity and joining' or V(D)J recombination of antigen receptors and thereby the development of functional B and T-cells but is also involved repair of DNA damage that could lead to cancer, thus independently predisposing toward cancer development as well as affecting immune function. Thus, aside from direct oncogenic effects of selected PID-proteins, the disturbed immune function of selected PID-protein variants can facilitate chronic inflammation or oncogenic virus infection, thereby generating conditions for cancer development.

2.1. Hematologic malignancies occur at increased incidence in PID-patients

The overall risk for cancer development in pediatric PID-patients is estimated to range from 4–25%, of which 60% of cases are lymphomas of B-cell origin with NHL being the greatest contributor [9,16]. These data are consistent with more recent data from analysis of the Australian and Dutch PID registries, demonstrating an 8 to 11-fold increased risk of NHL in all PID patients when compared with the general population [17,18]. We will discuss several PIDs of which data of larger cohorts of patients are known: common variable immunodeficiency (CVID), Wiskott–Aldrich syndrome (WAS), severe combined immunodeficiency (SCID), ataxia-telangiectasia (AT) and activated phosphoinositide 3-kinase δ syndrome (APDS). Of note, CVID forms the largest subcategory in which cancer was observed, due to the rarity of other PID disorders.

CVID patients have an overall increased lymphoma incidence, suggesting that B- and T-cell function and interplay contribute to immunological surveillance against lymphoma development [19]. The latter is further highlighted by data from the Danish and Swedish Immunodeficiency Register of patients with CVID and IgA deficiency [18]. This study demonstrated a significantly increased general cancer risk among patients with CVID, but not IgA deficiency, with a 12-fold increased risk of NHL in CVID patients. Among relatives of patients with CVID no increase in the risk of cancer was found, suggesting that the increased cancer incidence in patients with CVID is related to the immunodeficiency itself rather than other genetic traits shared by relatives.

WAS is an X-linked, combined immune-deficiency caused by mutations in the WAS protein, which is an important actin cytoskeleton regulator of hematopoietic cells [20], for example for the formation of immunological synapses between T-cells and NK-cells with antigen presenting cells (APCs) or target cells. A patient with WAS usually presents with thrombocytopenia from infancy, eczema and progressive immunodeficiency [20]. Up to 90% of cancers in patients with WAS consist of frequently EBV-positive lymphoma or leukemia [8,20]. Predisposition to these malignancies very likely involves both NK-cell and T-cell activation defects.

SCID is caused by different mutations in proteins involved in V(D)J recombination of antigen receptors during B and T-cell development, causing dysfunctional B and T-cells. Although SCID has been associated with malignancy, of which NHL is again the greatest contributor, these patients usually not survive beyond 1 year without treatment due to severe infections [9,21].

The Ataxia-Telangiectasia mutated (ATM) protein, mentioned briefly earlier, is a defective protein kinase in AT, that is involved in the detection and repair of double-stranded DNA breaks and activation of cell-cycle checkpoints [22]. Patients with AT have progressive neurological degeneration [23] and cellular and humoral immunodeficiency [24]. These patients have a high risk of developing lymphoid malignancies at a young age, of which NHL comprises 40% of all cases [9]. Two recent cohort studies from a French and a UK/Dutch PID registry with 240 and 296 AT patients respectively, showed cancer development in 22.1% (53/240), and 22.3% (66/296) of AT patients in these cohorts [9,25]. Of these patients, 70–80% were diagnosed with hematologic malignancies, most commonly NHL. The mean age at diagnosis was under 16 years in both studies. Although genetic instability overall is a consequence of a defective ATM protein, the high incidence of lymphoma and not other cancers at a young age is suggestive of a protective function of ATM kinase activity against the development of lymphomas.

A novel defined PID is APDS, an autosomal dominant condition caused by heterozygous gain-of-function mutations in the *PIK3CD* gene encoding the p110δ protein, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ) [26]. PI3K p110δ mutant patients show clinical and phenotypic overlap with many other PID syndromes; the majority was previously diagnosed with hyper-IgM syndrome or CVID [27]. The symptoms of patients with APDS are variable but they usually present with respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production. The mutant PI3K p110δ affects both T- and B-cells, resulting in dysfunctional $CD4^+$ and $CD8^+$ T cell activation and survival, as well as defective immunoglobulin class switch recombination [28]. A large international patient cohort study of 53 patients with genetically confirmed APDS showed that 13% (7/53) of the patients developed lymphoma between the age of 18 months and 27 years [29] but no other types of malignancy.

2.2. Epstein-Barr virus infection contributes to increased lymphoma incidences in PID-patients

The majority of cancers in patients with PID is of hematologic origin and is moreover associated with an infectious agent [14,30]. Infection with oncogenic viruses, such as the human papillomavirus (HPV), human T-cell lymphotropic virus and the Epstein-Barr virus (EBV) results in the transduction of copies of the viral genome into cellular

genes that can activate proto-oncogenes, inactivate tumor suppressor cells or stimulate growth factors. Especially EBV appears to be an important co-factor for the development of PID-associated lymphomas [11,31]. EBV infection causes polyclonal activation and proliferation of B-cells. Immunity against this virus is primarily carried out by $CD8^+$ cytotoxic T-cells and to a lesser degree by other immune mechanisms such as humoral responses or natural killer cell activity [31]. Thus, PIDs with T-cell dysfunction are expected to be particularly susceptible to EBV-related lymphomas.

In accordance to this, a rare subset of pediatric patients with CD27 deficiency, a tumor necrosis factor (TNF) receptor superfamily member involved in T-cell function, suffer from persistent EBV viremia, hypogammaglobulinemia and EBV-driven B-cell lymphoproliferative disorders including the development of EBV positive malignant lymphoma [32,33]. Studies in murine and human immune cells have shown that CD27 interaction with its ligand CD70 on activated B and T-cells, plays an important role in T-cell expansion and survival, germinal center formation, B-cell activation and NK-cell function [34]. In addition to this, five patients with CD70 deficiency were described that share this clinical phenotype including the development of EBV-associated Hodgkin's lymphoma (HL) [35,36].Interleukin-2-inducible T-cell kinase (ITK) deficiency is another novel defined PID in which T-cell function is deficient, and in which association with massive EBV-driven B-cell lymphoproliferation in pediatric patients was described [37]. ITK is an intracellular tyrosine kinase expressed in T-cells which, upon activation, triggers signaling towards cytokine production and T-cell proliferation. In a cohort of nine pediatric patients with ITK-deficiency 56% (5/9) developed Hodgkin lymphoma (HL) or other B-cell lymphomas before the age of 10 years. More recently, homozygous mutations in *RASGRP1* were reported in four patients with combined immunodeficiency associated with persistent EBV infection including the development of EBV-driven HL at a very young age [38–40]. The *RASGRP1* gene codes for a diacylglycerol (DAG)-regulated guanidine exchange factor (GEF), which is expressed in T- and NK-cells and is essential for T-cell proliferation after encountering EBV [40].

Although not hematological of origin, a few cases of pediatric patients with PID were reported to develop Kaposi Sarcoma (KS), an inflammatory neoplasm affecting cells of endothelial origin. The human herpesvirus 8 (HHV-8) is the causal infectious agent to all known forms of KS. HIV co-infection and immunosuppression are strong predisposing factors for KS development (also known as epidemic or iatrogenic KS), while classic KS in childhood is rare. The observation that most children with isolated, classic KS are born to consanguineous parents suggested that single-gene inborn errors of immunity might cause such cases. Thus far, four unrelated children with inherited PID and classic KS were described. A 10-year-old Turkish child with autosomal recessive complete interferon (IFN)-γ receptor-1 (IFN-γR1) deficiency presented with KS and complete $CD4^+$ lymphopenia [41] and a Tunisian child with WAS who developed KS before the age of two [42]. More recently, two genetic etiologies of classic KS in childhood were discovered: STIM1 deficiency and OX40 deficiency, which are both involved in T cell function [43]. A 2-year old female born to Turkish consanguineous parents was diagnosed with aggressive KS and died 4 months after initial presentation. Although T-cell count was normal, she harbored a homozygous splice-site mutation in *STIM1* encoding stromal interaction molecule 1, causing functional T-cell immunodeficiency [44]. OX40 (also known as TNFRSF4 or CD134) is a member of the TNF receptor superfamily and functions as a co-stimulatory molecule expressed on activated T-cells. Its ligand OX40L is expressed on endothelial cells. A case report of classic KS in a 14-year old female born to Turkish consanguineous parents showed a causal relationship between complete OX40 deficiency and KS development in this patient [44].

Taken together, these studies highlight that defective T-cell mediated immune surveillance, allowing for viral transformations to occur and persist, is an important contributor to the development of lymphoid malignancies in children. However, specific genetic defects such as faulty DNA repair and impaired NK-cell mediated cytotoxicity can contribute to lymphomagenesis. Further genetic profiling of pediatric tumors is needed to establish whether oncogenic viruses or underlying genetic causes exist to explain the increased incidence of cancer in PIDs. Pediatric patients with lymphoma may carry mutations in PID genes related to B and T-cell activation [45]. Assessment of their function within the immune surveillance could provide new targets for immunotherapy.

2.3. Promising immunotherapy strategies for pediatric hematological malignancies

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is an effective approach to cure refractory or recurrent hematological malignancies, in which donor T-cells contribute most anti-tumor reactivity, also known as graft-versus-leukemia (GVL) effect [46]. Here, immune-mediated responses can eradicate chemotherapy-resistant cancer cells, highlighting the great potential of exploiting the immune system in cancer therapy. With the additional discovery that humanized murine antibodies could induce remissions in B-cell lymphoma, two pillars of immunotherapy in hematological malignancies, i.e. enhancing effector T-cell reactivity and direct targeting tumor surface antigens with antibodies, were raised [47]. We will next discuss these two main immunotherapy pillars in detail, starting with antibody and next T-cell based immunotherapy approaches.

2.4. Antibody immunotherapy in hematological malignancies

Various antibody-based therapies now have demonstrated significant impact in the treatment of hematological malignancies. Monoclonal antibody (mAb) technology allows the targeting of unique epitopes on the surface of tumor cells and immune cells. Upon binding of these cell surface epitopes, mAbs may facilitate anti-tumor effects through direct or indirect mechanisms of action (Fig. 1). Engagement of mAbs with their targets on the tumor cell surface may directly kill cells, i.e. by inhibiting proliferation signals, by inducing apoptosis or by delivering conjugated toxins to the tumor cell [48]. Alternatively, antibody binding marks tumor cells as targets for immune-mediated killing. Such opsonized cells are eliminated through phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), or complement-dependent cytotoxicity (CDC) [48].

The chimeric anti-CD20 mAb rituximab was the first antibody therapy that was approved for the treatment of lymphoma with great success in adult NHL, acute lymphoid leukemia (ALL) and chronic lymphoid leukemia (CLL) of B-cell origin [49]. Rituximab eliminates B-cell lymphomas through direct signaling effects as well as ADCC and CDC, and is typically used in combination with chemotherapy-based treatment.

Several studies and case reports have demonstrated that rituximab in combination with chemotherapy can also be effective in the treatment of B-cell lymphomas in pediatric patients [50,51]. For example, in a phase II pilot study, rituximab combined with ifosfamide, carboplatin, and etoposide in pediatric patients (aged 5–20 years) with relapsed/refractory B-cell NHL achieved a complete remission or partial response in 12/20 (60%) patients [52]. An ongoing trial in young patients (aged 3–31 years) investigates whether reducing cytotoxic regimens and adding rituximab is safe and effective in patients with intermediate risk *de novo* $CD20^+$ B-NHL or B-ALL (NCT01859819; Table 1).

Next-generation anti-CD20 antibodies ofatumumab and obinutuzumab now aim to increase efficacy and, more importantly, to overcome resistance against anti-CD20 antibody treatment. Ofatumumab is a fully human mAb targeting an alternative epitope of CD20 that shows higher rates of CDC and lower resistance in tumor cells compared to rituximab and is now FDA approved as an additional treatment in adult refractory CLL [53,54]. Obinutuzumab is a humanized

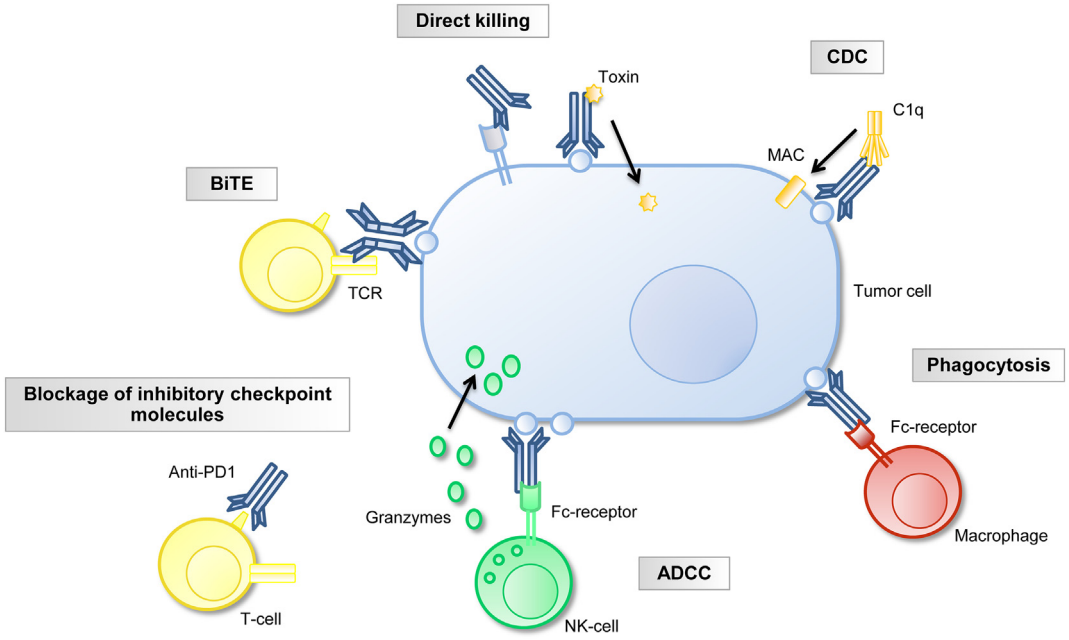

Fig. 1. Mechanisms of action in monoclonal antibody immunotherapy. Induction of direct tumor cell killing by mAbs follows after binding of tumor cell surface receptors, such as growth factor receptors or death ligand receptors, through which the downstream signaling is altered and apoptosis ensues. Conjugated antibodies can also induce direct tumor cell killing by delivering drugs or toxins into the cells while limiting systemic exposure. | mAbs can also activate effector cells that have Fc receptors, such as NK-cells or macrophages. Activated macrophages can kill tumor cells by initiation of phagocytosis, while activated NK-cells are very potent tumor killers by a process known as antibody-dependent cellular cytotoxicity (ADCC). Additionally, mAbs can also initiate complement-dependent cytotoxicity (CDC). | Bispecific mAbs (BiTE) bind simultaneously to the tumor surface and to an activating receptor of effector cells, such as T-cells. Activated effector cells can subsequently execute their anti-tumor responses. | mAbs that bind inhibitory checkpoints in T-cells, such as CTLA4 or PD1, results in amplification of anti-tumor responses carried out by these effector cells. | Abbreviations: BiTE, bi-specific T-cell engagers; CTLA4, cytotoxic T-lymphocyte-associated protein 4; mAb, monoclonal antibody; MAC, membrane attack complex; MHC, major histocompatibility complex; NK, natural killer; PD1, programmed cell-death 1.

mAb that differs from rituximab in glycosylation to enhance Fc receptor affinity, resulting in enhanced ADCC by effector cells [55]. After showing its clinical superiority over rituximab in adult patients with *de novo* CLL [56], obinutuzumab is now FDA approved as an additional treatment in this setting [57]. The safety and effectiveness of administration of obinutuzumab in combination with chemotherapy are currently being investigated. One of these trials recruits young patients (aged 3–31 years) with relapsed CD20$^+$ B-NHL and should provide insight in the application of obinutuzumab in pediatric lymphoma (NCT02393157).

Given the success of anti-CD20 antibodies, other targets are being explored for mAb immunotherapy. Only a limited number of these targets and complementary mAb are being studied in pediatric cancer. One of these targets is CD22, which is widely expressed on mature and malignant B-cells. The anti-CD22 humanized mAb Epratuzumab is, in combination with chemotherapy, effective in pediatric patients with relapsed B-ALL [58]. Complete responses were seen in 65% of patients and toxicity profiles were similar to those observed with chemotherapy alone.

2.4.1. Conjugated antibodies

Brentuximab vedotin (Bv) is a conjugated anti-CD30 mAb containing the toxin microtubule stabilizer monomethyl auristatin E (MMAE). CD30 is expressed on subpopulations of activated T- and B-cells but also on the surface of anaplastic large cell lymphoma (ALCL) cells and HL Reed-Sternberg cells, making CD30 an ideal target for directed therapies against ALCL and HL. Binding of Bv to CD30 leads to internalization of the toxin-conjugated antibody into the cell and release of the toxin. MMAE in turn causes cell cycle arrest and apoptosis [59]. It was FDA-approved for the treatment of refractory HL and systemic anaplastic large cell lymphoma in adults in 2011. The Children's Oncology Group (COG) now investigates Bv in combination with chemotherapy in young patients (aged 2–18 years) with *de novo* HL (NCT02166463).

2.4.2. Bispecific antibodies

Newly engineered, bispecific monoclonal antibodies are artificial proteins that can bind simultaneously to the tumor surface and to an activating receptor of effector cells using two distinct epitopes [60]. Through this means bispecific antibodies directly recruit effector cells to the tumor cell and activate them to induce anti-tumor responses [61]. Bi-specific T-cell engaging (BiTE) Abs link a tumor-targeting domain to an activating domain of a receptor of effector T-cells. As a consequence, BiTE antibodies promote the recruitment and activation of a polyclonal T lymphocyte population in close proximity to cancer cells, avoiding both the need for antigen specificity and putative tumor immune evasion through HLA downregulation [62].

Table 1
Ongoing clinical trials of mAb therapy in pediatric hematological and lymphoid malignancies.

Tumor	Intervention	Status	Age	Phase	ID number
de novo CD20$^+$ B-NHL *de novo* CD20$^+$ B-ALL	Lower dose FAB chemotherapy + rituximab (anti-CD20)	Recruiting	3–31	Phase 2	NCT01859819
R/R CD20$^+$ B-NHL	ICE chemotherapy + Obinutuzumab (anti-CD20)	Recruiting	3–31	Phase 2	NCT02393157
de novo HL	Chemotherapy + brentuximab vedotin (anti-CD30-MMAE)	Recruiting	2–18	Phase 3	NCT02166463
R/R solid tumors (including HL and NHL)	Ipilimumab + nivolumab	Recruiting	1–30	Phase 1/2	NCT02304458
R/R solid tumors (including HL and NHL)	Pembrolizumab	Recruiting	0–18	Phase 1/2	NCT02332668

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoid leukemia; FAB, 5-fluorouracil, adriamycin, and BCNU; ICE, ifosfamide, carboplatin, and etoposide; HL, Hodgkin lymphoma; MMAE, microtubule stabilizer monomethyl aurastin E; NHL, non-Hodgkin lymphoma; R/R, recurrent/refractory.

One such BiTE antibody is Blinatumomab; a CD19/CD3 BiTE antibody that targets B lymphoma cells. Safety and efficacy of blinatumomab were shown in a small study involving post-transplant relapsed pediatric patients (aged 4–19 years) with B-ALL in which 67% showed remission [63]. However, three patients experienced cytokine release syndrome (CRS), resulting from excessive T-cell activation. In severe cases, CRS can be fatal and management of CRS should be an important component of T-cell stimulating therapies. Additional treatment with tocilizumab (anti-interleukin 6) can ameliorate symptoms in patients experiencing CRS [64].

2.4.3. Inhibitory checkpoint antibodies

Instead of targeting tumor cells directly, antibody binding to immune cells can also potentiate anti-tumor responses [65]. Negative immune regulators, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell-death 1 (PD1) are highly expressed on activated immune cells and transmit inhibitory signals to downmodulate T-cell activity. In physiological circumstances, these checkpoint inhibitors reduce autoimmunity and support self-tolerance [66]. However, tumor cells hijack this mechanism to evade anti-tumor responses of T-cells [67].

Interference with immune checkpoint pathways by mAbs allows the reestablishment of anti-tumor responses and induces tumor regression [65]. Ipilimumab (anti-CTLA4), nivolumab (anti-PD1), pembrozilumab (anti-PD1) have already been approved as first-line or second-line treatments for melanoma and non-small cell lung cancer [68–70]. Antibodies that block the natural ligands of PD1, i.e. PD-L1 and PD-L2, are also being scrutinized [71].

Safety and effectiveness of ipilimumab as a single therapeutic agent was investigated in pediatric patients (aged 2–21 years) with recurrent or progressive solid tumors (i.e. melanoma, sarcoma, renal/bladder carcinoma and neuroblastoma). While immune-related toxicities were comparable with those described in adults, no tumor regression was observed [72]. Ongoing trials are investigating combinational therapy with ipilimumab with nivolumab and pembrolizumab (anti-PD1) in pediatric patients (aged 1–30 years and 0–18 years respectively) with relapsed or refractory solid tumors also including HL and NHL (NCT02304458 and NCT02332668). Nivolumab in pediatric HL patients was granted breakthrough therapy designation in 2016.

2.5. Novel mechanisms in immunotherapy

Several therapeutic strategies were developed during the last decade especially to enhance T-cell anti-tumor responses towards an expansion of the cellular anti-cancer immune cell arsenal. Strategies that made it to the arena of pediatric hematological malignancies include the already discussed blocking of immune inhibitory checkpoints with mAb and adoptive cell therapy (Fig. 2), including the transfer of tumor-antigen specific T-cells and, more recently, chimeric antigen receptor (CAR) T-cells.

The priming of T-cells to become effector cells requires the cognate interaction of the antigen-specific T-cell receptor (TCR) with antigen-loaded MHC displayed at the surface of antigen-presenting cells (APCs). Besides this initial binding event, co-stimulation is essential to fully activate T-cells. This 'signal two' is usually provided through binding of the co-stimulatory receptor CD28 on the T-cell surface with CD80/CD86 on the APC [73]. Upon activation, inhibitory receptor CTLA4 are shuttled to the surface where it can outcompete CD28 for its ligands, thereby downregulating activation and downstream signaling [74]. Other receptors on the T-cell surface such as CD2 and SLAM receptors may provide additional co-stimulatory input [75].

Adequate priming leads to active tumor-specific $CD8^+$ cytotoxic T-cells that recognize and eliminate tumor cells through cognate interaction of their TCR and MHC loaded with tumor-associated antigens (TAAs) on tumor cells [76,77]. However, downregulation of MHC on tumor cells allows tumor cells to prevent presentation of TAAs and, therefore, enables escape from tumor-specific $CD8^+$ cytotoxic T-cells [78].

The oldest adoptive T-cell therapy in hematological malignancies is allo-HSCT in which, after a rigorous conditioning regime, donor

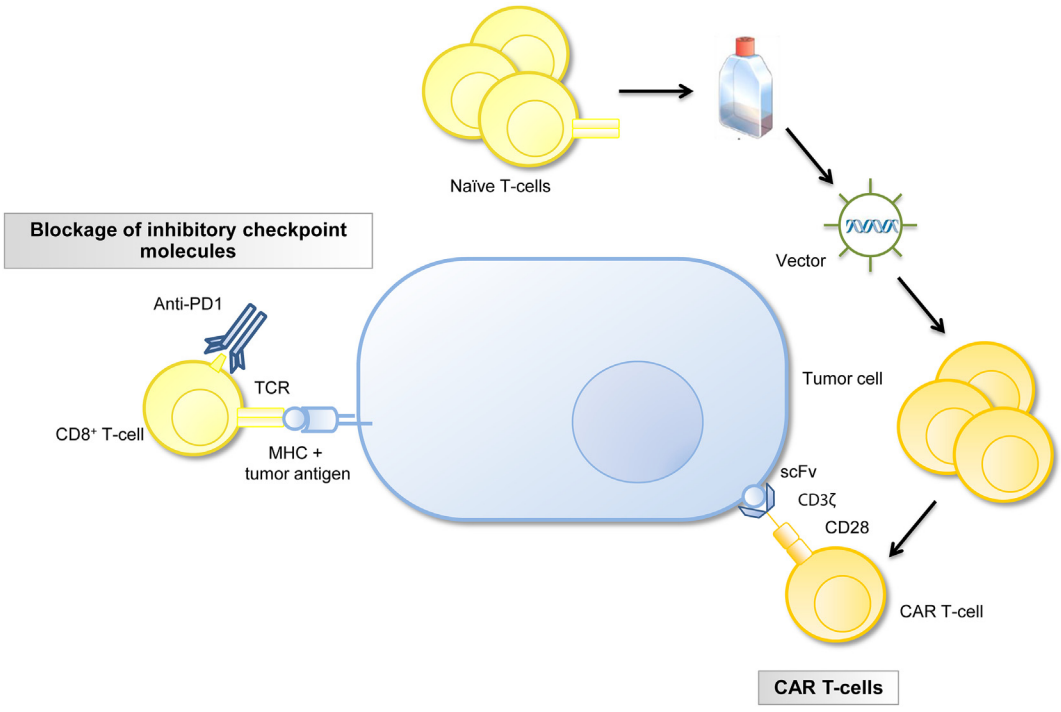

Fig. 2. Novel mechanisms in immunotherapy. Blockage of inhibitory checkpoint molecules in T-cells by mAbs, such as CTLA-4 or PD-1, results in amplification of anti-tumor responses carried out by these effector cells. | Adoptive cell therapy (ACT) extracts T-cells from the patient and to genetically engineer them to express tumor-reactive chimeric antigen receptors (CARs). | Abbreviations: CAR, chimeric antigen receptor; MHC, major histocompatibility complex; PD-1, programmed cell-death 1; scFv, single-chain variable fragment; TCR, T-cell receptor.

hematopoietic stem cells, often still including T-cells, are infused into the patient. Accordingly, transferred donor cells attack and kill remaining leukemic cells that have survived the earlier conditioning phase through elicitation of a GVL (Graft-Versus-Leukemia-effect). However, this method is far from selective towards tumor cells and risks potentially fatal Graft-versus-Host-Disease (GvHD) [79].

Emerging, safer methods of adoptive cell therapy (ACT) involve the reinfusion of *in vitro* expanded autologous tumor-reactive T-cells into the patient to generate a robust and specific anti-tumor response by effector T-cells without risking GvHD. Initially, these methods depended on ex vivo expansion and reinfusion of donor tumor-specific T-cell clones, which was highly time-consuming and not usually successful. Alternatively, ex vivo TAA-loaded autologous dendritic cells can be introduced to induce the expansion of anti-TAA specific autologous T-cells in vivo, however such studies in pediatric hematological malignancies are still limited in scope [80–82].

In recent years, advances in safe methods of genetic engineering have allowed the development of new interventions in which tumor-reactive T-cells are deliberately created. This is accomplished through the introduction of tumor-reactive chimeric antigen receptors (CARs) into T-cells [83]. CARs are non-native receptors that consist of a single-chain variable fragment (scFv) imitative from the variable heavy and variable light chain of an antibody fused with a transmembrane domain and the CD3ζ chain (i.e. the signaling domain of TCR) (Fig. 3). This design enables highly specific targeting of antigens in an MHC-independent fashion, which is favorable considering the frequent downregulation of MHC in tumor cells [78].

Such CAR T-cells however, known as first-generation CARs, only provide tumor antigen recognition and usually result in anergy upon repeated T-cell stimulation [84] likely due to an absence of co-stimulatory signals. Second-generation CARs contain additional co-stimulatory domains, such as CD28, to provide 'signal two' and to increase *in vivo* longevity [83]. Meanwhile, third- and fourth-generation CARs are developed and in clinical trials for various tumors. These novel CARs contain multiple co-stimulatory domains such as 4-1BB (also known as CD137 or TNFRSF9) and OX40 [85].

To overcome immune escape by tumor cells, CAR T-cells are designed to carry additional receptors for supplementary features. These include co-expressing anti-tumor cytokines (TRUCK CAR T-cells), carrying a controllable suicide gene as safety switch (self-destruct CAR T-cells) or lacking the expression of immune checkpoint inhibitors to allow resistance to such immunosuppression by tumors (armored CAR T-cells) [86,87].

First clinical results in pediatric hematological and lymphoid malignancies with CAR therapy came from a study from the Children's Hospital of Philadelphia, in which 25 out of 30 patients were young patients (aged 5–22 years) with refractory or recurrent $CD19^+$ B-ALL (and one $CD19^+$ T-ALL). CD19-CAR therapy (second generation) mediated complete remissions for 24 months in 27/30 (90%) of patients [88]. All patients developed CRS and in 8/30 (27%) of patients, the severity required additional treatment with tocilizumab (anti-interleukin 6). Next, a phase I trial studied the safety and effectiveness of a preparative regimen including cyclophosphamide and fludarabine regimen, followed by a second generation CD19-CAR therapy [89]. The enrolled patients were children (aged 1–30 years) with refractory or recurrent ALL or NHL. This study reported complete response rates in 14/21 (66.7%) patients. All toxicities were reversible, including severe CRS with tocilizumab. Currently, the potential of CAR therapy is being explored by targeting other receptors than CD19, using different transduction methods for CAR expression and designing the receptors with beneficial features for optimal anti-tumor responses. Several clinical studies are open and enrolling pediatric patients with B-cell malignancies (Table 2).

2.6. Virus-targeted antigen-specific lymphoma therapies

The expression of viral antigens by lymphoma cells provides a handle for selective targeting and eliminating these cells. Considering the high proportion of lymphomas in PID that are virus-associated, immunotherapies that target viral antigens are explored for the treatment of PID-related lymphomas.

EBV-antigen specific T-cells were first employed in the mid-1990s to successfully treat EBV-associated post-transplant lymphoproliferative disease (PTLD) [90]. Based on allogeneic donor T-cell transplantation, the first generation of this therapy was unfortunately accompanied by GvHD. This complication was eliminated in later generations of EBV-specific adoptive T-cell therapy, in which antigen-specific allogenous T-cells were *ex vivo* expanded prior to infusion into the patient [91–93]. More recently, EBV-specific CD19-CAR T-cells [94] were developed. Also, the *in vivo* stimulation of transferred EBV-specific T-cells by vaccination has yielded encouraging results with respect to their persistence *in vivo* [95].

The success of EBV-specific T-cells in part originates from the antigens towards which they are directed. In PTLD, the absence of adequate immune surveillance, due to the HSCT conditioning regime, leads to viral re-activation and the development of type III latency tumors [96].

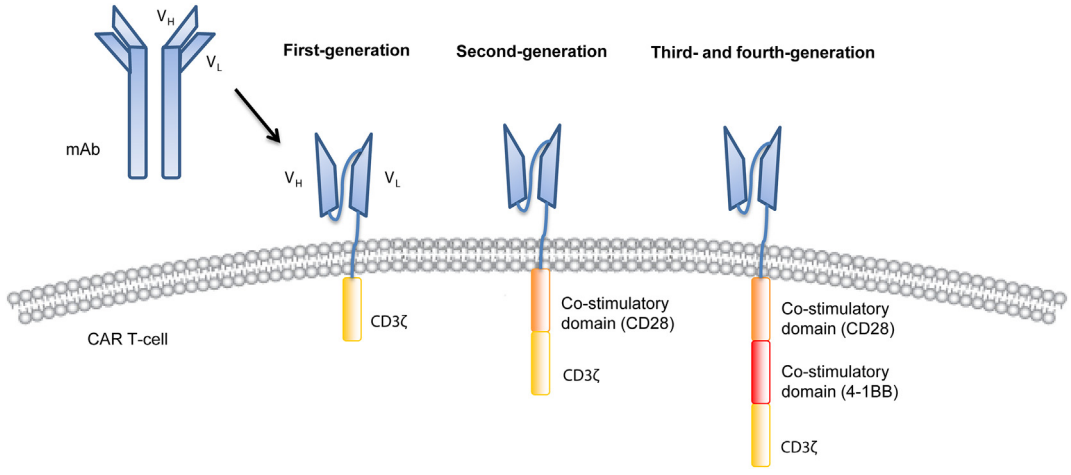

Fig. 3. CAR T-cells. Chimeric antigen receptors (CARs) are non-native receptors that are designed to target surface molecules on tumor cells in an MHC-independent manner. | First generation CARs consist of an extracellular domain that contains a single-chain variable fragment (scFv) mimicking the variable heavy (VH) and variable light chain (VL) of a monoclonal antibody. This is fused with an intracellular domain that contains the signaling domain of the T-cell receptor (TCR), the CD3ζ chain. | Second-generation CARs also have a co-stimulatory molecule build in, such as CD28. | Third- and fourth-generation CARs contain two or more co-stimulatory molecules or are genetically engineered to have additional features (such as cytokine expression) to evoke optimal anti-tumor responses. 4-1BB is also known as CD137 or TNFRSF9 | Abbreviations: CAR, chimeric antigen receptor; mAb, monoclonal antibody; VH, variable heavy; VL, variable light.

Table 2
Ongoing clinical trials of CAR T-cells in pediatric hematological and lymphoid malignancies.

Tumor	Intervention	Status	Age	Phase	ID number
Refractory B-cell lymphoma Refractory B-cell leukemia	Chemotherapy + CD19-CAR	Ongoing, not recruiting	1–30	Phase 1	NCT01593696
R/R B-cell lymphoma R/R B-Cell leukemia	Chemotherapy + CD19-CAR	Ongoing,not recruiting	1–24	Phase 1/2	NCT01626495
R/R B-ALL	CD19-CAR + EGFRt	Recruiting	1–26	Phase 1/2	NCT02028455
R/R B-ALL	Chemotherapy + CD19-CAR	Ongoing, not recruiting	0–26	Phase 1	NCT01860937
R/R B-ALL	Chemotherapy + CD19-CAR	Recruiting	2–21	Phase 1/2	NCT02625480
R/R B-cell lymphoma R/R B-ALL	Chemotherapy + CD22-CAR	Recruiting	1–30	Phase 1	NCT02315612
R/R B-Cell leukemia	Chemotherapy + CD22-CAR + EGFRt	Recruiting	1–26	Phase 1	NCT03244306
R/R B-ALL	CD19-CAR prior to planned allo-HSCT	Recruiting	0–17	Phase 1	NCT02808442

Abbreviations: ALL, acute lymphoid leukemia; CAR, chimeric antigen receptor; EGFRt, truncated epidermal growth factor receptor; R/R, recurrent/refractory.

These malignancies are hallmarked by the expression of an array of EBV-antigens including highly immunogenic EBV nuclear antigen (EBNA) 3 proteins, which induce strong T-cell responses and are thus well suited as antigens for antigen-specific cell therapy [96]. In contrast, most EBV-associated Hodgkin and Non-Hodgkin lymphomas, at least in immunocompetent individuals as well as ITK-deficient patients, are type II latency malignancies [97,98] which only express antigens with a much lower immunogenicity, such as EBNA1, latent membrane protein 1 (LMP1), and LMP2, and are thus much more difficult to target. However, antigen-presenting cells that express LMP1 and/or LMP2 are capable of expanding antigen-specific T-cells *ex vivo* [99]. Several studies with expanded autologous LMP-cytotoxic lymphocytes (CTL) have been performed [99–102]: In multiple-relapse EBV-associated lymphoma patients, including several pediatric patients, this treatment resulted in a clinical effect in 61.9% (13/21) (of cases, of which 52.4% achieved complete remission [101]. Used as adjuvant therapy, 82% of mixed lymphoma patients [101] and 90% of NK/T-cell lymphoma patients [102] remained in remission for at least 2 and 4 years respectively. However, transfer of CD137-selected LMP2a T-cells only resulted in an objective response and partial remission in 3/8 patients [100]. Most recently, LMP1/2 specific T-cells that were made TGF-beta resistant through forced expression of a dominant negative receptor variant, gave encouraging results in the treatment of relapsed HL [103]. Numerous ongoing clinical trials that include children are investigating LMP1/2-specific T-cells as a therapy for EBV-related lymphomas (Table 3).

2.7. Prospects

Advances in the understanding of cancer biology and the genomic sequencing of tumors have paved the way towards an impressive array of immunotherapies for adult cancers. Immunotherapies successful in adults must therefore now also be tested in clinical trials in pediatric patients [104]. Amendment of current treatment protocols with new immunotherapies, therefore, might improve clinical outcomes of pediatric cancer patients and ensure a reduction in dose intensity of toxic drugs. Although limited data is available in pediatric patients, based on reported preliminary results immunotherapy approaches incorporating mAbs or CAR T-cells hold promise. Simultaneously, the genetic tumor landscapes are being clarified and experimentally related to the development and behavior of pediatric hematologic malignancies [105–107]. In this regard, the relationship between the genetic gaps in the immune repertoire in PIDs and the development of pediatric lymphoma remains to be clarified. EBV, however, is a risk factor that can originate or contribute to the development of lymphoma in these patients [108,109] and should be investigated further.

Some challenges remain to ensure the continued progress in this field. Emerging evidence strongly suggests that the efficacy and clinical benefit of inhibitory checkpoint immunotherapy are based on the high mutational load and subsequent immunogenic neo-antigens presented by tumor cells, which is not a trait of most pediatric cancers [110,111]. And although hematological and lymphoid malignancies occur both in children and adults, the spectrum of mutations in children is very distinctive from those observed in adults [110,112]. Meanwhile, immunotherapies are usually implemented in pediatric patients when shown safe and effective in adults, without knowing whether the targeted antigens are highly expressed in pediatric tumors. Thus, translation of immunotherapies into pediatric cancers also needs novel and more specific immunotherapy targets for pediatric malignancies [104].

The selection of immune targets or therapeutics for testing in future clinical trials remains imperative, especially considering the relatively small number of pediatric patients with recurrent/refractory leukemia or lymphoma. Furthermore, future clinical trials should include management of novel toxicities related to these immunotherapies including off-target toxicity and uncontrolled T-cell activity resulting in CRS. Approaches embracing incorporation of suicide domains into CAR T-cells (self-destruct CAR T-cells) and the treatability of CRS with tocilizumab are promising developments for the near future. Additionally, it is also important to determine how and when we can incorporate these immunotherapies in established regimens. It is likely that in the first place immunotherapy will be used in combinational strategies with chemotherapy, to stimulate immunogenicity [113–115]. Although current trials tend to focus on one intervention, it is also more likely that combination of different strategies, i.e. simultaneously exploiting mAbs and cellular immunotherapy or simultaneously targeting tumor antigens and immune inhibitory checkpoints, will show additive effects. To this end, clinical trials investigating combinatorial regimens are in development.

As many lymphomas in PID seem to be virus-associated, antigen-specific T-cells that target viral antigens will prove a valuable addition to the treatment of these diseases. For EBV, both latency type II and

Table 3
Ongoing clinical trials of LMP1/2-specific T-cells in EBV-related lymphomas.

Tumor	Intervention	Status	Age	Phase	ID number
EBV-positive lymphoma	TGF-b resistant LMP1/2-specific CTLs	Ongoing, not recruiting	All	Phase 1	NCT00368082
EBV-positive lymphoma	LMP, BARF1 & EBNA1 specific CTLs	Recruiting	All	Phase 1	NCT01555892
EBV-positive lymphoma	Chemotherapy + LMP, BARF1 & EBNA1 specific CTLs	Recruiting	All	Phase 1	NCT02287311
EBV-positive lymphoma	LMP1/2-specific CTLs	Recruiting	All	Phase 1	NCT01956084
EBV-positive lymphoma	LMP1/2-specific CTLs	Ongoing, not recruiting	All	Phase 1	NCT00062868
EBV-positive lymphoma	HLA matched LMP1/2-specific CTLs	Ongoing, not recruiting	All	Phase 1	NCT01447056
EBV-positive $CD20^+$ PTLD	Rituximab + LMP1/2-specific CTLs	Ongoing, not recruiting	1–29	Phase 2	NCT02900976

Abbreviations: BARF1, EBV BamHI-A rightward frame 1; CTLs, cytotoxic T-lymphocytes; EBNA1, Epstein–Barr nuclear antigen 1; EBV, Epstein–Barr virus; HLA, human leukocyte antigen; LMP, latent membrane protein; PTLD, post-transplant lymphoproliferative disease; TGF-b, tumor growth factor beta.

latency type III malignancies occur in PID ([31,98]). We propose that the careful characterization of the EBV latency stage will be instrumental for generation of an immunotherapy for such virus-associated lymphomas.

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