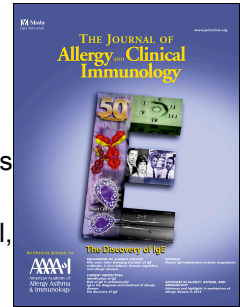


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**INTRINSIC AND EXTRINSIC CAUSES OF MALIGNANCIES IN PRIMARY IMMUNODEFICIENCY
DISORDERS**

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Summary

Malignancies occur with a higher incidence rate and manifest earlier in life in patients with primary immunodeficiency disorders (PID) than in the general population. However, no universal mechanism of malignancy predisposition in PID can be determined. Despite the strong support for the physiological role of tumor immunosurveillance and increasing success of strategies in immunological tumor therapy, which include checkpoint inhibition, monoclonal antibodies, and engineered T cell antigen receptors, the incidence and pattern of malignancies in PID do not reflect an increased tumor immune escape *per se*. In contrast, malignancies appear to be restricted to either *i)* tissue types bearing the same molecular defect that underlies the PID such as syndromes of DNA repair deficiency or immune cell-specific maturation or functional defects that suggest a cell-*intrinsic* oncogenic basis, or *ii)* other tissues when they are infected by transforming viruses or chronically inflamed, pointing towards *extrinsic* causes for transformation that are potentially facilitated by but not predominantly owed to a lack of immunosurveillance. Based on recent studies of preexisting conditions in malignancy patients and on malignancies in large PID cohorts, we conclude that a large part of tumor predisposition in PID is derived from the same molecular defect as the immunodeficiency itself. The presented concept elucidates diverse pathomechanisms and risks of malignancies in PID in the light of current tumor immune therapies.

Key Messages

Malignancies occur in patients with primary immunodeficiencies due to:

- cell-intrinsic molecular pathomechanisms (*i.e.* tumor predisposition *in parallel* to the immunological defect) or
- extrinsic factors (following chronic infections, inflammation, and/or loss of immunosurveillance).

Introduction

Malignancies occur more frequently and earlier in life in patients with primary immunodeficiencies (PID) than in the general population and comprise B or T cell lymphoma, Hodgkin's disease, (myelodysplastic syndrome-related) leukemia, carcinoma, and rarely melanoma, medulloblastoma, neuroblastoma, or other tumors^{1, 2}. The recognized tumor immunosurveillance theory proposed by *Burnet and Thomas*^{3, 4} (reviewed in⁵) has been controversially discussed but was rehabilitated as one of the *emerging hallmarks of cancer* early in this millennium⁶. With the increasing availability of technical tools to establish a molecular diagnosis in patients with PID and/or malignancy, one might expect that it would be possible to gain more detailed insight into the pathophysiology of tumor surveillance in the context of inborn errors of the immune system. The occurrence of malignancy is considered to be a hallmark of primary and secondary immunodeficiencies² and is listed as a PID-associated feature (e.g., in the PID classification of the *International Union of Immunological Societies*⁷). Additionally, malignancies are described as diagnostic criteria in the database of the *European Society for Immunodeficiencies* (ESID)⁸ and in a prospective study of profound combined immunodeficiencies (PCID)⁹. Nevertheless, the proportion of PID patients among patients with cancer are surprisingly small and the subgroups of PIDs that are predominantly involved are few.

An array of mostly indirect pieces of evidence has been collected that corroborates the physiological role of immunosurveillance *in vivo* (recently reviewed by A. Corthay¹⁰), such as the incidence of malignancy in secondary immunodeficiency disorders that include pharmacological immunosuppression in transplant recipients or acquired immunodeficiency syndrome, immune reactions against tumor cells and tumor immune evasion mechanisms, and, last but not least, the clinical success of checkpoint inhibition via CTLA4 and PD1 blockade¹⁰. However, it remains unclear as to why malignancies like melanoma and renal cell carcinoma, which have historically been considered and used as proof of immunotherapy principles, are not found more frequently in patients with PID than in members of the immunocompetent population. Furthermore, the spectrum of malignancies in PID appears to be restricted to a few oncological entities. With rare exceptions, these are predominantly of either hematological origin and are linked to the cell type harboring the underlying immunodeficiency, of hematological or epithelial origin in DNA repair deficiencies, or can be

85 explained by the co-occurrence of chronic inflammation or infection with oncogenic viruses¹,
86 ².

87 To clarify the picture of the factual association of malignancies with PID, a synopsis of
88 mechanisms potentially involved in tumor predisposition in patients with PID is provided in
89 this article, and most recent descriptive studies are interpreted from both the oncological
90 and the immunodeficiency view focusing on the correlation of malignancies with PID.

The immunological and biological perspective: Categories of PID-associated tumor predisposition

Malignancies that occur in PID may arise from six categories of causes that can additionally be divided into primary or *intrinsic* and secondary or *extrinsic* groups (Figure 1 I.1-3 and E.1-3, respectively, panels 1-7; and Table 1). These tumor-predisposing factors are not mutually exclusive, but may add to or even depend on each other. We propose that *intrinsic* factors play a predominant role in the PID in which the malignant transformation occurs either in the same cell type that has been primarily affected by the immunodeficiency or in another cell type but on an identical molecular basis. Such categories of PID with *intrinsic* tumor predisposition are: *I.1*, Stem cell, myeloid, and lymphoid development, differentiation and apoptosis defects; *I.2*, Lymphocyte (co-)signaling, cytoskeleton, cytotoxicity, and metabolism defects; and *I.3*, Defects in chromosome stability, telomere maintenance and DNA repair (Table 1, left column; Figure 1, panels 1-4). For example, impairments in the repair of DNA double-strand breaks lead to (severe) combined immunodeficiency [(S)CID] via defective V(D)J-recombination and can give rise to malignant lymphoma on the basis of the DNA repair defect. In the categories I.1-3, the risks of malignancy and immunodeficiency exist *in parallel*, rather than in serial connection, with one another. Thus, the *intrinsic* tumor predisposition in PID implies that any PID-dependent specific loss of tumor immunosurveillance might only be an additional, modifying factor for tumorigenesis but not the primary cause. Other reasons for malignant transformation are *extrinsic* to the affected immune function in PID and mainly cause malignancy in other tissues than the cell type that is primarily affected by the PID. Such *extrinsic* causes of tumor predisposition in PID are: transforming viral infection (*E.1*), chronic tissue inflammation (*E.2*), and impaired specific tumor immunosurveillance (*E.3*) (Table 1, right column; Figure 1, panels 5-7). In the scenarios *E.1-3* the risk of cancer arises secondarily to the PID, because malignant transformation is either indirectly facilitated by the underlying PID through failure to eliminate or control oncogenic viruses or chronic inflammation, or directly due to the failure to recognize and neutralize or remove transformed cells. Only the latter mechanism (*E.3*) represents failed immunosurveillance in the strict sense.

The distribution of the distinct types of malignancies in various categories of PID corroborates the proposed hypothesis of the existence of *intrinsic* and *extrinsic* causes of

oncogenesis and will be explained along a gross developmental order as depicted clockwise in Figure 1 (starting from the top center with panel 1). For example, the risk of myeloid malignancies predominates in the first group, termed “stem cell and myeloid developmental defects (Figure 1; top center panel 1). Severe congenital neutropenia (SCN) are classified as defects of phagocyte number, function, or both and are characterized by a stem cell and myeloid differentiation defect that leads to neutropenia and, depending on the genetic cause, to myelodysplastic syndrome (MDS) and acute myelogenous leukemia (Figure 1, category I.1, panel 1, reviewed in ^{11, 12}). The genetic causes and, consequently, the pathophysiology of SCN are variable. This implies that protein and vesicle mistrafficking, endoplasmic reticulum stress, the unfolded, protein response, destabilization of the mitochondrial membrane potential, disturbed energy metabolism, dysglycosylation and deregulated actin polymerization are taking place (*reviewed in* ¹²). The resulting *intrinsic* stem cell and myeloid development defects, but not the neutropenia as such, infer tumor predisposition. Additionally, evidence exists that high-dose treatment with granulocyte colony stimulating factor continuously overstimulates the defective system and adds to the overall risk of malignancy, at least in a subgroup of patients with SCN-causing *ELANE* mutations (reviewed in ¹³). Mutations leading to haploinsufficiency of *GATA2*, a key zinc finger transcription factor of hematopoiesis, are responsible for Emberger and MonoMac syndromes^{14, 15}. Patients with these syndromes display a wide spectrum of symptoms ranging from deafness, lymphedema, alveolar proteinosis, infections, B and dendritic cell hypoplasia, NK and monocytopenia, neutropenia, familial thrombocytopenia, and myelodysplastic syndrome or myeloid leukemia (category I.1; ¹⁴⁻¹⁸). Other bone marrow failure syndromes that stem from ribosome biogenesis defects such as Shwachman-Bodian-Diamond Syndrome (SBDS) and cartilage hair hypoplasia (CHH) impose a tumor-predisposition syndrome, and, in the case of CHH, might be associated with a state of combined immunodeficiency with variable severity (*reviewed in* ¹⁹; Figure 1, category I.1, panel 1). SBDS is associated with exocrine pancreas insufficiency and neutropenia or pancytopenia and an increased risk of myelodysplasia and AML^{20, 21}. Again, the risk of malignancy in SBDS and CHH cannot be attributed to immunosurveillance in the strict sense but rather to the *intrinsic* hematopoietic/myeloid cell defect based on ribosome pathology (category I.1).

The second example for an immune cell-intrinsic risk of malignant transformation comprises lymphocyte development, maturation, and apoptosis defects (Figure 1, category I.1, top right panel 2). The lymphocyte apoptosis defect in FAS/FASL-linked autoimmune lymphoproliferation syndrome (ALPS) primarily impairs lymphocyte differentiation, apoptosis, and senescence^{22, 23} to an extent that immune dysregulation as well as lymphoma predisposition arise²⁴, but does not cause or is associated with diminished T cell effector function against opportunistic infections. Similarly, impairments in B cell maturation such as in the heterogeneous group of common variable immunodeficiency (CVID) primarily yield humoral immunodeficiencies that are associated with a congenital disorder of B cell differentiation, B cell receptor editing, and altered B cell life cycle. Some CVID patients develop lymphoma that is probably linked to chronically impaired lymphocyte differentiation (Figure 1, category I.1, panel 2). Furthermore, CVID can predispose to the development of other cancers such as adenocarcinoma, yielding a higher incidence as compared to the general population²⁵⁻²⁷. Because epithelial tumors in hypogammaglobulinemia and CVID are typically located in the gut or lungs and are also seen in patients with IgA deficiency alone², chronic infection may play a pathogenetical role on the ground of IgA deficiency, and subsequent chronic inflammation might be suspected to be an additional, tumor-predisposing factor (category E.2; Figure 1, panel 5). In severe cases of combined immunodeficiencies (SCID), the risks of malignancy due to cell-*intrinsic* defects in the T cell life cycle cannot be clearly separated from those associated with defects in the molecular functional circuits (categories I.1-2, panel 2-3) and the *extrinsic* lack of T cell-mediated specific immunosurveillance (Figure 1, category E.3, panel 5). This has been best illustrated in patients with deficiencies in the recombinase activating genes *RAG1* and *RAG2* and the Wiskott-Aldrich syndrome gene *WAS*, (Figure 1, panels 1-2). Patients with SCID have an increased risk of malignancies² but mostly die due to infections early in life unless their T cell system is replaced by hematopoietic stem cell transplantation (HSCT) or corrected by gene therapy. With rare exceptions (*reviewed in*²), these patients die before a malignant disease evolves on the basis of their PID. Although a large U.S. study on the outcome of HSCT for SCID did not report any pre- or post-HSCT cancers²⁸, anecdotal reports of cancers in transplanted SCID survivors also exist, mainly human papilloma virus-associated skin cancer (A. Schulz, *personal communication*). It is unclear whether this is due to poor immune reconstitution after HSCT, the underlying germline gene defect, or toxicity of the HSCT itself.

Recently, researchers demonstrated *in vitro* that mutations in *RAG1* from patients with SCID or Omenn syndrome cause genotype-specific distinct DNA breaks and differentiation blocks in T cell development²⁹ that may explain both the immunodeficiency phenotype as well as the potential lymphoma and leukemia predisposition, supporting the *intrinsic* oncogenesis hypothesis, at least for this molecular SCID entity.

Thirdly, an important subgroup of CID deserves special attention because many of them are predisposed to Hodgkin's and Non-Hodgkin's B-cell lymphoma, Burkitt lymphoma, and non-malignant but, nevertheless, potentially fatal lymphoproliferative disorders including hemophagocytic lymphohistiocytosis (HLH)^{7, 30-36}. Substantial molecular heterogeneity exists in this subgroup, and the *intrinsic* defects comprise lymphocyte (co)-signalling, cytoskeleton, cytotoxicity, and metabolism defects (Figure 1, category I.2, panel 3). Functionally, the pathomechanisms result in impaired T-B cell crosstalk and effector or memory T cell generation upon encounters with EBV and other transforming (herpes) viruses. Representative (co-)signalling defects are impairments in TCR-mediated T cell activation (MAGT1 deficiency), CD28-co-signaling (CARMIL2 deficiency)³⁷, and – most prominently – CD27:CD70-axis^{30, 32, 38} and SLAM-receptor family (switch)-signalling deficiencies (Purtilo syndrome, SAP deficiency)³⁹. Purtilo syndrome is a prominent and instructive example of this category as the deficiency of the intracellular adaptor molecule SAP changes the signalling outcomes of homotypic and heterotypic SLAM-receptor interactions in hematopoietic cells. In particular, SAP deficiency results in an NK:B-cell and T:B-cell interaction disorder that severely interferes with the elimination of EBV-infected B cells and thus, after primary EBV-infection, leads to EBV-triggered HLH. Next, and if SAP deficient individuals survive this initial HLH due to sufficient treatment or somatic SAP reversions, that potentially occur in EBV-specific cytotoxic CD8 T cells, they are at risk of EBV-induced malignant transformation and especially can develop mucosa-associated lymphoid tissue (MALT) lymphoma, again as a consequence of impaired NK:B- and T:B-cell interactions. Additionally, EBV naïve individuals or survivors of primary EBV infection can develop hypogammaglobulinemia as a consequence of inefficient interactions of follicular helper T-cells and germinal center B-cells. Thus, Purtilo syndrome clearly exemplifies how a unique molecular defect leads to a particular cell intrinsic disorder that in combination with an extrinsic factor can lead to malignancy⁴⁰⁻⁴². Cytoskeletal defects impair the formation of the immunological synapse, which are particularly well illustrated in patients with Wiskott-

Aldrich syndrome (WAS)⁴³. Metabolic disorders such as cytidine triphosphate synthase 1 (CTPS1) deficiency suppress effector T cell expansion and virus-specific memory T cell differentiation⁴⁴.

If the physiological detection of DNA double strand breaks (DSB) fails, or other DNA repair defects that lead to genetic instability are present, uncontrolled cell cycle progression and oncogenesis occurs, and at the same time, the repair of physiologically induced DSB such as T and B cell antigen receptor (TCR and BCR) V(D)J rearrangement and class switch recombination is abrogated (Figure 1, category I.3, panel 4). The impaired DNA damage response causes immunodeficiency *in parallel* with tumor predisposition, which is in line with the hypothesis mentioned above (Table 1, category I.3). Prime examples for this subgroup of PID are ataxia teleangiectasia (AT), Nijmegen breakage syndrome (NBS), and Bloom syndrome, which are caused by mutations in *ATM*, *NBN*, and *RECQL3*, respectively⁷. Others include constitutive mismatch repair deficiency (CMMRD) and radiosensitive disorders like deficiencies of DNA Ligase 4 (*LIG4*), DNA-dependent protein kinase catalytic subunit (*PRKDC*), Cernunnos (*NHEJ1*), Artemis (*DCLRE1C*), and others^{7, 45-47}. The association between AT and NBS and malignancies has been analyzed recently in large French and European cohorts, respectively^{48, 49}, and its quantitative contribution exceeds that of all other PIDs by far¹. Although the vast majority of malignancies are T-NHL in AT, B-NHL in NBS, other lymphomas, and leukemias that often involve 14q aberrations in AT occur. Additionally, other types of malignancies such as carcinoma that occur later in life than hematological malignancies but much earlier than in the general population, as well as sarcoma, medulloblastoma, or neuroblastoma were observed, especially in NBS, Bloom syndrome and CMMRD (Table 2)^{1, 48}. The recently reported association of profound CID, monoclonal lymphoproliferative disease, and increased chemosensitivity in a patient with familial tumor predisposition and mutated *RAD52* fits in this picture⁵⁰. Up until now, no malignancies have been reported in patients with radiosensitive (S)CID caused by mutations in *PRKDC* or *MRE11*, probably because DNA-PKcs-deficient humans have no T and B cell development at all (*reviewed in*⁴⁷), and *MRE11* deficiency might be partially compensated by other components of the NBN/RAD50/MRE11 complex. Given the particular requirement for DSB repair in the immune system and the overall importance in maintaining genomic stability, (S)CID frequently observed in these patients may be seen as a by-product rather than the cause of the tumor predisposition⁴⁷. Nevertheless, the relevant contribution of

functional T cell immunosurveillance was demonstrated recently in T cell deficient *atm* knockout mice that developed B cell lymphoma that was not transplantable to immunocompetent mice⁵¹.

Prime examples of primarily *extrinsic* causes of oncogenic transformation are shown in panels 5-7 (Figure 1; bottom left to top left panels 5-7). The chronic inflammation of epithelial surfaces or tissues or infections with oncogenic viruses may induce malignant transformation. This is known to occur more frequently in patients with primary or secondary immunodeficiency disorders than in members of the general population (Figure 1, categories E1-2, panels 5-6). Epidermodysplasia verruciformis (EV) is caused by mutations in the *TMC6* and *TMC8* genes and, for example, predisposes patients to papilloma virus infections and skin cancer (Figure 1, category E.1, panel 5)⁵². However, malignancy associated with chronic inflammation and infection also occurs in otherwise immunocompetent individuals (*e.g.*, HCV and hepatocellular carcinoma, *Helicobacter pylori* and gastric cancer)^{53, 54}. Hence, it might be argued that whether the increased frequency of chronic tissue inflammation due to an inability to fend off mostly viral infections in PID alone (category E.2) or a combination with impaired cancer immunosurveillance (category E.3) leads to malignancy in this scenario. Cytotoxicity defects underlie fatal lymphoproliferative disorders and are classified as familial hemophagocytic lymphohistiocytosis (FHL)^{7, 55}. As described above, they represent an overlap subgroup with respect to the basis of malignant transformation, because in addition to the T cell *intrinsic* defects (Figure 1, category I.2, panel 3), strong *extrinsic* contributions in the form of oncogenic viral infection and impairments in specific immuno-surveillance exist in this group (Figure 1, categories E.1 and E.3, panels 5 and 7).

Lastly, natural killer cell activity is known to play a major and undoubted role in tumor immunosurveillance, as do other components of the innate immune system such as dendritic cells, cytokines, and intra- and extracellular receptors⁵. It is surprising that, apart from disorders of cytotoxic granule formation or their secretion and NK and T cellular cytotoxicity defects resulting in primary hemophagocytic lymphohistiocytosis⁵⁶, patients with congenital defects in NK cell number or function do not have an increased risk of developing cancers in the context of impaired immunosurveillance⁵⁷.

280 A comprehensive list of primary immunodeficiencies with reported or expected
281 malignancy, the causal genes, mode of inheritance, and references is provided in the *eta*
282 *Repository* (Supplemental Table 1).

283

The oncological perspective: Types and characteristics of malignancies observed in PID

Two large retrospective registry studies were published on AT and NBS in 2015^{48, 49}, and the main patient characteristics and conclusions are presented in Table 2. While the AT study focused on malignancies in a national cohort and was more detailed with regard to histological subtypes of malignancies and treatments⁴⁹, the NBS study was performed Europe-wide as a retrospective ESID survey and provided an overview of the most relevant clinical presentations and complications of patients with NBS⁴⁸. The results of both studies reflected previous knowledge as the incidence of lymphoma was much greater in both DNA repair defects/immunodeficiencies as in the general population and as in other PID. The proportion of T prolymphocytic leukemia in AT was smaller than had been expected in the French cohort on the basis of previous studies⁴⁹. Malignancy was the strongest negative factor affecting survival in both AT and NBS^{48, 49}. Although toxicity has been a serious concern in the treatment of malignancy in patients with DNA repair deficiencies that are radio- and/or chemosensitive^{58, 59}, HSCT has been performed relatively successfully in NBS and was proposed for patients in first remission^{48, 60}, given its potential to replace the tissue that is prone to future primary and secondary malignant transformation. Recently, a large retrospective multicenter study was conducted to evaluate the feasibility and outcome of HSCT in DNA repair defects, with 29 transplantations indicated for immunodeficiency-related infections, 21 for malignancy, 13 for bone marrow failure, 13 for pre-emptive reasons, and 11 for unknown or multiple reasons⁶¹. The cohort of 87 patients included NBS, LIG4 deficiency, Cernunnos-deficiency, and AT with a survival of 69%⁶¹. Deaths mostly occurred in early post-HSCT and significantly more frequently in patients who had been treated with myeloablative conditioning as compared to being placed on reduced intensity regimens, which correlated with increasingly toxic effects in these patients⁶¹. AT patients had the poorest outcome with only 25% survival, leading to the conclusion that HSCT should not be routinely recommended in AT⁶¹. No secondary malignancies were observed in this cohort during the relatively short median follow-up period of 35 months⁶¹.

In addition, at least four recent studies have been conducted to investigate the more general associations between malignancy and PID: First, a Dutch national survey of PID patients in the ESID registry was conducted to analyze the incidence and type of malignancy⁶². This study included patients of all age groups and showed that the most

prevalent subcategory of PID, namely predominant antibody deficiency, was associated with the highest number of malignancies, mostly squamous cell carcinoma of the skin with a 2.3-fold higher risk than in the general population⁶². When the lymphoma incidence was calculated, the risk in PID patients from the Netherlands was increased 11-fold, and again these cases were derived mainly from the largest group of PID, namely hypogammaglobulinemia and CVID patients⁶².

Second, as a result of a database search using the key phrases „childhood cancer“ and „genetic syndrome / disorder“ for relevant literature from the past 50 years¹, PID-linked syndromes were found to be accountable for only a minority of malignancies in overall pediatric oncology as compared to other well-known tumor-predisposition syndromes such as Li-Fraumeni, Noonan, Beckwith-Wiedemann, and Down syndromes, neurofibromatosis, and familial adenomatous polyposis coli. However, many hematological malignancies were found in syndromes known to cause PID (Table 2)¹. The preliminary results of an ongoing study in Austria indicate that similar conclusions can be reached (Table 2; *Voss and Seidel, unpublished data*).

Third, a multicenter study on NHL linked to preexisting conditions in children and adolescents conducted by the European Intergroup for childhood NHL (EICNHL) and the international Berlin-Frankfurt-Münster (iBFM) study group led to the identification of 213 PID patients for whom AT (n=32) and NBS (n=26), followed by CMMRD (n=21), unspecified PID (n=21), SAP-deficiency (n=11), WAS (n=7), and CVID (n=8) made up the majority of syndromic NHL. Other PID included ALPS, CHH, STK4 deficiency, Hyper-IgM and Hyper-IgE syndromes (each n=2), and other non-PID tumor predisposition syndromes (Table 2)⁶³. A similar study on acute lymphoblastic leukemia (ALL) was conducted within the European AIEOP-BFM ALL 2000 trial group and led to the identification of 233 patients out of 4939 children and adolescents diagnosed with ALL between 1999 and 2009 who had a preexisting condition⁶⁴. Among those that were detected more often than once, AT (n=8) and NBS (n=6) were the only PID, whereas other diagnoses included Gilbert's disease, neurofibromatosis, thalassemia, and Noonan and Klinefelter syndromes⁶⁴. The directors of both studies concluded that patients with ALL and preexisting conditions required adjustments in chemotherapy and intensified supportive care.

Conclusions and perspectives

These observations of the types of malignancies and their frequent manifestations in defined pathophysiological PID subtypes raise the following questions and allow us to reach several conclusions.

A) Why is the malignant cell lineage in a PID-associated malignancy often identical to the cell type affected by the immunodeficiency, or why is the malignancy attributable to the same underlying molecular defect, rather than attributable merely to a defect in tumor antigen presentation or recognition? Why are melanoma, renal cell carcinoma, and non-small cell lung cancer (NSCLC) relatively rare in PID patients, although they are tumors with high response rates to various immune therapies and, thus, should be prevented by a healthy immune system? Given the supposed importance of NK cells in tumor immunosurveillance, why has no increased malignancy risk been reported in cases of quantitative or qualitative NK cell deficiencies⁵⁷?

In line with these questions is the observation that in the human diseaseome, a network of human disorders, disease genes, and their respective gene product interactions, PID do not cluster with malignancy, with a few exceptions such as NBS, AT, and ALPS-related autoimmune diseases⁶⁵. Importantly, Fanconi anemia (FA) lies near the center of the diseaseome malignancy cluster close to *TP53* and *PTEN*⁶⁵ and has been associated with an increased risk of bone marrow failure with leukemic transformation in childhood or adolescence and of ear-nose-throat and other carcinomas early in adulthood without being typically associated with clinically relevant immunodeficiency⁶⁶. Because FA is based on a comparable DNA repair deficiency such as AT and NBS but does not disrupt immunoglobulin production or detectable T cell dysfunction, FA causes a similar tumor predisposition as AT or NBS without any major loss of immunosurveillance⁶⁷. In addition, the fact that DBA causes a predisposition towards malignancies comparable to CHH and SBDS (*e.g.*, myelodysplastic syndrome and myeloblastic leukemia, but rarely lymphoma or osteosarcoma) without being associated with immunodeficiency indicates that immunosurveillance does not substantially contribute to these malignancies^{1, 68, 69}. In conclusion, we argue that particularly genomic instability as well as defects in DNA repair and ribosome biogenesis strongly favor oncogenesis and that impaired immunosurveillance may represent an additional, but probably minor, risk factor in PID with strong *intrinsic* tumor predisposition (I.1-3).

B) Given the success of combined checkpoint inhibition in the current treatment of malignant melanoma, NSCLC, and other malignancies investigated in clinical trials (*reviewed in*⁷⁰), one would expect to find a reduced tumor predisposition in patients with inborn loss of function defects in programmed cell death protein 1 (PD1), its ligands, or other inhibitory immune checkpoint modifiers, while those individuals would be expected to suffer from autoimmunity and immune dysregulation. Presumably, a reduced risk of malignancy might be impossible to identify in the clinical epidemiological practice. To date, inborn PD1/PD-L1 defects with autoimmunity have been identified in mice⁷¹ but have not been found in humans, and gain-of-function mutations with increased tumor predisposition are currently unknown. On the contrary, patients with haploinsufficiency of cytotoxic T lymphocyte antigen-4 (CTLA4) have autoimmunity but, at the same time, are not entirely protected from malignancies such as lymphoproliferation, lymphoma, or gastric cancer⁷²⁻⁷⁶. Tumor immune surveillance and protection from autoimmunity may be seen as two sides of a coin named 'tolerance'. Thus, autoimmune phenomena occur in oncological patients treated with checkpoint inhibition (*see comment in*⁷⁷) and, consequently, one may suspect that tumors will arise in patients undergoing long-term abatacept or belatacept treatment such as, for instance, patients who have rheumatoid arthritis, organ transplant recipients, or patients who are CTLA4- or LRBA deficient⁷⁸.

It has been shown that a positive response to immune checkpoint inhibition correlates with the mutational load of a tumor^{79, 80}, which is expected to be higher in tumors with genomic instability such as CMMRD or, potentially, other repair defects. This suggests that more tumor-associated, mutation-derived neoantigens may be identified and targeted by the immune system in such malignancies^{79, 80}. In fact, MMR-deficient colorectal cancers responded substantially better to a PD-1 blockade than MMR-proficient ones as illustrated by an immune-related, progression-free survival rate of 78% vs. 11%, respectively⁸¹. Whether the same will hold true for germline CMMRD mutations or other DNA repair defects, the predominant group of cancer-predisposing PID, is currently unknown. In this case, tumors could show a higher mutational burden, but simultaneously, patients have a variable degree of combined immunodeficiency and, therefore, might have an inefficient anti-tumor immunity even if enhanced by pharmacological checkpoint inhibition. By conducting a critical review of the specific pattern of actual tumor predisposition of PID patients, we might optimistically hypothesize that checkpoint inhibition could serve as an

411 extremely helpful addition to conventional oncological therapy, especially in these highly
412 radio- and chemosensitive patients. At the same time, the success of that strategy would be
413 the prime piece of evidence that would weigh against the predominant role of lost tumor
414 immunosurveillance as the cause of cancer in PID. On the contrary, if patients with
415 checkpoint inhibition therapy exhibited poorer responses after developing PID-related
416 cancers despite PD-L1 expression than otherwise healthy individuals with the same types of
417 malignancies, this might provide support for the argument that patients must possess the
418 respective immune mechanism to eradicate tumor cells.

419

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Table 1. Overview of immune cell *intrinsic* and *extrinsic* causes of tumor predisposition in primary immunodeficiency disorders.

Intrinsic	Extrinsic
I.1 . Stem cell, myeloid and lymphoid development, differentiation and apoptosis defects	E.1 Transforming (viral) infection
I.2 Lymphocyte (co-)signaling, cytoskeleton, cytotoxicity and metabolism defects	E.2 Chronic tissue inflammation
I.3 Defects of chromosome stability, telomere maintenance and DNA repair	E.3 Impaired specific tumor immunosurveillance

648 **Table 2. Recent studies on malignancies in primary immunodeficiency disorders (PID).**

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Study	year	Study type	Primary patient cohort	Cohort size (n), Median age (yrs)	Malignancies (n patients)	Malignoma incidence (%), median age at dx (yrs)	Pre-dominant PID	Predominant malignancy	Main finding	Other conclusions
<i>Suarez et al., J Clin Onc; 2015; 33(2):202⁴⁹</i>	2015	Retrospective (national, France)	Ataxia teleangiectasia (AT)	279 26 yrs	70 in 69 patients	24.5 12.6 yrs	n.a. (100% AT)	B-NHL, HD, ALL in childhood and adolescence; from young adulthood also PLL and carcinoma	More increased incidence of lymphoma and leukemia than in general population; AT patients with cancer have shorter survival than those without	Immunodeficiency (Ig substitution, IgA and B cell deficiency) associated with higher cancer incidence; type of <i>ATM</i> mutation not linked to risk of malignancy
<i>Wolska-Kuśnierz et al., J Clin Immunol. 2015; 35(6):538⁴⁸</i>	2015	Retrospective (European, ESID registry)	Nijmegen Breakage Syndrome (NBS)	149 14.3 yrs	80 in 63 patients	42 10.25 yrs	n.a. (100% NBS)	B-NHL, T-NHL, T-ALL, HD, other malignoma including medullo-blastoma, neuroblastoma	More increased incidence of lymphoma and leukemia than in general population; NBS patients with cancer have shorter survival than those without	HSCT feasible (n=14 patients, all due to relapse of malignoma, of whom 9 survived 1.4-11 years); no predictive clinical or laboratory biomarker for cancer development detectable
<i>Jonkman-Berk et al., Clin Immunol. 2015; 156:154⁶²</i>	2015	Retrospective (national, ESID registry Netherlands)	PID	745 all age groups	60	8.1 43.0	Predominant antibody deficiency	40 solid tumors (mainly squamous cell carcinomas of skin), lymphoma, leukemia	risk of any malignancy is 2.3-fold higher in PID than in general population; that of	Cancer occurs earlier and with increased frequency in PID patients than in the general population; lymphoma showed male predominance

Study	year	Study type	Primary patient cohort	Cohort size (n), Median age (yrs)	Malignancies (n patients)	Malignoma incidence (%), median age at dx (yrs)	Pre-dominant PID	Predominant malignancy	Main finding	Other conclusions
									lymphoma, 11-fold	
<i>Zimmerman et al.</i> , <i>Pediatr Blood Cancer</i> 2015; 62:2071 ¹	2015	Literature search 1960-2012	„Childhood cancer“ AND „genetic syndrome / disorder“	n.a.	n.a. (PID-linked leukemias: n= 66; PID-linked lymphoma: N=105)	n.a. (100%) n.d.	NBS (also het. NBN mutations), GATA2, AT, SCN, Bloom	Leukemias, NHL, HD; rarely also medullo-blastoma, others	leukemia and lymphoma are most prevalent cancer in PID	Minority of cancer predisposition syndromes is associated with or categorized as immunodeficiency
<i>Attarbaschi et al.</i> , <i>Haematologica</i> 2016; 101:1581 ⁶³	2016	EICNHL and iBFM survey 1984-2015	NHL AND „underlying condition“	213 (only lymphoma patients included) n.d. (detected at diagnosis of lymphoma)	213	n.a. (100%) 9-10 (depending on inborn error, range 4.5-15.5)	AT (n=32), NBS (n=26), CMMRD (n=21), unspecified PID, XLP (n=11), WAS (n=7), CVID (n=8), DGS; in addition to other cancer predispositions syndromes	B-NHL, T-NHL	Inferior survival as compared to patients without preexisting condition, mostly due to treatment-related toxicity	High rate of relapse and secondary malignancy; HSCT feasible (n=31, of whom 25 survived long-term)
<i>Schütte et al.</i> ; <i>Eur J Med Genet.</i> 2016; 59(3):143-151; ⁶⁴	2016	Retrospective international AIEOP-BFM ALL 2000 trial 1999-2009	ALL	4939 ALL, of which 233 inborn conditions pediatric ALL cohort,	n.a.	n.a. (100%) age of onset detected but not specified for PID patients	AT (n=8 of 233), NBS (n=6/233), other non-PID conditions	Only ALL	Same as above	Chemotherapy needs to be adjusted, supportive care intensified in patients with preexisting conditions
Voss, Seidel et al.; <i>unpublished data</i>	2016	Retrospective (national, ESID registry Austria)	PID	184 all age groups, from selected pediatric and adult centers	8	4.4 n.d.	XLP1, AT	NHL, HD	Increased incidence of lymphoma than in general population	Guidelines for treatment of patients with underlying chemo-sensitizing condition needed

Legends

Figure 1. Categories of tumor predisposition in primary immunodeficiencies (PID).

The infographic delineates broad categories of the mechanisms of the supposed risk factors of malignant transformation with large ellipsoid bubbles; corresponding groups of primary immunodeficiencies (PID) or monogenetic diseases that are associated with this pathomechanisms are enclosed in thin rectangles. Immune cell intrinsic disorders that cause (mostly hematological) malignancies within the same cell type are grouped according to myeloid or lymphoid development, differentiation or apoptosis defects ("intrinsic" I.1), lymphocyte co)-signalling, cytoskeleton, cytotoxicity and metabolism defects (I.2), or chromosome stability, telomere maintenance and DNA repair defects (I.3). Tumor predisposition arising from factors independent from or secondary to the immunodeficiency are grouped under *extrinsic* oncogenic risk factors such as transforming (viral) infections (E.1), chronic tissue inflammation with or without chronic infection and increased tissue turnover (E.2), or a loss of specific tumor immunosurveillance *per se* (E.3). The infographic does not reflect the level of incidence in or relative contribution of each category.

Abbreviations ALPS = autoimmune lymphoproliferative syndrome, AML = acute myelogenous leukemia, AT = ataxia telangiectasia, CHH = cartilage hair hypoplasia, CVID = common variable immunodeficiency, DKC = dyskeratosis congenita, EV= epidermodysplasia verruciformis, FA = Fanconi anemia, HLH = hemophagocytic lymphohistiocytosis, IBD = inflammatory bowel disease, ICF = immunodeficiency with centromeric instability and facial anomalies, LPD = lymphoproliferative disorder, MDS = myelodysplastic syndrome, NBS = Nijmegen breakage syndrome, (S)CID = (severe) combined immunodeficiency, SCN = severe congenital neutropenia, SDS = Shwachman-Diamond syndrome, SMT = smooth muscle tumor, WHIM = warts, hypogammaglobulinemia, immunodeficiency and myelokathexis.

Footnotes:

1. No malignancy as such but having the potential to progress to and/or requiring chemotherapy and/or HSCT
2. ALPS caused by germline and/or somatic mutations
3. Only (S)CID caused by defective non-homologous-end-joining
4. Defects listed in I.1 and I.2 facilitate malignant transformation caused by virus species such as EBV, HHV8 and HPV
5. Defects listed in I.1-3 and E.1 lead to chronic inflammation and infection
6. Defects listed in I.1-3 facilitate immune escape of cells that independently underwent malignant transformation

± any PID,
defects of adaptive immunity

SCN, GATA2, SDS, CHH

(S)CID, CVID, ALPS², ...

7. Impaired
specific immuno-
surveillance

(I.1-3)

↓
E.3⁶

Carcinoma

1. Stem cell and
myeloid
development defects

(MDS)¹, AML

I.1

2. Lymphocyte
development,
differentiation and
apoptosis defects

(LPD/HLH)¹, **lymphoma**, leukemia

I.1

6. Chronic tissue
inflammation

(I.1-3 + E.1)

↓
E.2⁵

Carcinoma

**Malignancy
in PID**



I.2

(S)CID, CVID, ...

3. Lymphocyte
(co)-signalling,
cytoskeleton,
cytotoxicity and
metabolism defects

(LPD/HLH)¹, **lymphoma**, leukemia

± any PID, IBD,
defects of innate
immunity

(I.1-2)

↓
E.1⁴

5. Transforming
(viral) infection

(S)CID, EV,
WHIM...

(LPD/HLH)¹, **lymphoma**, leukemia,
carcinoma, SMT, sarcoma

ICF, DKC,
(S)CID³, AT,
NBS, Bloom,...

I.3

Lymphoma, leukemia,
carcinoma, sarcoma

4. Defects of
chromosome stability,
telomere maintenance
and DNA repair

Supplementary Table 1. Primary immunodeficiencies with reported or expected risk of malignancy.

PID	Gene, inheritance OMIM	Pathomechanism [#]	Malignancy	Reference
1. Stem cell and myeloid development defects				
Severe congenital neutropenia (SCN)	<i>ELANE</i> , AD, 130130 <i>GFI1</i> , AR, 600871 <i>HAX1</i> , AR, 605998	Intrinsic (I.1)	MDS, AML	1–3
GATA2-deficiency	<i>GATA2</i> , AD (HI), 137295	Intrinsic (I.1)	MDS, AML	4,5
Shwachman-Bodian-Diamond syndrome (SBDS)	<i>SBDS</i> , AR, 607444	Intrinsic (I.1)	MDS, AML	6–8
Cartilage hair hypoplasia (CHH)	<i>RMRP</i> , 157666	Intrinsic (I.1)	MDS; AML	9
2. Lymphocyte development, differentiation and apoptosis defects				
(Severe) combined immunodeficiency [(S)CID]	<i>IL2RG</i> , XR, 308380 <i>JAK3</i> , AR, 600173 <i>IL7RA</i> , AR, 146661 <i>RAG1</i> , AR, 601457, 233650 <i>RAG2</i> , AR, 601457, 233650 <i>CORO1A</i> , 615401	Intrinsic (I.1)	Lymphoma , leukemia, (LPD/HLH)*	10–12
DiGeorge syndrome	22q11.2 (HI) or <i>TBX1</i> , AD, 602054	Intrinsic (I.1)	Lymphoma	13–15
Class-switch-recombination deficiency (CSR)	<i>AICDA</i> , AR, 605258 <i>UNG</i> , AR, 608106	Intrinsic (I.1)	Lymphoma , leukemia, (LPD/HLH)*	16–19

PID	Gene, inheritance OMIM	Pathomechanism [#]	Malignancy	Reference
Common variable immunodeficiency (CVID)	<i>CD19</i> , AR, 107265 <i>CD20</i> , AR, 112210 <i>CD21</i> , AR; 120650 <i>CD81</i> , AR, 186845	Intrinsic (I.1)	Lymphoma , leukemia, (LPD/HLH)*	12,20
Autoimmune lymphoproliferative syndrome (ALPS)	<i>TNFRSF6</i> , AD, (AR) 134637 <i>TNFRSF6</i> , somatic [§] , 134637 <i>TNFSF6</i> , AR, 134638	Intrinsic (I.1)	Lymphoma , leukemia, (LPD/HLH)*	21–23
RAS-associated autoimmune leukoproliferative disease (RALD)	<i>KRAS</i> , somatic [§] , 190070 ⁴ <i>NRAS</i> , somatic [§] , 164790	Intrinsic (I.1)	(LPD)*, leukemia,	24,25
Good syndrome	Unknown,	Intrinsic (I.1)?	Lymphoma , leukemia	26
3. Lymphocyte (co)-signaling, cytoskeleton, cytotoxicity and metabolism defects				
Combined immunodeficiency (CID)	<i>STAT3</i> (GOF ^{§§}) <i>ZAP70</i> , AR, 269840 <i>RHOH</i> , AR, 602037 <i>ITK</i> , AR, 613011 <i>CARD11</i> , AR (LOF), 615206 <i>CARD11</i> , AD (GOF), 606445 <i>MALT1</i> , AR, 615468 <i>ORAI1</i> , AR, 610277 <i>STIM1</i> , AR, 605921 <i>MAGT1</i> , XR, 300715 <i>PIK3CD</i> , AD (GOF) 615513 <i>PIK3R1</i> , AD (LOF), 616005	Intrinsic (I.2)	Lymphoma , leukemia, (LPD/HLH)*	12,27–44

PID	Gene, inheritance OMIM	Pathomechanism [#]	Malignancy	Reference
	STK4, AR, 604965 CD27, AR 615122 CD70, AR, 602840 OX40, AR, 615593 CARMIL2, AR, 610859 CTLA4, AD (HI), 616100 LRBA, AR, 614700 WAS, XR, 300392 WIPF1, AR, 614493 DOCK8, AR, 243700 ADA, AR, 608958 PNP, AR, 613179 CTPS1, AR, 615897			
Common variable immunodeficiency (CVID)	TNFRSF13B, AD/AR, 240500 TNFRSF13C, AR, 613494 NFKB1, AD, 616576 NFKB2, AD, 615577 IKZF1, AD, 616873	Intrinsic (I.2)	Lymphoma , leukemia, (LPD/HLH)*	12,45,46
Familial hemophagocytic lymphohistiocytosis (FHL)	PRF1, AR, 603553 UNC13D, AR, 608898 STX11, AR, 603552 STXBP2, AR, 613101 SH2D1A, XR, 308240	Intrinsic (I.2)	(LPD/HLH)*, lymphoma, leukemia	47–49
4. Defects of chromosome stability, telomere maintenance, and DNA repair⁵				
(Severe) combined immunodeficiency [(S)CID]	RAG1, AR, 601457, 233650 RAG2, AR, 601457, 233650 DCLRE1C, AR, 602450 PRKDC, AR, 615966	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma	12,50,51

PID	Gene, inheritance OMIM	Pathomechanism [#]	Malignancy	Reference
	<i>NHEJ1</i> , AR, 611291 <i>LIG4</i> , AR, 606593			
Immunodeficiency with centromeric instability and facial anomalies (ICF)	<i>DNMT3B</i> , AR, 242860 <i>ZBTB24</i> , AR, 614069 <i>CDCA7</i> , AR, 616910 <i>HELLS</i> , AR, 616911	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma	52
Dyskeratosis congenital (DKC)	<i>DKC1</i> , XR, 305000 <i>NOLA2</i> , AR, 613987 <i>NOLA3</i> , AR, 224230 <i>RTEL1</i> , AD/AR, 615190 <i>TERC</i> , AD, 127550 <i>TERT</i> , AD/AR, 613989 <i>TINF2</i> , AD, 613990 <i>ACD</i> , AD/AR, 616553 <i>DCLRE1B</i> , AR, 609683 <i>PARN</i> , AR, 616353	Intrinsic (I.3)	MDS, AML, carcinoma	53–56
Ataxia teleangiectasia (AT)	<i>ATM</i> , AR, 208900 <i>MRE11A</i> , AR, 604391	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma	57,58
Nijmegen Breakage syndrome (NBS)	<i>NBN</i> , AR, 251260	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma	59–61
Bloom syndrome	<i>RECQL3</i> , AR, 210900	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma	62
Constitutive mismatch repair deficiency (CMMRD)	<i>PMS2</i> , AR, 276300 <i>MSH6</i> , AR, 276300	Intrinsic (I.3)	Lymphoma , leukemia, carcinoma, sarcoma, medulloblastoma	63
Other syndromes	<i>INO80</i> , AR, 610169 <i>RNF168</i> , AR, 611943 <i>POLE1</i> , AR, 174762 <i>STN1</i> , AR, 612199	Intrinsic (I.3)	MDS	64–66

PID	Gene, inheritance OMIM	Pathomechanism [#]	Malignancy	Reference
5. Transforming viral infection				
Epidermodysplasia verruciformis (EVER)	<i>TMC6</i> , AR, 226400 <i>TMC8</i> , AR, 226400	Extrinsic (E.1)	Carcinoma	67
Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome	<i>CXCR4</i> , AD, 193670	Extrinsic (E.1)	Carcinoma Lymphoma	68,69
6. Chronic tissue inflammation				
Chronic mucocutaneous candidiasis (CMC)	<i>IL17RA</i> , AR, 613953 <i>IL17RC</i> , AR, 616445 <i>IL17F</i> , AD, 606496 <i>STAT1</i> , AD (GOF), 614162 <i>TRAF3IP2</i> , AR, 615527	Extrinsic (E.2)	Carcinoma	70–72
Immune dysregulation with colitis	<i>IL10RA</i> , AR, 613148 <i>IL10RB</i> , AR, 612567	Intrinsic (I.2)	Lymphoma	73
7. Impaired specific immunosurveillance				
See 2. and 3.	See 2. and 3.	Extrinsic (E.3 facilitated by I.1-3)	Carcinoma	
NK cell deficiency	<i>FCGR3A</i> , AR, 615707 <i>MCM4</i> , AR, 609981	Extrinsic (E.3)	Carcinoma	74

[#], see Table 1 and Figure 1 for categorization

^{*}, no malignancy as such but having the potential to progress to and/or requiring chemotherapy and/or HSCT

^{\$}, heterozygous germline *TNFRSF6* mutation plus somatic mutation or loss of the the second allele

[§], somatic heterozygous gain of function mutation

^{§§} risk of malignancy persists in extra-hematopoietic tissues after HSCT

Abbreviations: AD = autosomal dominant, AR = autosomal recessive, GOF = gain of function, HI = haploinsufficiency, HLH = hemophagocytic lymphohistiocytosis, LOF = loss of function, LPD = lymphoproliferative disease, XR = X-linked recessive

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