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Review

Genetics of Immune Dysregulation and Cancer Predisposition: Two Sides of the Same Coin

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Abstract

Approximately 10% of cancers have a hereditary predisposition. However, no genetic diagnosis is available in 60%-80% of familial cancers. In some of these families, immune dysregulation-mediated disease is frequent. The immune system plays a critical role in identifying and eliminating tumors; thus, dysregulation of the immune system can increase the risk of developing cancer. This review focuses on some of the genes involved in immune dysregulation the promote the risk for cancer. Genetic counseling for patients with cancer currently focuses on known genes that raise the risk of cancer. In missing hereditary familial cases, the history family of immune dysregulation should be recorded, and genes related to the immune system should be analyzed in relevant families. On the other hand, patients with immune disorders diagnosed with a pathogenic mutation in an immune regulatory gene may have an increased risk of cancer. Therefore, those patients need to be under surveillance for cancer. Gene panel and exome sequencing are currently standard methods for genetic diagnosis, providing an excellent opportunity to jointly test cancer and immune genes.

Key words: immune dysregulation; immune surveillance; pathogenic mutation; germline/somatic mutation; penetrance.

Abbreviations: AID, autoimmune diseases; ALL, acute lymphoblastic leukemia; ALPS, autoimmune lymphoproliferative syndrome; AML/CML, acute/chronic myeloid leukemia; APDS, activated PI3K-delta syndrome; CLL, chronic lymphocytic leukemia; CLPD-NK, chronic NK lymphoproliferative disorders; CNS, central nerve system; CTLA-4, cytotoxic T-lymphocyte-associated protein; DISC, death-inducing signaling complex; EBV, Epstein-Barr virus; FasL, Fas-ligand; FoxP3, Forkhead box protein P3; GoF, gain of function; GWAS, genome-wide association study; HIES, hyper-IgE syndrome; HL, Hodgkin's lymphoma; HPV, human papilloma virus; IBD, inflammatory bowel disease; IEIs, inborn errors of immunity; IKK, inhibitor of kappa B kinase; IKZF1, Ikaros family zinc finger 1; JAK, Janus kinase; LoF, loss of function; LOH, loss of heterozygosity; LRBA, LPS Responsive Beige-Like Anchor; MAPK, mitogen-activated protein kinase; MDS, familial myelodysplastic syndrome; MDSCs, myeloid-derived suppressor cells; NA, not available; NEMO, NF-κB essential modulator gene; NF-κB, nuclear factor-kappa B; NHL, non-Hodgkin's lymphoma; NHLPL, nodular lymphocyte-predominant Hodgkin's lymphoma; NR, not relevant; NSCLC, non-small-cell lung carcinoma; pDCs, plasmacytoid dendritic cells; PI3Ks, phosphatidylinositol 3 kinases; PIRD, primary immune regulatory disorders; PTCL, peripheral T-cell lymphoma; SCID, severe combined immune deficiency; SLE, systemic lupus erythematosus; STAT, signal transducer and activator of transcription; T-ALL, T-cell acute lymphoblastic leukemia; Th, T-helper cells; T-LGL, T-cell large granular lymphocytic leukemia; TNF-R, tumor necrosis factor receptor; Tregs, regulatory T cells; TYK2; tyrosine kinase 2; XLP1, X-linked lymphoproliferative disease type 1; ZF1/2, zink finger domains.

Introduction

Despite a known familial predisposition for cancer in 10% of cases, the molecular cause in a substantial number of families remains undefined. Genetic diagnosis is missing in approximately 60%-80% of familial cancers [1, 2]. In some families, poly-autoimmunity and increased susceptibility to infections occur frequently, often in the same individual, with an early age of onset [3–5]. In recent years, a well-established relationship has been reported between immune dysregulation and an increased risk of cancer due to immune surveillance failure [6]. Therefore, it is not surprising that individuals with

dysregulated immune systems harbor an increased risk of developing cancer.

Cancer develops through an accumulation of gene variants involved in the transformation of normal cells to cancer cells. It is important to differentiate between somatic and germline cancer-inducing gene variants. Most cancers are sporadic, resulting from pathogenic gene variation in the body tissues (i.e. somatic mutation). In cases of hereditary cancers, every cell of the body harbors this mutation (i.e. germinal mutation) and malignancy can develop through somatic variation, including a somatic mutation in the trans-allele of the predisposition

gene to initiate tumorigenesis [3]. Although somatic and germline variants may predispose an individual to cancer, their function may be unrelated to the immune system.

Inborn errors of immunity (IEIs) consist of a heterogeneous group of diseases caused by gene variants affecting the immune system. In this group of diseases, one can find primary immune regulatory disorders (PIRD), which consists of IEI with loss or gain of functions of regulatory proteins of the immune system. This results in immune dysregulation, which manifests by lymphoproliferation, autoimmunity, atopy, and malignancy, as well as increased susceptibility to infections [7]. Since the introduction of next generation sequencing, more than 400 IEI disorders have been identified [8].

Various biological processes are involved in cell balance and are important for cancer prevention. Pathogenic variation in critical genes, including genes involved in DNA repair, suppressor genes, and oncogenes, cause genetic instability, uncontrolled cell growth, and progressive loss of differentiation [3]. Other mechanisms that can contribute to cancer development include escape of tumor cells from immune surveillance and chronic viral infections, which modulate the host immune response, disrupting immune surveillance and inducing cancer [9].

In some patients, cancer-inducing gene variants are related to the immune system. These patients may not harbor tumor-inducing somatic or germline gene variants; however, some have a history of familial cancer and immune dysregulation. Thus, shedding light on the relationship between immune dysregulation and cancer disposition may help identify individuals with an elevated risk of cancer, promoting early diagnosis and intervention [10].

PIRD may induce cancer via various mechanisms [11]. Here, we review the immune-related biological pathways and genes that affect cancer predisposition, with a focus on immune dysregulation. The review will be structured according to different underlying mechanisms: chronic inflammation, oncogenic viral infections in IEIs, disorders of apoptosis, dysfunction of immune checkpoints, disruption of cell signaling, hematopoietic defects, and abnormal transcriptional control of inflammatory genes. Each mechanism will be further discussed regarding its specific gene defects. Thus, we hope to shed light on the association between IEIs and cancer.

Chronic inflammation can lead to tumorigenesis

Several autoimmune conditions associated with an increased risk of cancer are listed in Table 1 [5, 12–19]. Autoimmune diseases are typically characterized by recognition of self-antigens as non-self, which leads to tissue damage and a chronic inflammatory steady state [20–22].

Inflammation has acute and chronic stages, but the link to tumorigenesis is through chronic inflammation [23]. Acute inflammation is governed by effector T-helper (Th)1 lymphocytes attracted by innate immune cells that secrete cytokines, such as IL-2 and interferon (IFN)-γ. In contrast, chronic inflammation controlled by Tregs and Th2 lymphocytes, which secrete pro-tumorigenic factors, such as IL-4, IL-10, IL-13, and TGF-β [23]. The high levels of pro-inflammatory cytokines activate myeloid-derived suppressor cells (MDSCs), preventing immune activation and leading to immune dysregulation, immunosuppression, and eventually dysfunction of the innate and adaptive effector arm of the immune system. This harmful environment results in tissue damage and several complications, including an increased risk of cancer initiation and progression [24].

The etiology of autoimmune diseases tends to be multifactorial. Among other inducers, environmental and genetic factors are known to contribute to the onset of autoimmune diseases [25, 26]. A possible link between autoimmunity and cancer is also strongly suggested by epidemiological studies and research findings showing that some of the genes that significantly contribute to autoimmunity elevate cancer risk (Table 2).

Viral infections, immune dysregulation, and cancer predisposition

Chronic infection with viruses, such as Epstein-Barr virus (EBV) or human papilloma virus (HPV), is known to increase the risk of malignancy. EBV contributes to tumorigenesis by inducing a persistent inflammatory environment and expressing viral oncogenic proteins. This is specifically seen in patients with IEIs. For example, patients with X-linked lymphoproliferative disease type 1 (XLP1), which is caused by variants in the SH2D1A gene, have impaired CD8 + T and

Table 1: association between autoimmune diseases and cancer

Reference	Cancer association	Autoimmune disease
[20, 21]	Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL)	ALPS
[14, 17]	Hepatocellular carcinoma	Autoimmune hepatitis
	Gastric adenocarcinoma	Autoimmune gastritis
	Colorectal cancer	Crohn's disease, ulcerative colitis, bowel disease
	Nasopharyngeal carcinoma, Barrett's esophagus, gastrointestinal adenoma, ovarian cancer, thyroid cancer	Dermatomyositis
[5]	Lymphoma, lung cancer	Rheumatoid arthritis
[16]	lung cancer, Breast, prostate, bladder, rectal, hematological cancers	Scleroderma
[18, 19]	Hematological cancers: leukemia, HL and NHL, multiple myeloma	Systemic lupus erythematosus
	Solid cancers: cervical, bladder, gastric, lung, non-melanoma skin, thyroid, ovarian, hepatobiliary, vulva-vagina, cervix, pancreas, oropharyngeal cancer	
[15]	Liver, pancreatic, colorectal, endometrial, kidney cancers	Type 1 diabetes

Abbreviations: ALPS, autoimmune lymphoproliferative syndrome; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

Table 2: main characteristics of genes associated with immune-dysregulation diseases and elevation of cancer risk.

Somatic mutation in cancers	Cancer risk	Clinical penetrance	Main immune manifestations	LoF/GoF	Mutation characteristics	Gene
Childhood and adult T-cell leukemia; multiple myeloma; non-Hodgkin's lymphoma; urinary bladder cell carcinoma; non-small cell lung cancer; malignant melanoma; gastric cancer	B-cell and T-cell lymphoma	30%-90%	ALPS; splenomegaly; hepatomegaly; autoimmune cytopenias	LoF	Germline heterozygous mutation, and/or somatic mutation	FAS
NA	Esophageal SCC; NSCLC; Lung cancer; Breast cancer	NA	NA	NA	Functional polymorphism (GWAS):	FAS
Carcinoma; Melanoma; Neuroblastoma; Rhabdomyosarcoma; Osteosarcoma and Ductal breast carcinoma.	Lymphoma, multiple myeloma; gastric cancer, metastatic melanoma.	60%	ALPS like syndrome; autoimmune cytopenia; Atopic dermatitis; hypogammaglobulinemia; lymphoproliferation; and more	LoF	Germline heterozygous mutation	CTLA-4
Burkitt lymphoma, low-grade Epstein Barr virus positive (EBV+) marginal zone lymphoma, lymphomatous central nervous system pseudotumor, and dysplastic tubular adenoma and polyps	Lymphoma. Low risk: gastric cancer, malignant melanoma, Malignancies of the central nervous system	NA	Immunodeficiency, IBD-like enteropathy, and AID; ALPS like syndrome.	LoF	Germline homozygous or compound heterozygous mutation	LRBA
Renal, Pancreatic, Colorectal, Lung, Breast, and CNS cancers; Adenocarcinoma, Carcinoid, and Small-cell lung cancers.	NA	NA	NA	GoF	Somatic mutation	LRBA
NA	NA	Complete	SCID	LoF	Germline homozygous mutation	JAK3
T-ALL	NA	Not determine	CLPD-NK, lymphadenopathy, splenomegaly, and autoimmune symptoms	GoF	Germline heterozygous mutation	JAK3
NA	early-onset bladder carcinoma	Not known/incomplete	Innate immune deficiency (decline NK); mycobacterial infection sensitivity.	LoF	Germline homozygous mutation	JAK1
Acute leukemia, lung carcinoma, breast carcinoma	Elevate risk to hematological cancers.	Incomplete	Systemic immune dysregulation	GoF	Germline heterozygous mutation	JAK1
NA	NA	Not known	Sensitivity to mycobacterial and/or viral infections	LoF	Germline homozygous mutation	TYK2
NA	NA	100%	Probably lethal	LoF	Germline homozygous mutation	JAK2

Table 2. Continued

Somatic mutation in cancers	Cancer risk	Clinical penetrance	Main immune manifestations	LoF/GoF	Mutation characteristics	Gene
Myeloproliferative cancers. Polycythemia vera (95%); Essential thrombocytosis and primary myelofibrosis (50%); Chronic neutrophilic leukemia(20%); chronic myelomonocytic leukemia (3-13%); Juvenil chronic myelomonocytic leukemia (20%).	NA	incomplete	Familial myeloproliferative neoplasms	GoF	Germline heterozygous mutation	JAK2 (V617F)
Several cancer subtypes include Breast cancer; SCC; Renal cell carcinoma and Melanoma (6.93%)	elevate risk to different cancers (6%) and encourage tumor growth. SCC (4%), Gastrointestinal carcinoma (0.7%), laryngeal carcinoma (0.36%), melanoma (0.36%), and acute leukemia (0.36%)	High penetrance	Immune dysregulation, pathogens infection; autoimmunity	GoF	Germline heterozygous mutation	STAT1
T-LGL-leukemia (40%); CLPD-NK; Breast; Lung, Pancreatic; Head and neck; Prostate; ovarian; melanoma cancers.	Two cases were reported: Hodgkin's lymphoma and LGL leukemia.	82%	Early-onset multi-organ autoimmunity and lymphoproliferative disease	GoF	Germline heterozygous mutation	STAT3
NA	NA	High penetrance	Hyper IgE syndrome	LoF	Germline heterozygous mutation	STAT3
NR	NA	High penetrance	Dwarfism, Prominent forehead, Eczema, a high-pitched voice an Immunodeficiency	LoF	Germline homozygous mutation	STAT5B
NR	NA	NA	Growth failure and hyper-IgE syndrome	LoF	Germline dominant negative mutation	STAT5B
Breast and Liver cancer	NA	NR	NR	LoF	somatic mutation	STAT5B
Breast; Lung; Prostate; pancreatic and other hematological malignancies	NA	NR	NR	GoF	somatic mutation	STAT5B
Hematological malignancies mainly B cell precursor acute lymphoblastic leukemia (70%); T-ALL (4%); T Cell precursor ALL (13%). Lung; ovarian/ Liver; colorectal cancer	Risk factor to ALL	immune dysregulation—high penetrance; ALL-incomplete penetrance	PID; immune dysregulation; dysgammaglobulinemia; Autoimmune disease.	LoF	Germline heterozygous mutation	IKZF1

Table 2. Continued

Somatic mutation in cancers	Cancer risk	Clinical penetrance	Main immune manifestations	LoF/GoF	Mutation characteristics	Gene
NA	Risk factor to ALL	NA	Immune thrombocytopenia; Arthritis; systemic lupus erythematosus; antiphospholipid syndrome; inflammatory bowel disease (IBD)	NA	Polymorphism (GWAS)	IKZF1
1.13% of all cancers. Mostly Colon adenocarcinoma; Lung adenocarcinoma; Acute myeloid leukemia; Prostate adenocarcinoma; and endometrioid adenocarcinoma.	familial m—MDS (84%) and leukemia (AML-14%; CMML- 8%	Incomplete penetrance	Immunodeficiency with monocytopenia/NK/dendritic cells deficiency.	LoF	Germline heterozygous mutation	GATA2
Lymphoma; Gastrointestinal; Genitourinary; Gynecological; Thoracic; Head and neck cancers; Pancreatic adenocarcinoma.	Different cancers	NA	Immunodeficiency	GoF	Germline mutation	NFKB core components
NA	NA	NA	Syndromes with different variable symptoms and severe immunodeficiency	LoF	Germline mutation	NFKB core components
NA	Different skin tumors, hematological cancers	Incomplete penetrance	Familial Cylindromatosis	LoF	Germline heterozygous mutation	CYLD
T-ALL and CLL. Hepatocellular carcinoma; Uterine cervix carcinoma; kidney cancer; Colon; Breast; melanoma censers.	Different skin tumors, hematological cancers	Complete penetrance	Familial Cylindromatosis	LoF	Germline homozygous mutation	CYLD

LoF, loss of function; GoF, gain of function; NA, not available; NR, not relevant; ALPS, autoimmune lymphoproliferative syndrome; IBD, inflammatory bowel disease; AID, autoimmune disease; SCID, severe combined immune deficiency; CLPD-NK, chronic lymphoproliferative disorder; PID, primary immunodeficiency; SCC, squamous cell carcinoma; T-ALL, T-acute lymphoblastic leukemia; T-LGL-leukemia, T-large granular lymphocyte (LGL) leukemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; NSCLC, non-small-cell lung carcinoma; MDS, familial myelodysplastic syndrome; GWAS, genome-wide association study.

natural killer (NK) cell activation and are, therefore, unable to kill transformed cells [9, 27].

In contrast, HPV modulates the host immune response by diverse mechanisms including inhibition of IFN synthesis and signaling, decreasing T- and NK-cell cytotoxic responses, and evading the innate immune response. Thus, HPV disrupts immune surveillance and may trigger cancer, especially in IEIs, such as GATA2 deficiency, as the patients are prone to HPV infections [27, 28].

Disorders of apoptosis

The Fas cell surface death receptor, ALPS1A, APO-1, APT1, CD95, FAS1, FASTM, and TNFRSF6, belong to the tumor necrosis factor receptor (TNF-R) family. Fas and Fas-ligand (FasL) play a critical role in the immune response, particularly in killing pathogen-infected target cells, damaged cells, and autoreactive lymphocytes by triggering apoptosis [29]. Germinal and somatic mutations in *FAS* are the leading cause of autoimmune lymphoproliferative syndrome (ALPS) [30, 31], a rare condition characterized by defective apoptotic mechanisms that disrupt lymphocyte homeostasis. The apoptotic defects lead to chronic lymphadenopathy, hepatomegaly, and splenomegaly. ALPS is also characterized by expansion of double-negative (CD4-CD8-) T cells and autoimmune pathology, mostly autoimmune cytopenia [30–33].

Germline heterozygous pathogenic mutations in *FAS* cause 70% of genetically defined ALPS, whereas somatic heterozygous mutations account for 10% of cases. In some instances, there are germinal and somatic mutations. Other causes of ALPS are mutations in additional genes encoding proteins in the Fas–FasL pathway, such as those that participate in the death-inducing signaling complex (DISC) apparatus, the Fas natural ligand, *FASLG* (<1%), and *CASP10* (<1%). In approximately 20% of ALPS cases, the responsible gene has not been determined [32, 33].

Family studies suggest differences in the penetrance of the cellular phenotype, as expressed through defective Fas-mediated apoptosis and the clinical phenotype. Some individuals with *FAS* mutations present with defects in apoptosis at the cellular level almost as severe as in patients with ALPS but are clinically asymptomatic. Among individuals within a family, some have biomarker evidence of disease with no symptoms, whereas others have very mild disease symptoms (e.g. mild thrombocytopenia or very mild anemia). The clinical penetrance can range from 30% to 90% [19, 30, 32]. Thus, when diagnosing a pathogenic mutation in *FAS*, other asymptomatic family members should be assessed, as they may also be positive for this mutation.

There are two main FAS-dependent mechanisms that can lead to tumorigenesis: dysregulation of cell division and differentiation and disruption of apoptosis [18]. Fas is a cell surface receptor that initiates programmed cell death in activated lymphocytes. As such, it is not surprising that somatic mutations in *FAS* and *FASLG* in malignant cells are widespread in a broad range of cancers, preventing apoptosis of cancer cells and encouraging immortality [34]. Furthermore, inherited defects in the Fas–FasL pathway contribute to the development of lymphoma. Individuals with ALPS and pathogenic germline mutations in *FAS* are at 14-fold increased risk of non-Hodgkin's lymphoma (NHL) and 51-fold increased risk of Hodgkin's lymphoma (HL), with 15% cumulative risk before 30 years of age [18, 19]. Thus, lymphomas can occur at any age in ALPS-Fas, but there is a cumulative increase with age [19, 35, 36]. Individuals with *FAS* germline mutations are also at high risk of solid tumors [34, 37].

Functional polymorphisms in the FAS receptor–ligand pathway increase the risk of developing metastatic esophageal squamous cell carcinoma, affect the survival of patients with early-stage non-small cell lung cancer, and increase the risk for esophageal, breast, and lung cancers [38–42]. Loss of FAS receptor function results in loss of apoptosis and defines *FAS* as a tumor suppressor gene. Taken together, findings indicate that, in patients with lymphoma or other cancers who have a family history of ALPS, a genetic test for mutations in the FAS–FASL pathway is highly recommended. Similarly, in patients with ALPS who have mutations in the FAS–FASL pathway, genetic testing should be carried out within the family, starting with the proband's biologic parents if available. Thus, genetic testing will facilitate close monitoring and early diagnosis of cancer and treatment if needed.

Dysfunction of immune checkpoint pathways

Immune checkpoint receptor CTLA-4

CTLA-4 encodes cytotoxic T-lymphocyte-associated protein and is a key negative regulatory protein of the immune system. Following activation, CTLA-4 is expressed on the surface of T cells, attenuating T-cell activation. CTLA-4 is also expressed constitutively on induced and natural Tregs and helps maintain peripheral tolerance [43]. The link between CTLA-4 haploinsufficiency and autoimmunity has been demonstrated in mice lacking CTLA-4 [44] and in patients with haploinsufficiency. *CTLA-4* mutations cause several diseases of autoimmune and immune dysregulation, including autoimmune cytopenia (62%), atopic dermatitis (56%), hypogammaglobulinemia (84%), lymphoproliferation (73%), sinopulmonary infections and lymphocytic interstitial lung disease (68%), and inflammatory bowel disease (IBD; 59%) [43, 45–47]. The penetrance of CTLA-4 haploinsufficiency with autoimmune infiltration disease is incomplete, with an estimated 40% of family members with variants in *CTLA-4* appearing clinically healthy [48]. CTLA-4 insufficiency due to heterozygous mutations can cause ALPS-like syndrome, which is clinically similar to ALPS and elevates cancer risk [49]; 12.9% of patients with haploinsufficiency *CTLA-4* mutations develop various cancers, including lymphoma (7.6%-8.8%), multifocal gastric cancer (3.3%-3.8%), multiple myeloma (0.7%), and metastatic melanoma (0.7%) [46, 50, 51].

CTLA-4 is an immune checkpoint receptor involved in the immune suppression signal via the induction of Tregs. Therefore, checkpoint inhibitors that block CTLA-4 are in use as anti-cancer therapies [20, 21]. Paradoxically, genetically predisposed patients with CTLA-4 haploinsufficiency are at increased risk of cancer development. Two major mechanisms can explain this paradox. First, a deficiency in CTLA-4 causes unbalanced lymphoproliferation, leading to hematological cancers. Second, the inflammation triggered by host-intrinsic immune dysregulation initiates tumorigenesis and causes malignancies, such as gastric cancer [22, 23].

LRBA encodes the LPS-responsive beige-like anchor protein

LPS responsive beige-like anchor (LRBA) is involved in vesicle trafficking that regulates CTLA-4 turnover in endosomes

and helps maintain an intracellular vesicular pool of CTLA-4 for immediate mobilization to the cell surface after T-cell activation. Loss of LRBA leads to the degradation of CTLA-4 vesicles by lysosomes. Thus, LRBA deficiency causes a secondary loss of CTLA-4. Homozygous or compound heterozygous germline mutations in *LRBA* have been linked to diseases of immune dysregulation, including immunodeficiency, IBD-like enteropathy, and autoimmune disease [48, 52].

Similar to CTLA-4 insufficiency, LRBA deficiency syndrome can cause ALPS-like syndrome, including all of the symptoms of ALPS, elevating the risk for lymphomas [49]. In a long-term retrospective analysis of patients with LRBA deficiency, malignancies occurred in 3.9% of patients. Over a median follow-up of 10 years, one patient developed gastric cancer (at 19 years of age) and malignant melanoma (at 27 years of age), and two patients had malignancies of the central nervous system (CNS): an astrocytic tumor and CNS lymphoma [53, 54].

Therefore, in patients with hematological or other cancers, including gastric cancer, melanoma, and malignancies of the CNS, who have a self or familial history of immune diseases, genetic testing of *CTLA-4* and *CTLA-4* pathway genes is recommended.

Disruption of cell surface signaling

The JAK-STAT pathway

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway play a significant role in signal transduction and orchestration of the immune system [55]. Jak/STAT dysfunction impacts immunodeficiency, susceptibility to infection, autoimmunity, and protection against cancer [56].

JAKs play an essential role in the regulation of cytokine signaling. They control cell survival, proliferation, differentiation, immune responses, and hematopoiesis [57]. The mammalian JAK family has four protein members, including three JAKs (JAK1-3) and tyrosine kinase 2 (TYK2), which selectively bind to the cytoplasmatic chain of different cytokine receptors, such as IL-12 and IFNγ. After ligand binding, the JAK-kinase enzyme is activated and undergoes auto-phosphorylation, which leads to selective trans-phosphorylation of transcription factors from the signal transducers and activators of the transcription (STAT) family. These, in turn, translocate to the nucleus and regulate the transcription of various inflammatory cytokine genes [58, 59].

Mutations in JAK family proteins are related to several immune-related diseases [56, 58]. A homozygous mutation in *JAK3* causes severe combined immune deficiency (SCID) [59–62], and *JAK1* loss of function (LoF) leads to innate immunodeficiency, which mainly results in a decrease in NK cells and increased sensitivity to mycobacterial infections [63, 64]. A *JAK1* gain-of-function (GoF) mutation causes systemic immune dysregulation [65], an autosomal recessive pathogenic variant with a complete absence of TYK2 causes mycobacterial and viral infections [66], and JAK2 plays a critical role in the maintenance and function of adult hematopoietic stem cells [67].

During the last few years, dysregulation of JAK signaling has been associated with hematological malignancies, and even solid tumors [57]. Somatic mutations in the JAKs have increasingly been recognized in primary oncogenic lesions [56]. *JAK2* mutations have been identified in hematological neoplasms, mainly in myeloproliferative diseases, including polycythemia vera, essential thrombocythemia, primary myelofibrosis, and leukemia [68]. Although most myeloproliferative neoplasms are sporadic, there are also familial cases. In this context, first-degree relatives of patients with myeloproliferative neoplasm were found to have a 5- to 7-fold increased risk of developing myeloproliferative cancer [69].

JAK2 abnormalities, including chromosomal abnormalities (trisomy, translocation, and insertion/deletion) and point mutations, have been found in hematological cancers. The majority of these abnormalities affect the inhibitory domain of JAK2, leading to constitutive activation of the kinase and subsequent aberrant engagement of downstream signaling pathways [68, 70]. The *JAK2* V617F somatic mutation is present in most patients with myeloproliferative cancers. This mutation can be found in 95% of patients with polycythemia vera, approximately 50% of patients with essential thrombocytosis and primary myelofibrosis, 20% of patients with chronic neutrophilic leukemia, 3%-13% of patients with chronic myelomonocytic leukemia, and 20% of patients with juvenile chronic myelomonocytic leukemia [68–70]. Interestingly, a germline mutation in *JAK2* V617F was associated with an elevated risk of myeloproliferative neoplasms in individuals harboring this mutation [69–71].

JAK1 has a significant impact on the homeostatic numbers of NK cells. According to Witalisz-Siepracka et al., an LoF mutation in *JAK1* leads to a decline in NK cell numbers and interferes with immune surveillance. According to this study, the loss of one *JAK1* allele is sufficient to impair the control of tumor growth [63]. Patients with a biallelic homozygote germline mutation in the *JAK1* gene suffer from a lack of functional JAK1 and have early-onset bladder carcinoma, indicating the role of JAK1 in the immunological surveillance of cancer [64].

Overall, it appears that homozygous LoF mutations in JAK genes can be lethal (*JAK2*) or highly debilitating (*JAK3*, in severe combined immunodeficiency). Furthermore, heterozygous GoF mutations in JAK genes can give rise to hematological cancers, such as myeloproliferative neoplasms [72].

Disruption of STAT proteins

The STAT family of proteins includes seven cytoplasmic transcription factors that regulate cellular proliferation, apoptosis, angiogenesis, malignancy, and the immune response. These proteins participate in the pathogenesis of inflammatory, autoimmune, and neoplastic diseases due to their involvement in diverse signaling events downstream of IL and growth factor receptors. Several STAT proteins are linked to cancer pathology. For example, constitutively active STAT1, STAT3, and STAT5 are found in breast, lung, prostate, and pancreatic cancers, as well as hematological malignancies. The upregulation of these STAT signaling pathways promotes tumor growth and survival due to increased cell proliferation, migration, invasion, inhibition of apoptosis, and dysregulated immune surveillance [73–75].

STAT1

STAT1 is a transcription factor activated by type I and type II IFNs. GoF mutations in *STAT1* elevate functions known to be associated with dominant syndromes of immune deficiency, including chronic mucocutaneous candidiasis, mycobacteriosis recurrent respiratory infections, immune

dysregulation, and autoimmunity [76, 77]. STAT1 activates genes that mediate immune functions, such as antiviral/anti-pathogen signals, suppression of cell proliferation, and induction of apoptosis. As a result, STAT1 signaling is generally considered a tumor-suppressive pathway [78]. Conversely, accumulating evidence indicates that increased STAT1 activation leads to increased tumor progression in multiple types of cancer. Some of the IFN-stimulated genes are likely tumor promoters and type I IFN can protect cancer cells from CD8 + T-cell-mediated toxicity by upregulating the immune checkpoints and downregulating anti-apoptotic signaling [79]. Moreover, STAT1 induces pro-inflammatory cytokines, such as TNF-α, TGFβ, IL-13, and IL-4, and recruits suppressive granulocytic MDSCs to the tumor microenvironment, which suppress immune cell functions and promote a microenvironment that supports tumor formation [80, 81]. In a mouse model of late-stage mammary carcinoma, researchers showed that *STAT1* overexpression promotes aggressive tumor growth, whereas gene knockdown of *STAT1* significantly delays tumor progression [80]. Notably, somatic overexpression of *STAT1* has been found in several cancers. In melanoma, *STAT1* is the most frequently mutated gene in the STAT family [73]. Overexpression of *STAT1* in human breast cancer is related to increased disease progression from ductal carcinoma *in situ* to invasive carcinoma [80].

Interestingly, some patients with germline *STAT1* GoF mutations have various kinds of cancers, including squamous cell carcinoma (4%), gastrointestinal carcinoma (0.7%), laryngeal carcinoma (0.36%), melanoma (0.36%), and acute leukemia (0.36%), with an overall cancer rate of 5.8% [82]. In one family with GoF mutations, 2 out of 4 family members had nodular lymphocyte-predominant Hodgkin's lymphoma (NHLPL) [83].

From the above, it seems that individuals with a GoF mutation in *STAT1* have an increased risk of cancer [79].

STAT3

STAT3 is involved in the regulation of immune cell activation and differentiation. This transcription factor plays a significant role in several critical cellular processes, including the cell cycle, cell proliferation, cellular apoptosis, and tumorigenesis, and has been heavily implicated in cancer. A GoF germline mutation in *STAT3* leads to an early-onset autoimmune and lymphoproliferative disease, whereas an LoF mutation in *STAT3* causes hyper-IgE syndrome (HIES) [84–87]. The average age of onset of first symptoms in the GoF disease is 3 years, but not all mutation carriers become symptomatic, with a penetrance rate of 82% [86].

Constitutive activation of STAT3 via somatic mutations is relevant in the oncogenesis of both solid and hematopoietic cancers. Persistent activation of STAT3 followed by STAT5 is frequently detected in human tumor tissues, including breast, lung, pancreatic, head and neck, prostate, ovarian, melanoma, and pancreatic cancer cells [74]. However, hyperactive STAT3 in tumors is mainly associated with T-cell large granular lymphocytic (T-LGL) leukemia (40%) and chronic NK lymphoproliferative disorders (CLPD-NK). Patients with T-LGL leukemia are often characterized by autoimmunity and autoimmune cytopenia. In these patients, germline mutations in *STAT3* should be detected [73, 86, 88]. Recently, *STAT3* GoF germline mutations have been reported in two cases of malignancy. One adult patient had early childhood-onset autoimmune thrombocytopenia and late-onset HL, and

one patient developed LGL leukemia at 14 years of age [85, 87]. Whether the influence of germline *STAT3* GoF variants is similar to the impact of somatic LGL variants regarding proliferation and impaired apoptosis is still unknown. Given the young average age of patients with *STAT3* GoF mutations and patients with LGL leukemia, and the fact that some of the *STAT3* GoF carriers are asymptomatic, long-term follow-up is crucial to understanding the risk of malignancy in *STAT3* GoF syndrome.

STAT5

STAT5 plays a crucial role in the development of the mammary gland and immune system homeostasis. In various cancers, aberrant expression of STAT5 results in increased cell proliferation, survival, and metastasis. There are two isoforms, STAT5a and STAT5b, with more than 90% peptide sequence identity. However, due to structural differences in the C-terminal region, the two genes have a redundant and non-redundant functions [89]. STAT5 plays a critical role in regulating hematopoiesis and is responsible for the proliferation, differentiation, and apoptosis of hematopoietic cells in response to IL-3 signaling [90]. Aberrant regulation of STAT5b has been reported to cause or correlate with autoimmune disorders, such as systemic lupus erythematosus (SLE), and various cancers by overexpression of the anti-apoptotic protein Bcl2 [91]. However, no disorders associated with a germline mutation in *STAT5a* have been reported. Another critical function of STAT5 in immune surveillance and auto-immunity is to regulate Forkhead box protein P3 (FoxP3) for the development and function of regulatory T cells [75, 92]. Recently, aberrant STAT5 signaling, due to constitutive activation or lack of activity, in combination with constitutive activation of STAT3 has been found to contribute to tumor aggressiveness and cancer progression in various cancers, including breast, colorectal, lung, prostate, liver, and hematological malignancies. Different combinations of STAT3 and STAT5 activity have been shown to contribute differently to cancer progression and, in different situations, STAT5 can act as a tumor suppressor or an oncogene [75].

The importance of STAT5 in the pathology of many hematological cancers is related to its role in the regulation of hematopoiesis. STAT5 is often constitutively activated in various leukemias, including acute/chronic myeloid leukemia (AML/CML), acute lymphoblastic leukemia (ALL), and peripheral T-cell lymphoma (PTCL). Notably, in AML, STAT5 is constitutively activated in 70% of patients [75].

A few *STAT5* germline mutations have been found in patients. Homozygous missense or nonsense mutations with no expression of *STAT5b* result in an autosomal disorder characterized by dwarfism, prominent forehead, eczema, high-pitched voice, and immunodeficiency. Dominant-negative germline mutations in *STAT5b* lead to growth failure and HIES [93, 94]. A hyper-activated *STAT5* variant in humans has not yet been reported. Transgenic mouse models that express an activated *STAT5b* mutation (N642H) in the hematopoietic compartment rapidly develop T-cell neoplasms [93, 95]. However, this gene should be included in the hereditary hematopoietic malignancy gene panel due to its impact on the development of cancers and its influence on transgenic mouse models.

Dysfunction of phosphatidylinositol 3 kinases

Other important signal transduction proteins are the phosphatidylinositol 3 kinases (PI3Ks). Activation of PI3K

is critical for lymphocyte survival, proliferation, and activation. PI3Ks contain two subunits: a catalytic subunit, p110, and a regulatory subunit. In immune cells, the most abundant isoform is p110d. GoF autosomal-dominant variants in *PIK3CD*, which encodes p110d, cause activated PI3K-delta syndrome (APDS1), whereas variants in the PIK3R1 gene, which encodes the p85a regulatory subunit of PI3Kd, cause a similar syndrome, ADPS2.

APDS1/2 are immunodeficiency syndromes combined with autoimmunity. Chronic respiratory and viral infections are the most common feature of APDS. The autoimmune phenotypes including increased autoantibodies, lymphoproliferation, cytopenia, and gut and lung lymphoid aggregation [96–98].

One of the characteristics of APDS, observed in 75% of patients, is non-neoplastic lymphoproliferation including lymphadenopathy, splenomegaly, and hepatosplenomegaly. Approximately 13% of APDS patients develop lymphomas. Reinforcement of this finding was observed in a mouse model harboring a GoF mutation in PI3K; 20% of the mice developed spontaneous pre-malignant and/or tumors at 10-14 months of age [98]. The formation of tumors in APDS may result from higher proliferation, altered metabolism, and/or reduced apoptosis of B lymphocytes, which allow the accumulation of mutations in tumor suppressor and/or oncogenes. Defective tumor surveillance by T cells may also contribute to oncogenesis [96–98].

Hematopoietic defects

IKZF1

The Ikaros family zinc finger 1 gene (*IKZF1*) encodes the transcription factor Ikaros, which is broadly expressed in hematopoietic cells. Ikaros acts as an essential transcription factor in controlling and regulating lymphocyte differentiation, proliferation, and self-tolerance [99, 100]. It is also expressed in other cell lineages, including myeloid, plasmacytoid dendritic cells (pDCs), megakaryocytes, and erythroid cells [101, 102]. Germline heterozygous *IKZF1* mutations are associated with immune dysregulation, dysgammaglobulinemia, B-cell deficiency, hematological abnormalities, and autoimmune diseases. Based on genome-wide association studies, polymorphisms in *IKZF1* are also associated with several autoimmune diseases, such as immune thrombocytopenic purpura, arthritis, SLE, antiphospholipid syndrome, IBD, and primary Sjoègren's syndrome [99–101, 103].

IKZF1 acts as a critical regulator of lymphoid differentiation and as a tumor suppressor gene [104, 105]. Somatic genetic alterations in *IKZF1* are common in different childhood and adult hematological malignancies, mainly in B-cell precursor acute lymphoblastic leukemias [104, 106]. *IKZF1* defects occur in more than 70% of BCR-ABL1-positive and BCR-ABL1-like cases of acute lymphoblastic leukemia, ~4% of T-cell acute lymphoblastic leukemia (T-ALL), and ~13% of early T-cell precursor ALL [104, 107, 108]. In addition, Ikaros has been demonstrated to be involved in the progression of many solid tumors, including lung, ovarian, liver, and colorectal cancer [100].

In recent years, a coding germline variation in *IKZF1* was reported to be a risk factor for a genetic predisposition to ALL. Most germline variants are LoF variants or dominant-negative variants and, therefore, adversely affect *IKZF1* function [100, 109]. It seems that *IKZF1* haploinsufficiency

promotes tumorigenesis in a process that involves the accumulation of additional genetic alterations, including second hits that interfere with lymphoid development [108]. Importantly, identified variants in *IKZF1* also reduce the drug responsiveness of leukemic cells, possibly affecting the treatment of patients [100, 109]. Studies in families with germinal variants in *IKZF1* demonstrate high penetrance of immune dysregulation, mainly a progressive loss of serum immunoglobulins and B cells and incomplete penetrance of ALL [109, 110].

GATA2 deficiency

GATA2 is a zinc finger regulatory transcription factor that controls hematopoiesis by regulating the maintenance and self-renewal of hematopoietic stem cells. It is critical in stimulating differentiation to progenitors and mature blood cells. Unregulated hematopoiesis and differentiation is a common oncogenic mechanism [4–6].

GATA2 deficiency, a germline disease characterized by a broad spectrum of phenotypes, includes immunodeficiency with monocytopenia; B, NK, and dendritic cell deficiencies; common mycobacterium, fungal, and viral infections; cytopenias; myelodysplasia; myeloid leukemias; pulmonary alveolar proteinosis; and lymphedema [111]. The penetrance of this syndrome is highly variable, with unpredictable presentations in children and adults. Some of those harboring *GATA2* mutations are asymptomatic, though one of their family members will likely have a GATA2 deficiency syndrome [112].

Somatic *GATA2* mutations are found in 1.13% of all cancers. The most considerable prevalence of alterations is in colon adenocarcinoma, lung adenocarcinoma, acute myeloid leukemia, prostate adenocarcinoma, and endometrial adenocarcinoma [113].

GATA2 mutations are associated with distinct leukemogenic mechanism. GATA2-deficient patients with germline mutations are at an increased risk of developing familial myelodysplastic syndromes (Emberger syndrome), MDS (84%) and leukemia (AML-14%; CMML- 8%), based on the characterization of the clinical features of a large cohort of patients with GATA2 deficiency [114].

Most of the mutations (74%) are missense mutations in one of the two Zink finger domains (ZF1/2) and cause impaired binding to GATA-DNA motifs. The other mutations are mostly nonsense or frameshift mutations located outside the ZF domains and reduce the overall expression of GATA2 protein. Both are loss of function mutations [115].

Abnormal transcriptional control of inflammatory genes

The nuclear factor-kappa B (NF-κB) signaling pathway is a multi-component pathway involved in many critical cellular processes, including cell proliferation and survival, apoptosis, innate immunity, and inflammation. The NF-κB transcription factor family comprises five members and multiple regulatory IKb proteins that, together, regulate the expression of hundreds of genes: p50/p105 encoded by *NFKB1*, p52/p100 encoded by *NFKB2*, c-Rel encoded by *REL*, RelA (a.k.a. p65) encoded by *RELA*, and RelB encoded by *RELB*. Therefore, as expected, pathogenic mutations in different proteins along the NF-κB pathway cause many diseases, mainly those associated

with immune dysregulation. The mutations can be germline or somatic, GoF, or LoF resulting from copy number variants due to gene amplification or deletions, point mutations, and chromosomal translocations [116].

Deregulated IKK and NF-κB activities contribute to tumorigenesis in two ways: by triggering anti-apoptotic and pro-proliferative responses and by initiating inflammatory cytokine secretion. Some of the NF-κB subunits are proto-oncogenes, including c-Rel and RelA. Overexpression of NF-κB leads to chronic inflammation and, therefore, can cause cancer and/or autoimmune diseases [117, 118]. Constitutively activated NF-κB has been detected in various malignancies, including lymphoma, gastrointestinal, genitourinary, gynecological, thoracic, head, and neck tumors [119]. Overexpression of several NF-κB subunits has been described in pancreatic adenocarcinoma [118]. Notably, activated NF-κB in a tumor is not necessarily the initiating cause. Thus, mutations in different genes along the NF-κB pathway can be involved in immune dysregulation and cancer [117, 118].

Most germline LoF mutations in the core signaling components of the NF-κB pathway cause a syndrome with different variable symptoms and complete penetrance. For example, a pathogenic mutation in the regulatory subunit NF-κB essential modulator gene (*NEMO*) causes a syndrome that can include incontinentia pigmenti, dental abnormalities, ocular problems, hair defects, and sometimes even CNS dysfunction. A mutation that does not eliminate NF-κB function can cause anhidrotic ectodermal dysplasia with severe immunodeficiency [116]. Thus, finding such a mutation in asymptomatic patients who developed cancer is less reasonable.

However, a mutation in some of the genes in the NF-κB signaling pathway may elevate the risk of cancer development. For example, CYLD is a negative regulator protein of the NF-κB signaling pathway and the mitogen-activated protein kinase (MAPK) pathway. Pathogenic mutations in *CYLD* cause familial cylindromatosis, an autosomal dominant disease characterized by the formation of benign tumors, approximately 90% on the head and neck [116, 120], multiple familial trichoepithelioma, Brooke-Spiegler syndrome, and other skin tumors [121, 122]. Homozygous cases are more severe, with 100% penetrance, but clinical severity, tumor location, and types may vary among homozygous and heterozygous patients [123]. Approximately 70% of familial cylindromas exhibit loss of heterozygosity (LOH) around the tumor and have the genetic attributes of a tumor-suppressor gene [120, 121]. Most *CYLD* mutations identified in cylindromatosis are frameshift or nonsense mutations that remove all or part of the catalytic domain of CYLD. The mechanism by which CYLD inactivation contributes to tumorigenesis is chronic NF-κB activation leading to chronic inflammation [116, 124]. LOH of *CYLD* is not clearly associated with any known cancer. However, accumulating evidence indicates that the lack of CYLD may promote the development of other cancers, mainly hematological malignancies, because CYLD regulates the proliferation, development, and activation of lymphoid cells. *CYLD* mutation is widespread in multiple myeloma, with a high frequency of LOH in chromosome 16q, including *CYLD*. *CYLD* LOH in myeloma highly correlates with poor prognosis. Its expression is also significantly reduced in other hematological malignancies, such as acute T-lymphoblastic leukemia and chronic lymphocytic leukemia. Abnormalities in CYLD have been recognized in some solid tumors, including hepatocellular carcinoma, uterine cervix carcinoma, and renal cancer. Reduced expression of *CYLD* has also been detected in the colon, breast, hepatocellular carcinomas, melanoma, and other solid tumors [121, 122].

Conclusions and future directions

The immune system plays a critical role in identifying and eliminating tumors, a process called immune surveillance [125, 126]. Thus, immune dysregulation can elevate the risk of cancer development. The penetrance of clinical symptoms is diverse, and some asymptomatic individuals carry variants with no immune abnormalities, whereas other patients with the same variants present with evidence of disease. These asymptomatic individuals may develop symptoms later in life and have autoimmune diseases and/or cancer with late onset. There is a need for long-term surveillance of autoimmune disease and cancer in patients and families with mutations in genes known to cause immune dysregulation.

Typically, genetic counseling for patients with cancer concentrates on known genes that increase the risk of cancer. However, there is a significant number of missing genetic diagnoses. We hope our review illuminates the need for prompt workups in select patients with immune dysregulation.

Clinicians should use proper genetic and immune diagnostic tools in patients with IEIs or cancer with a strong family history. This constitutes flow cytometry of lymphocyte subsets, immunoglobulin levels, including IgG titers to past vaccines, and flow cytometry of other targeted lymphocyte subpopulations, such as Tregs and Th17. Complementing the immune workup with next generation sequencing, such as whole exome sequencing, will offer better genetic diagnosis and counseling. Moreover, patients can be treated with targeted biological treatment, such as abatacept for LRBA deficiency, and hematopoietic stem cell transplantations. Surveillance for cancer development will be part of the follow-up for these patients. For example, annual bone marrow biopsies for GATA2-deficient patients, who are prone to cytogenetic abnormalities, myelodysplastic syndrome, and myeloid leukemia, will reduce mortality and morbidity, and promote early detection of cancer in these patients.

Conflict of Interest

The authors have no competing interests to report.

Data Availability

Data is available upon request from the corresponding author.

Author contributions

S.P.—writing of manuscript and review of the literature, OS-manuscript design and supervision.

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Not applicable.

Clinical trial registration

Not applicable.

Animal research adheres to the ARRIVE guidelines

Not applicable

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