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Review Article

Immune surveillance and lymphoid malignancy in immunocompromised host

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Abstract: Immune surveillance is a dynamic process that involves an intact immune system to identify and protect the host against tumor development. The increased understanding of the genetics, infections and hematological malignancies in congenital immune deficiency states supports the concept that impaired T cells and Natural-killer/T cells leads to B-cell lymphoma. Furthermore, severe combined immunodeficient mice are prone to spontaneous tumor development and therefore serve as experimental models. Here we discuss the acquired conditions and mechanisms involved in dysregulation of the immune system that lead to lymphoma. Preemptive strategies to improve immune regulation and response and restore a competent immune system may lead to a decrease in lymphoid malignancies.

Keywords: Lymphoma, immune surveillance, immune deficiency

Introduction

Over the past several decades the incidence of lymphoma has increased drastically from 6.9 per 100,000 in the 1950's to 19.6 per 100,000 in 2008. Part of this change is reflected in the HIV/AIDS epidemic of the 1980's and more efficient diagnostic practices likely play some role in this change, however do not fully explain the increase in incidence. This review will aim to focus on the development of lymphoma in the setting of dysregulation of the immune system, particularly in the setting of HIV, autoimmune disorders, or post-transplantation. The human immune system is a complicated system of checks and balances that allows for control of response to pathogens while allowing for self-tolerance. There are several known conditions which cause dysregulation of this balance, leading to an increased risk of uncontrolled response and proliferation, presenting as lymphoma or lymphoproliferative disorders. Particularly in this process, the B-cell is of utmost importance; in a properly functioning immune system, B-cells function as precursors to antibody producing plasma cells and play an important role in antigen presentation. Furthermore they function to regulate T-cell subset activation and anergy, production of cytokines and chemokines, as well as auto regulation of their own activation. Modern medical therapy such as that associated with stem cell transplantation (SCT) and solid organ transplantation lead to dysfunction in the host immune system by aggressive immunosuppression. Diseases such as human immunodeficiency virus (HIV) and autoimmune disorders such as systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) lead to chronic activation of the immune system and increased proliferation. In order to more effectively treat hematologic malignancies associated with these conditions it is important to understand the pathogenesis of immune derangement and thereby more effectively target therapy (**Figure 1**).

Regulation of normal lymphocyte development

Lymphocyte development and maturation occur in the bone marrow or thymus in various stages. The antigen mediated differentiation of B cells is mediated by changes in gene expression that

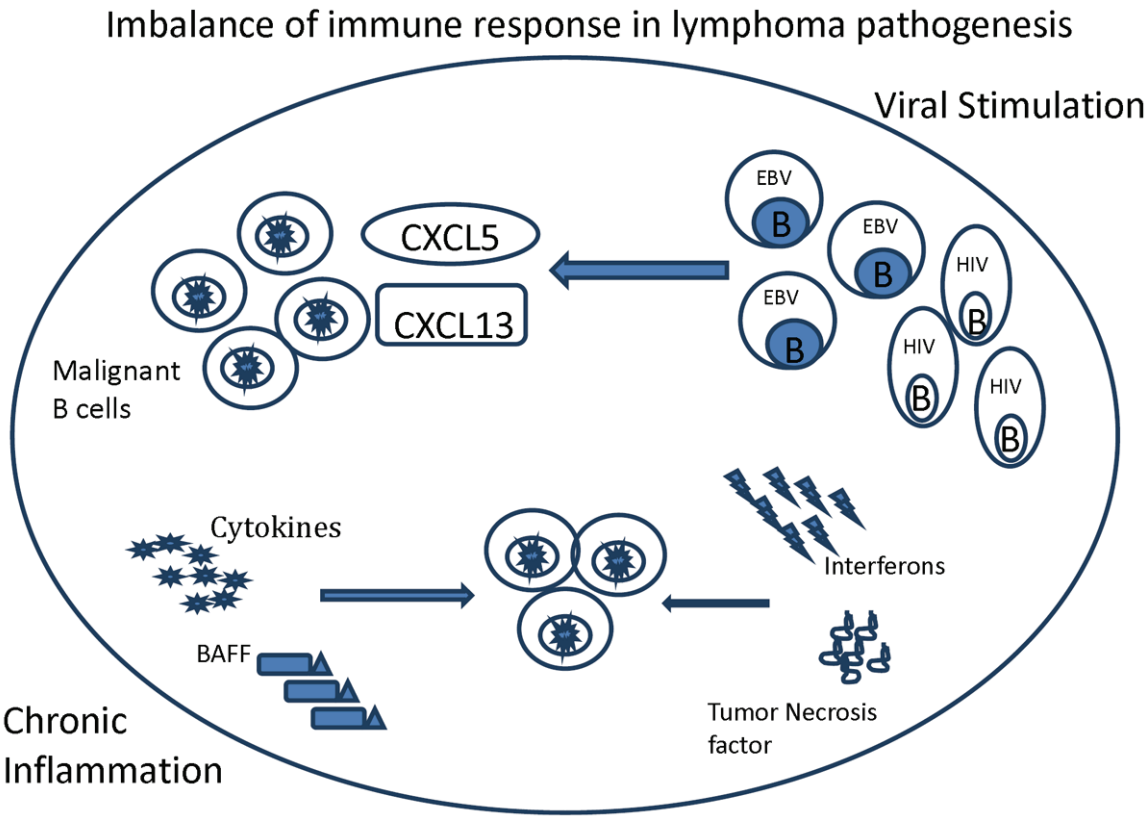

Figure 1. Interaction between CCR5 with its ligand CCL5, promotes B-cell activation. The cytokine milieu plays an important role in the immortalization and survival of EBV infected cells. In a state of chronic inflammation, such as autoimmune conditions, it is presumed that a common multistep -process that eliminates checkpoints that prevent uncontrolled B-cell clonal expansion is involved.

give rise to the germinal center reaction. The clonal expansion of B cells, class switch recombination at the IgH locus and somatic hypermutation of VH genes occurs in the germinal center via activation- induced cytidine deaminase. (AID). AID can also collaborate with other enzymes to generate chromosomal translocations involving c-myc and the IgH locus in some B-cell lymphomas. Lymphocyte development requires a harmonious network of cytokines and transcription factors that regulate gene expression. Interleukin-7 (IL-7) is a cytokine for murine B-cell development that promotes V to DJ rearrangement and mediates survival/proliferation signals. The ligation of CD40 by activated T-cells and Interleukin-21 play a key role in B cell development [1]. Transcription factors such as E2A, EBF and PAX5 regulate the early stages of B-cell development and differentiation. Pax5-deficient mice have an arrest in B-cell development at the transition from DJ to VDJ rearrangement. Similarly, cytokines are centrally important for T cell maturation and function. Immune stimulatory and suppressive cytokines regulate T cell growth. Helper T cells secrete cytokines such as Interleukin 4 and 5 that promote B ell development. Regulatory T cells (Treg) and natural killer cells also regulate immune responses and may prevent chronic or potentially damaging immune responses. Therefore the magnitude of immune regulation is determined by the balance between lymphocyte activation and the ability to dampen a response.

Immune dysregulation in acquired conditions

Association of HIV and lymphoma

Development of lymphoma is a well-documented cause of morbidity and mortality in patients with HIV. The historical incidence of NHL is a startling 70- to 200-fold higher in the HIV seropositive population [2-4]. Fortunately, since the advent of highly active anti-retroviral therapy (HAART) in the 1990's, the incidence of lym-

phoma has decreased. The COHERE study, a multi-cohort European study, revealed a decreased incidence of around 50% when comparing patients patient's receiving HAART with those who were not [5]. As reported by Besson et al. the incidence of systemic lymphoma and primary CNS lymphoma (PCNSL) rose from 15.6 to 253.8 per 10,000 patient-years and 2 to 93.9 per 10,000 patient years respectively when CD4 count of greater than 350 cells/μL were compared to less than 50 cells/μL. Since HAART therapy aims to maintain CD4 count above 350 cells/μL, it has aided in reducing incidence of those lymphomas most commonly seen with low CD4 counts, such as PCNSL [6]. Furthermore, prior to the advent of HAART, those patients being treated with chemotherapy required reduced dose therapy secondary to their numerous co-morbidities [7]. However despite the changes brought about by HAART therapy, malignancy still is a major cause of mortality amongst the HIV population with documented rates of cancer related death as high as 30% [8]. The most recent World Health Organization update on lymphoma has divided HIV-related lymphoma into 3 distinct categories. The first category is NHL subtype which also occurs in immunocompetent hosts such as diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), MALT lymphoma, and the rare peripheral T/NK cell lymphoma. The second group involves lymphomas specifically seen in the HIV population including primary effusion lymphoma (PEL), plasmablastic lymphoma, and Castleman's disease. The last grouping is lymphoma occurring in other immunodeficiency states which includes Polymorphic B-cell lymphoma, similar to post-transplant lymphoproliferative disorders [9].

The pathogenesis behind the increased incidence of NHL is thought to be secondary to two mechanisms, namely loss of immune control of viruses, namely Epstein Barr Virus (EBV) and chronic B-cell activation from HIV infection. The role of EBV in lymphomagenesis has been well documented, with almost 100% of endemic African BL being EBV positive [10]. Certainly the role of immunosuppression plays a role in the oncogenicity of EBV, given that all PCNSL tumors are EBV positive and found typically in patients with low CD4 counts. However up to 30-50% of DLBCL and BL are also EBV positive and found in patients with relatively intact immune systems [11]. EBV in its active phase is the causative agent behind infectious mononucleosis, however the virus also causes latent infection of B lymphocytes [12]. To facilitate immune evasion in its latent phase EBV expresses a combination of nuclear antigens (including EBNA-1, -2), latent membrane proteins (LMPs), and small non-coding RNAs [13]. EBV can maintain 3 different latency patterns, of which Type III latency is most important in HIV-related and PTLD. In Type III latency all EBV antigens are expressed of which EBNA-2, -3A, -3C, and LMP1 have been found to be essential in *in* vitro studies. Several methods for EBV contributions to lymphomagenesis in its latent phase have been proposed, firstly by inducing DNA damaging activities by inducing somatic hypermutation (SHM) of the Ig variable genes of naïve B-cells [14, 15]. Aberrant SHM cause mutations in multiple proto-oncogenes causing amino acid substitutions with functional changes that lead to the pathogenesis of malignancy [16]. Secondly, EBV intracellular viral proteins such as EBNA2 and LMP1 upregulate the NF-κB pathway, cause overexpression of Bcl-2, and promote B-cell peripheral survival [17]. EBV induces certain cellular microRNA (miRNA) targets, notably mir-127 which plays a large role in regulating Bcl-6 and c-MYC expression [18]. Lastly EBV latency proteins promote genomic instability that lead to DNA breaks, and enhance the propagation of damaged DNA, by impairing cell cycle check points. This genomic instability caused by EBV leads to tumorigenesis [19].

There appear to be multiple levels at which the HIV virion itself contributes to the development of NHL. As disease progresses HIV reduces ability of the immune system to clear EBV-infected cells. Notably, in a study by van Baarle *et al.* it was shown that there was a significant decline in telomere length of EBV specific CD8 cells when compared to HIV negative patients indicating a reduced ability to mount an immune response [20]. Furthermore, HIV leads to chronic B-cell activation via persistent infection. It appears that gp120 on the surface of HIV cells is able to drive B-cell activation via class-switch reactions [21]. It was further demonstrated that HIV virions are able to acquire CD40L [22] which through interaction with CD40 upregulates activation-induced cytidine deaminase, an enzyme which is necessary for SHM and class switching. It has also been implicated as

a promoter of c-MYC/IgH translocations seen in genesis of germinal center lymphomas [23]. Research into genetic polymorphisms, most specifically regarding co-receptors for HIV entry, notably CCR5, has further delineated the role of the HIV virion in lymphomagenesis. Homozygous mutation of the CCR5 receptor is protective against HIV infection whereas heterozygotes show slower progression of disease. Notably heterozygotes also have decreased incidence of HIV-related NHL which appears to be independent of disease progression [24]. Recent pooled data excluding HIV patients revealed a decreased risk of DLBCL and FL in patients with CCR5 heterozygosity [25]. Interaction between CCR5 with its ligand CCL5, also known as RANTES, promotes B-cell activation. It is postulated that the mutation in CCR5 prevents this interaction, decreasing chronic B-cell activation via this pathway and thereby reducing risk of progression of NHL. HIV also causes an inflammatory milieu which further drives the activation and proliferation of B lymphocytes. Specifically levels of soluble CD30 have been noted to be elevated prior to diagnosis of NHL in HIV patients [26]. Other cytokines have also been implicated in this process, notably IL-6, IL-10, and TNF-α [27, 28] (**Figure 1**). Cytokine dysregulation, chromosomal translocations, single nucleotide polymorphisms in tumor suppressor genes, altered endothelial function are key factors in lymphomagenesis in HIV infected patients. Finally it is important to recognize that diverse pathogenetic pathways that are unique to the host's immune system and genetic makeup is responsible for lymphoma development [11].

Lymphoproliferative disorders following transplantation

Secondary cancers can be an especially devastating complication of both solid organ transplant (SOT) and hematopoietic stem cell transplant (HCT) [29]. These secondary cancers include post-transplant lymphoproliferative disorders (PTLD), myelodysplastic syndrome (MDS)/leukemia, and solid organ tumors. While PTLD is the most common secondary cancer in solid organ transplant it represents a relative minority in the HCT population [29]. The incidence of PTLD has double over the past 20 years rising to account for 16% of all cancer diagnoses. The risk of PTLD appears to be highest in intestinal and multi-organ transplants, followed by thoracic organ transplants, according to the most recent data [30, 31]. PTLD represent a diverse spectrum of disorders ranging on a continuous spectrum from early lesions to polymorphic PTLD to monomorphic PTLD [32]. Early lesions present as an infectious mononucleosis-like illness with polyclonal B cell proliferation with no underlying abnormalities in oncogene or tumor suppressors. Polymorphic PTLD are either polyclonal or monoclonal lymphoid proliferations that do not yet meet all criteria for lymphoma. Lastly, monomorphic PTLD are monoclonal lymphoid proliferations that meet criteria for NHL, most commonly DLBCL and BL. Of note, PTLD do not include small B-cell lymphoid neoplasms [32].

Accounting for an estimated 50-70%, the vast majority of PTLD is associated with proliferation of Epstein Barr virus (EBV) transformed B-lymphocytes, however non-EBV related cases have been identified [33-35]. As discussed above, suppression of the immune system, in particular loss of T-cell function seems to be a major contributor in the development of EBV related lymphoma. Given the association between EBV and development of PTLD, the American Society of Transplantation recommends checking monthly EBV viral load for one year post-SOT [36].

Ongoing research has involved examining genetic susceptibility to the development of lymphoma in SOT, particularly examining single nucleotide polymorphisms (SNPs) involving human leukocyte antigen (HLA) and cytokine genes. HLA genes are of particular interest because of their role in the adaptive immune system in antigen presentation and processing [37]. A recent case-report study revealed that expression of HLA-A26, haplotype B38 was an independent, statistically significant predisposing factor in the development of PTLD in a mainly Caucasian population. This effect was noted not only in the organ recipient, but also in the donated organ [38]. It may be postulated that this polymorphism may lead to impaired presentation of EBV specific-peptides to the immune system, thus leading to increased escape of EBV immortalized cells. Other studies also showed increased risk with HLA-A2, HLA-A11, HLA-B5, HLA-B18, HLA-B21 and HLA-B3, and a decreased risk with HLA-A03 and

HLA-DR7 [39, 40]. Further research has gone into the role of cytokines in the development of PTLD, given that the cytokine milieu plays an important role in the immortalization and survival of EBV infected cells. Given this hypothesis, several studies have aimed to discover if any SNPs in the genes encoding for major inflammatory cytokines, such as TNF-α, TGF-β, or IFN-γ play a role in the development of PTLD. Several of these groups have found an increased incidence of the *IFNG* +874 A/A genotype in patients with PTLD [41-44]. In this case, the polymorphism in the IFN-γ gene leads to low secretion and a decreased inflammatory state. Other implicated cytokine polymorphisms include IL10 promoter −1082 A/G* and TGF-β1 +915 C/C [44, 45].

Autoimmune related lymphomagenesis

Autoimmune Rheumatic Disorders (ARD) much like NHL represents a heterogenous group of conditions arising from lack of self-tolerance and lead to chronic inflammatory response [46]. The spectrum of autoimmune disease range broadly affecting either single organ systems (Hashimoto's thyroiditis, Type I Diabetes Mellitus) to systemic processes (SLE, RA). Many large population based studies, particularly in Scandinavian countries have examined the link between ARD and lymphoma development. Not all diseases of the autoimmune spectrum have been found to be associated with an increased risk of lymphomagenesis. For instance, weak correlation data exists on ulcerative Colitis, multiple sclerosis, and type I diabetes in regards to lymphoma development [47-49]. There is a potential association between other autoimmune conditions such as psoriasis and crohn's disease [47, 50, 51]. Psoriasis seems associated with cutaneous T-cell NHL this seems most likely to be misdiagnosis of early Mycosis Fungoides [50]. Meanwhile data for crohn's disease was found to be associated with moderate increase in NHL during initial evaluation, this was lost at 5 years follow-up [47, 51]. The ARD with the highest association with increased risk of NHL include RA, pSS and SLE which has been observed in numerous large studies on different populations [46, 52-58]. The association appears to be weakest with RA with studies revealing an average relative risk elevation of twofold [52-55], whereas the risk elevation is around 3-6x in SLE [56, 57]. The highest overall relative risk belongs to pSS with a 9- to 18-fold increase [46, 58]. Several studies have also examined which subtypes of NHL are most strongly linked with each autoimmune condition. Sjögren's syndrome (as well as Hashimoto's thyroiditis) seems to predispose toward formation of MALT type lymphoma in targeted tissues [59, 60]. However while the association is seen most strongly with Marginal Zone Lymphoma, pSS was also found to be associated with a 9-fold increase in DLBCL [60]. In SLE and RA population studies, the highest documented subtype is DLBCL at greater than 50% [57, 60, 61]. Interestingly these lymphomas have been further characterized as non-germinal center type. Loftsrom et al. actually noted that of 10 SLE-related DLBCL, 80% of these were found to be non-germinal center [62].

As with most complex conditions, the process of lymphomagenesis likely involves in interaction at the genetic and environmental level. Lymphoma and autoimmune disorders share in common the multistep -process which eliminates checkpoints that prevent uncontrolled B-cell clonal expansion [63]. For instance, *Fas* mutations, a pro-apoptotic protein have been associated with both the development of Autoimmune Lymphoproliferative syndrome (ALPS), a condition characterized by accumulating lymphoid mass and auto-reactive cells. These patients have also been found to be at an increased risk for development of NHL [64]. Furthermore in murine models of systemic lupus, *Fas* mutations have been strongly implicated. The *Fas* pathway may bear particular interest in the future in obtaining a genetic link between autoimmunity and lymphomagenesis.

The difference in subtype of NHL observed between pSS and SLE points towards differing pathophysiologic mechanism behind lymphoma development. The model of lymphomagenesis in pSS is the best researched and most well postulated. The natural history of pSS involves chronic lymphocytic inflammation with subsequent infiltration and destruction of exocrine salivary glands [65]. As disease progresses ectopic germinal center-like (GC) lymphoid aggregates begin to form in exocrine glands, in particular the parotid glands. Though the architecture of these germinal centers is similar to that of secondary lymphoid organs, their level

of functionality is poorly understood [66]. The speculated method of progression toward NHL is chronic auto-antigenic B-cell activation which leads to monoclonality and eventual malignant transformation, particularly MZL. It appears from tissue examination that IgV receptors on malignant clones often encode for Rheumatoid Factor (RF) [67]. It is further postulated that tertiary lymphoid tissues that arise during pSS may not effectively perform their function in eliminating auto-reactive B-cells by allowing them to evade B-cell receptor mediated apoptosis [68]. Furthermore, levels of B-cell activating factor (BAFF) which have been found to promote B-cell survival are found to be elevated in patients with autoimmune disease and may play a key role in lymphomagenesis. BAFF, a TNF family cytokine also known as B-cell lymphocyte stimulator (BLys), is a key regulator of B-cell homeostasis, which acts to rescue B-cells from apoptosis, particularly in the periphery [65]. BAFF transgenic mice have been found to manifest with B-cell hyperplasia of the exocrine glands with development of SLE and pSS-like disease [69]. Furthermore, BAFF transgenic mice have been found to have significantly elevated incidence of NHL with approximately 35% of mice developing tumor [70]. BAFF has also been found to be elevated in patient serum irrespective of autoimmunity [71]. It is not unreasonable to think that elevated levels of BAFF contribute to the overall cycle of chronic activation that drives toward B-cell monoclonality and malignancy.

The question of whether treatment of autoimmune disease plays a role in development of lymphoma has been a widely debated topic for which there is yet no clear answer. Treatment of autoimmune disease falls into two general categories, disease modifying anti-rheumatic drugs (DMARDs), notably including methotrexate (MTX) and azathioprine, and biologic therapy including tumor necrosis factor (TNF) antagonists such as etanercept and infliximab. Several studies in RA patients have shown that those patients receiving DMARDs, particularly MTX and azathioprine have an increased risk of developing lymphoma [61, 72], however this data is confounded by the fact that the population receiving these agents had the highest disease activity [61]. Also noted by Baecklund et al. was that 12% of lymphoproliferative disorders in RA were EBV positive. Interestingly there have been case reports [61, 73] in the literature showing spontaneous regression of lymphoproliferative disorders after withdrawal of MTX. Salloum et al observed 16 patients after withdrawal of MTX with 6 showing spontaneous CR, 3 with PR, and 7 with minimal or no response. Of note 8/9 responders had positive EBV by either In-Situ Hybridization (ISHS) or PCR with only 1 patient with no detectable EBV [73]. This may indicate an alternative cause of lymphomagenesis in these responding patients, but perhaps indicates that there may be utility to EBV testing versus trial of MTX withdrawal in this small population of NHL patients on MTX. Some historical studies have documented increased risk of Lymphoma in patients receiving TNF-blocking therapy [72, 74]. Notably, Wolfe et al. performed a prospective study of 18,572 Rheumatoid Arthritis patients on infliximab, etanercept, and methotrexate, finding an increased standardized incident ratio (SIR) of 2.9 with biologic use. However, these findings may correlate to the fact that patient's receiving biologic therapy, much like those receiving MTX, have more advanced disease with prolonged chronic activation of lymphocytes. The ARTIS study [75] observed Swedish patients with RA starting anti-TNF treatment from 1999 to 2002 seems to support this conjecture. Patients receiving anti-TNF drugs when they were first approved were most likely to have higher disease severity than those being enrolled at the study's conclusion.

Are there strategies to prevent lymphoma development in immunocompromised patients?

Chronic activation of the immune system either due to viral stimulation or chronic inflammation appears to be the inciting factor causing an imbalance between immune tolerance and response of lymphoma development. It is therefore imperative to eradicate the underlying risk factor. In the case of patients with HIV, the introduction of early HAART therapy has curbed the incidence of HIV associated lymphomas. Similarly in patients with post-transplant lymphoproliferative disorders, incorporating agents that can eradicate memory B cells or EBV transformed B cells would significantly reduce or prevent EBV reactivation and PTLD. Rapamycin, an mTOR inhibitor is a macrolide antifungal antibiotic has potent immunosuppressive properties. Experimental studies sug-

gest that rapamycin inhibits the growth of human EBV transformed B lymphocytes. Another benefit is that mTOR inhibitors are effective against a number of malignancies including lymphoma.

Conclusion

The cascade of events that lead to the development of lymphoma is still incompletely understood, however ongoing research in conditions where immune system derangements occur provide new insights. For instance, multiple agents are in development and clinical testing involving the BAFF pathway. Studies involving the anti-BAFF mAb Belimumab in SLE revealed a durable response in improving disease activity with decreased flares over a 6 year window [76]. Furthermore, two studies are currently ongoing studying BAFF in pSS (NCT01160666, NCT01008982). In the mouse model it was found that anti-CD20 treatment was most effective on circulating B-cells rather than those localized to the RES and particularly in the MZ compartment. However when combined with BAFF inhibitors the ability of rituximab to clear the MZ compartment with >90% clearance of B-cells [77]. While the role of BAFF inhibition is being carved out in rheumatology practice, further research in the mouse and human models will need to be performed to establish if BAFF inhibition will add further therapeutic options to the treatment of NHL. This however only represents a fraction of the therapeutic options that may be explored with an increased understanding of what drives lymphomagenesis. Studies into the pathogenesis of lymphoma may lead to promising breakthroughs in treatment and prevention of immune mediated hematologic malignancies in the future.

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