Published in final edited form as:

Expert Rev Hematol. 2016 June ; 9(6): 553–561. doi:10.1080/17474086.2016.1180972.

B cells gone rogue: the intersection of diffuse large B cell lymphoma and autoimmune disease

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Abstract

Introduction—Diffuse large B cell lymphoma (DLBCL) is characterized by genetic, genomic and clinical heterogeneity. Autoimmune diseases (AIDs) have recently been shown to represent significant risk factors for development of DLBCL.

Areas covered—Studies that examined the relationships between AIDs and lymphoma in terms of pathogenesis, genetic lesions, and treatment were identified in the MEDLINE database using combinations of medical subject heading (MeSH) terms. Co-authors independently performed study selection for inclusion based on appropriateness of the study question and nature of the study design and sample size.

Expert review—Identification of AID as a substantial risk factor for DLBCL raises new questions regarding how autoimmunity influences lymphomagenesis and disease behavior. It will be important to identify whether DLBCL cases arising in the setting of AID harbor inferior prognoses, and, if so, whether they also exhibit certain molecular abnormalities that may be targeted to overcome such a gap in clinical outcomes.

Keywords

B cell; lymphoma; non-Hodgkin lymphoma; diffuse large B cell lymphoma; autoimmune disease; systemic lupus erythematosus; epidemiology

1. Introduction

The association between autoimmune disease (AID) and increased incidence of lymphoma has long been described. However, examination of whether specific lymphoma subtypes arise in the setting of certain autoimmune disorders until lately has been limited by inadequate sample sizes to ascertain the significance of such associations, given the relative rarity of each disease subtype. Several recent large case-control studies revealed that

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Declaration of Interest:

CR Flowers has been an unpaid consultant for Gilead and Genentech/Roche and a paid consultant for OptumRx. Emory University receives research funding for his work from: Abbvie, Acerta, Celgene, Genentech/Roche, Gilead, Infinity, Millennium and TG Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) represent significant risk factors for diffuse large B cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma (NHL) in the Western world. [1–3] DLBCL is characterized by clinical heterogeneity: although about half of patients will be cured with standard frontline chemoimmunotherapy, others will relapse and often succumb to the disease despite salvage treatments.[4, 5] At least some of this heterogeneity in outcomes is reflected in the identification of two major DLBCL subtypes distinguished by gene expression profiling, each apparently derived from a distinct cell-of-origin and harboring disparate prognoses: germinal center B cell-like (GCB) DLBCL, and the more aggressive activated B cell-like (ABC) DLBCL.[6–8] Investigating the mechanisms by which autoimmunity contributes to development of DLBCL could yield unique insights into the complex events that underly lymphomagenesis. Here, we review the epidemiologic associations between DLBCL and AID and explore possible interactions between these diseases in terms of pathogenesis, genetic lesions, and treatment.

2. Epidemiology

While data from population-based cancer registries has helped to characterize the epidemiology of NHL as a single entity, identification of risk factors for the more than 40 individual NHL subtypes, each defined by distinct biologic and clinical features, has been difficult due to their relative rarity. In order to perform a comprehensive analysis of risk factors contributing to specific NHL subtypes, the International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001. By pooling large numbers of cases and controls across studies, the InterLymph group has been able to provide well-powered comparisons of factors such as medical and family history, lifestyle, and occupation as they relate to risk of developing certain lymphoma subtypes. In multivariable analysis of 4,667 DLBCL cases and 22,639 controls, B cell-activating AID (including autoimmune hemolytic anemia, Hashimoto's thyroiditis/hypothyroidism, myasthenia gravis, pernicious anemia, RA, SS, and SLE) emerged as a significant risk factor for DLBCL development, with an odds ratio (OR) of 2.45 (95% confidence interval [CI] 1.91–3.16). More specifically, personal history of SS conferred an OR of 8.77 (95% CI 3.94–19.5), and history of SLE an OR of 2.49 (95% CI 1.42–4.37). [9] Hepatitis C virus (HCV) infection was also confirmed as a risk factor for DLBCL (OR 2.33 with 95% CI 1.71–3.19),[10] representing yet another important intersection between lymphoma and autoimmunity: as reviewed by Ferri *et al*, the polyclonal B cell expansion often triggered by HCV may result in production of a variety of autoantibodies as well as lymphoproliferative disorders, as typified by the immune-mediated vasculitis mixed cryoglobulinemia.[11] Thus, although less than 1% of patients with autoimmune diseases experience a new diagnosis of lymphoma,[12] AID is associated with a meaningful relative risk increase in developing NHL and DLBCL.

Conversely, much work has been done to characterize incidence of NHL subtypes in large cohort studies of patients with autoimmune disease. In general, SS is known to carry the highest risk of lymphoma, with estimates of relative risk (RR) ranging from 4 to 40 times that of the general population. [13, 14] The majority of these are mucosa-associated lymphoid tissue (MALT) lymphomas, but DLBCL cases made up about 15% of SS-associated NHL in a 584-patient cohort. [15] There is evidence that at least some of these

DLBCLs may arise from MALT predecessors,[16] but it is unclear to what extent such transformation accounts for SS-associated DLBCL.[17] Intriguingly, preliminary reports show that certain polymorphisms may predispose SS patients to developing non-MALT lymphoma, but more work is needed to confirm these results.[18, 19] A 2005 cohort study involving 9,547 patients with SLE showed that of the cases in which NHL was diagnosed, aggressive subtypes predominated, with DLBCL accounting for over half of cases for which subtype was available. [20] There is significant heterogeneity in studies of NHL risk in RA, which preempted the InterLymph group from performing a focused analysis of lymphoma subtype risk in this patient population. [9] However, in a large Swedish study that included >74,000 RA patients, increased risk of NHL in general and DLBCL in particular (48% of cases) was seen in patients with higher indices of inflammatory activity. [21] Of these, 70% were found to harbor non-GCB phenotype by immunohistochemical profiling. [22]

The question of whether lymphoma risk in SLE and RA stems in fact from immunosuppressive therapy used to treat those disorders rather than the autoimmune disease itself remains controversial. In the case of RA, a systematic review of the literature revealed no significant association of either methotrexate or azathioprine with NHL risk.[23] The review's author notes that inconsistencies between the studies examined may in part stem from smaller studies' lack of statistical power to detect the relatively rare event of lymphoma. Notably, larger studies showed a relatively smaller risk of lymphoma associated with methotrexate, whereas risk estimates for azathioprine were heterogeneous.

There is some suggestion that use of tumor necrosis factor-alpha (TNF α) inhibitors may increase lymphoma risk, but this association is far from clear-cut. Interestingly, generation of BAFF-transgenic mice lacking TNF resulted in development of autoimmune disorders similar to those seen in BAFF-transgenic mice with TNF, as well as a much higher incidence of B cell lymphoma.[24] A 2006 meta-analysis investigating the effect of the monoclonal antibodies infliximab and adalimumab on lymphoma risk based on randomized clinical trial data found a summary OR of 3.3. [25] However, interpretation of that result is limited by inclusion of heterogeneous studies with short follow-up periods (1–4 years), and lack of data regarding etanercept, a soluble receptor TNF α inhibitor. A prospective French study investigating risk of lymphoma in patients with any inflammatory disease treated with anti-TNF therapy found that the two- to three-fold increased risk of lymphoma seen in this population was similar to that expected in patients with such disorders. [26] Interestingly, that study found that risk of lymphoma was increased with use of infliximab and adalimumab compared to etanercept. Further confounding this issue is the fact that patients with increased disease severity are more likely to receive toxic medications, making it very difficult to distinguish whether disease activity or specific medications contribute most to lymphoma risk. However, as alluded to above, there is some evidence that DLBCL risk specifically correlates with increased disease activity in RA. [21] In SLE, a large case-cohort analysis evaluating 75 lymphoma cases against almost 5000 cancer-free controls failed to show significant association between either disease activity or specific therapy, including cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil and hydroxychloroquine, and increased lymphoma risk. [27] In fact, many of the lymphoma patients had not been exposed to any of those medications prior to onset of malignancy.

3. Pathogenesis

AID and DLBCL are both characterized by B cells that fail to respond to physiologic regulatory cues: in AID, B cells become pathologically activated and produce autoantibodies; in lymphoma, B cells acquire oncogenic genetic “hits” that cause malignant transformation and unchecked proliferation. The complex biologic processes that predispose patients with AID to develop lymphoma at an increased rate compared to the general population remain poorly understood. Table 1 summarizes several biologic risk factors associated with both AID and DLBCL. Figure 1 depicts how dysregulation of molecular pathways in B cells may contribute to abnormal survival in these two entities. To offer some context for discussion of possible mechanisms of shared pathogenesis, a brief review of normal B cell maturation is provided below.

In order to produce a diverse and functional antibody repertoire, developing B cells pass through a series of stages to assemble and modify their immunoglobulin (Ig) genes. Ig gene rearrangement is monitored at each step, with successful modifications producing a protein chain that serves as a signal to progress to the next stage. This process begins in the bone marrow, where B cell progenitors undergo V(D)J recombination of the Ig gene that ultimately results in cell-surface expression of IgM. In addition to binding antigen, surface IgM is coupled to CD79a and CD79b subunits to form the B cell receptor (BCR), which allows maturing B cells to transduce survival signals (e.g., through activation of the NF- κ B, PI3K and MYC pathways) throughout development. [28] Many B cells undergo apoptosis in the bone marrow following failure to produce surface IgM, or if their IgM binds self-antigen.

Mature B cells that survive this first round of selection are exposed to antigen in secondary lymphoid tissues (e.g., lymph nodes and spleen), where the majority migrate to the germinal center. Here, B cells undergo further modification of the Ig gene via somatic hypermutation, in which point mutations, small deletions and insertions are introduced into the Ig gene’s variable region to increase antibody’s affinity for antigen. Those few B cells with antibodies exhibiting high antigen affinity receive survival signaling through the BCR; the rest will die. During the ensuing step of class switch recombination, exons in the constant region of the Ig heavy chain are replaced to produce secondary Ig isotypes: IgG, IgA and IgE. [29] B cells that escape the germinal center alive ultimately differentiate into either plasma cells or memory B cells. In AID, B cells with affinity for self-antigen pathologically elude the negative selection of the bone marrow and germinal center and thus become part of an immune response directed against self-structures, such as chromatin in SLE, rather than foreign antigens. [30]

The process of normal terminal B cell differentiation is coordinated by changes in the equilibrium between two opposing groups of transcription factors: those that sustain the pre-differentiated B cell status, including PAX5 and BCL6, and those that promote plasmacytic differentiation, such as Blimp1, IRF4 and XBP1. [31] In the germinal center, BCL6 serves as a transcriptional repressor required for massive proliferation. [32] Through its inhibition of the DNA damage response, BCL6 also permits the cell to tolerate the genetic changes induced by somatic hypermutation. [33] However, once cells proceed to differentiation, BCL6 is negatively regulated by Blimp1, whose repressive functions facilitate plasma cell

differentiation by blocking B cell receptor signaling, somatic hypermutation and CSR. IRF4 represents another pro-differentiation transcription factor that is required for isotype switching. [34] Perhaps not surprisingly, aberrancies in these key regulators are often found in lymphoma and contribute to oncogenesis; more recent evidence also suggests that dysregulation of certain pro-plasmacytic differentiation factors corresponds with increases in autoantibody production and disease activity in AID such as SLE. [35]

During normal differentiation, naïve B cells undergo massive clonal expansion and mutagenesis. Thus, the physiologic genetic instability inherent to generation of antibody diversity provides ample opportunity for acquisition of oncogenic mutations and subsequent transformation to lymphoma when these processes go awry.

3.1 B cell receptor activation

Hijacking BCR signaling (either by mutation in lymphoma or through sustained stimulation by self-antigen in AID) promotes unchecked survival and proliferation and represents an important intersection in the proposed pathogenesis of DLBCL and AID. Since both subtypes of DLBCL exhibit somatic hypermutation of their Ig variable regions, their cells of origin have presumably undergone T cell-dependent antigen exposure. [36] It is thereby hypothesized that most DLBCL and other post-germinal center B cell lymphomas in AID may be driven by the chronic BCR stimulation and antigenic drive that characterize the autoreactive disorders. Certainly, the role of antigen-driven immune stimulation in SS-associated parotid MALT lymphomagenesis is well described, [37] but much less is known about the pathogenesis of DLBCL in that disease. Of note, chronically active BCR is a prominent feature in ABC DLBCL that sometimes results from gain-of-function mutations in the signal-transducing subunits of BCR, CD79a and CD79b.[38] Moreover, both AID and B cell lymphomas exhibit increased resistance of B cells to apoptosis, presenting yet another possible nidus of DLBCL development in the setting of AID.

3.2 NF- κ B pathway

In DLBCL, such escape from apoptosis is often mediated by pathologic activation of NF- κ B transcription factors downstream of BCR. Controlled NF- κ B activity plays a key role in physiologic lymphocyte maturation, proliferation and survival, and is required for the normal immune response.[39] When the NF- κ B signaling cascade is activated (e.g., by proinflammatory cytokines such as TNF α , growth factors, or antigen receptors), dimeric transcription factors belonging to the REL family localize to the nucleus to upregulate expression of anti-apoptotic proteins such as BCL-XL, BCL2, XIAP and A1. While constitutive NF- κ B was historically thought to be a hallmark only of the ABC subtype, ABC and GCB DLBCL may in fact be characterized by distinct mechanisms of NF- κ B dysregulation, often by mutations in upstream proteins (e.g., biallelic deletion of negative regulator A20 in a significant proportion of ABC DLBCL).[40–42] Alternatively, some GCB lymphomas exhibit amplification and overexpression of the c-REL gene. [7]

It is interesting to note that germline variants in *TNFAIB3*, the gene that codes for A20, have been shown to increase risk of SLE, SS and RA. [43] [44] Similarly, two variants in *REL*, which codes for c-REL, were identified as novel risk loci for development of RA in 2009.

[45] However, a definitive link between such polymorphisms and transformation to lymphoma has yet to be established. Recent work from Wang et al. found that NHL risk across major subtypes (including DLBCL) increased in individuals with B cell-mediated AIDs such as SLE, particularly when these individuals also harbored certain variants in the gene encoding for TNF α . [46] This may suggest a common biologic pathway for AID and lymphoma in which a chronic inflammatory state is promoted through increased TNF α expression and subsequent NF- κ B activation.

3.3 Interleukin (IL)-10

Another strategy lymphomas employ to avoid apoptosis involves activation of JAK-STAT and its downstream effectors, the PI3K and RAS pathways, as seen in ~30% of primary mediastinal lymphomas and ABC-DLBCL. [47] Activation of this pathway may result from JAK2 locus amplification or from mutation in MYD88, which increases autocrine cytokine secretion of IL-13, IL-6 and IL-10. [48] IL-10's main function apparently involves suppressing cytokine production in helper T cells, and such suppression has been linked to cancer risk and tumor-mediated immune suppression. More specifically, increased serum levels of IL-10 have been described in DLBCL patients and associated with poor clinical outcomes. [49] In SLE, IL-10 is known to promote B cell autoreactivity, and elevated IL-10 levels correspond with increased disease activity. [50] Intriguingly, genome-wide association studies have identified multiple germline variants in IL-10 that correlate with higher IL-10 production and associate with increased risk of either DLBCL or SLE. At least one of these variants, the -1082A/G polymorphism (rs1800896) in the IL-10 promoter, was confirmed in a recent meta-analysis to associate significantly with increased DLBCL risk [49] and in several studies has been associated with increased susceptibility to SLE [51] and SS, [52] thus illustrating another possible nexus in the pathogenesis of AID and DLBCL.

3.4 BAFF and APRIL

Two other cytokines that have garnered significant interest in this regard are B cell activating factor (BAFF, or BLyS [B lymphocyte stimulator]) and a proliferation inducing ligand (APRIL). Both are members of the TNF ligand superfamily that have been found to be dysregulated with high serum levels in systemic autoimmune diseases such as SLE, SS and RA [53, 54] and are implicated in development of B cell malignancies in mouse models. [55] More specifically, certain "high-risk" gene variants in BAFF have been shown to predispose to DLBCL development and correspond with high BAFF serum levels. [56] BAFF plays key roles in B cell maturation and humoral immunity by binding to B cell surface receptors to costimulate them and promote immunoglobulin class switch; APRIL is similarly involved in the humoral immune response. [57] In a 2007 paper, APRIL upregulation was described in a proportion of DLBCL tumors but not in low-grade lymphomas, with neutrophils identified as the main source of APRIL bound to tumor cells. [58] A subsequent study investigated APRIL expression in DLBCL tumors in SLE and RA patients compared to DLBCL tumors in the general population, finding an increased OR for high APRIL expression in SLE-associated DLBCL but not RA-associated DLBCL, when compared to DLBCL not associated with AID. [59] Although the exact role of APRIL and BAFF in DLBCL remains unclear, some studies show that expression of these ligands may allow lymphoma cells to avoid apoptosis. [60] Taken together, these findings have led some

to speculate that dysregulation of the BAFF and APRIL pathways in AID may influence interactions between host and tumor cell during lymphoma development in these patients. [59]

3.5 IRF8

Chromosomal translocations that promote unrestricted expression of oncogenes are common events in several lymphoma subtypes. Likely because its associated gene undergoes so much processing during normal B cell development, the promoter of constitutively expressed Ig on chromosome 14 often serves as a translocation partner in these oncogenic fusions. Although no single balanced translocation characterizes all of DLBCL, a significant proportion of cases harbor translocations involving Ig heavy chain (IgH) and either BCL2, BCL6 or c-MYC. Some will have two or even three such fusions; these so-called double- and triple-hit lymphomas exhibit inferior prognosis when treated with standard frontline chemoimmunotherapy. [61] In addition, several novel translocations have been described in DLBCL more recently using next-generation sequencing techniques. One study of 78 DLBCL tumor samples identified translocations involving IgH with APRIL and IRF8, [62] two factors also associated with AID pathogenesis. Other mutations in the IRF8 gene have also been described in DLBCL, [41] but its role in lymphomagenesis has yet to be completely clarified. In normal B cells, IRF8 induces BCL6 and promotes expression and rearrangement of the Ig light chain gene. [63] A 2008 study of IRF8 expression in a large series of tumors and normal B cell subsets showed that IRF8 was co-expressed with PAX-5 and BCL6 in normal germinal center B cells, and demonstrated strong expression in lymphomas of germinal center origin, further establishing it as a germinal center marker. [64] Importantly, IRF8 also promotes dendritic cells' production of type I interferon (IFN), a cytokine that has been implicated as a key player in development of AID due to the significant over-expression of type I IFN-regulated genes seen in these disorders. [65] In SLE, several genome-wide association studies (GWAS) have identified multiple variants near and within the IRF8 gene as susceptibility loci for the disease, [66, 67] with evidence that individual variants result in increased IRF8 expression within B cells in SLE patients. [68] Thus, it is conceivable that dysregulated IRF8 activity may contribute to pathogenesis of both SLE and DLBCL, but more work is needed to determine whether it serves as an initiating event in DLBCL arising in the setting of SLE.

4. Treatment

At present, the chemoimmunotherapeutic regimen known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) remains the standard of care in first-line treatment of DLBCL. However, as we learn more about the distinct molecular pathways that underly the disease's clinical heterogeneity, there is mounting evidence that this regimen may be modified to better target certain DLBCL subsets characterized by inferior treatment responses and survival outcomes. For instance, phase III trials stratified by cell-of-origin subtype are currently underway to evaluate the addition to RCHOP of oral agents such as lenalidomide that show preferential activity in ABC DLBCL. [69] Moreover, several studies show that intensifying frontline therapy with a regimen such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide and

doxorubicin) or HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and dexamethasone) results in improved outcomes for patients with double-hit lymphomas. [70] It is possible that DLBCLs that arise in the setting of AID may represent a disease subset with characteristic pathogenesis and prognosis. Whether and how AID influences lymphoma outcomes, let alone DLBCL outcomes, are questions that remain understudied. For example, although preliminary data suggested that DLBCL patients with RA have inferior survival compared to patients with *de novo* DLBCL, [71] other studies have not borne out the same. [72] It is interesting to note that several immunosuppressive drugs such as cyclophosphamide and methotrexate represent cornerstones in the treatment of both lymphoma and certain AIDs such as RA and SLE. Indeed, several studies show that treatment of AID-related lymphoma with R-CHOP resulted in remission not only of the malignancy but also of the autoimmune condition. [73] [74] Given that DLBCL and AID are both characterized by pathologic B cell proliferation, agents that target these cells are of special interest in patients with DLBCL arising in the setting of AID. Here, we review several B cell-specific agents that may prove especially important in treating or even preventing AID-associated DLBCL.

4.1 Rituximab

The B cell-depleting anti-CD20 monoclonal antibody rituximab proved to be a game-changing addition to standard chemotherapy for treatment of DLBCL, with significant improvements in clinical outcomes shown in several randomized clinical trials of both frontline and salvage therapy since it was first approved for low-grade lymphoma treatment in 1997. [75–79] Rituximab has also demonstrated activity in B cell-related AID such as SLE, RA and SS. Although initially hypothesized to derive its effectiveness in these disorders via depletion of autoreactive antibodies, lack of correlation between autoantibody titers and clinical response suggests that rituximab may disrupt other pathogenic B cell functions as well, including autoantigen presentation to effector T cells, pro-inflammatory cytokine production, and inhibition of regulatory T cells. [80] In RA, rituximab is predominantly used for patients whose disease proves refractory to conventional treatments such as methotrexate and TNF α inhibitors, with several randomized trials showing efficacy in this setting. [81–84] Rituximab has also been shown to improve disease assessment scores and renal function in SLE refractory to conventional immunosuppressive drugs, disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids. [85, 86] While two randomized trials investigating the addition of rituximab to conventional therapy for SLE failed to show superiority of rituximab over placebo (EXPLORER, LUNAR), [87, 88] there is some evidence that combination with cyclophosphamide may potentiate rituximab's B cell-depleting effect and thus improve clinical outcomes. [89] Finally, rituximab has been proven effective in improving disease activity in SS in terms of saliva flow rate, serologic assays and patient-reported parameters. [90]

4.2 Ibrutinib

Ibrutinib is a tyrosine kinase inhibitor that selectively inhibits Bruton's tyrosine kinase (BTK), a key link between signal transduction through BCR and activation of NF- κ B. Given that BTK has been shown to be necessary for survival in ABC DLBCL cell lines with chronic active BCR signaling, [91] some researchers hypothesized that ibrutinib would show

activity in ABC, but not GCB DLBCL; results from a recent phase I/II study supported this reasoning, with 37% patients with relapsed/refractory ABC DLBCL obtaining partial or complete response after treatment with single-agent ibrutinib, compared to just 5% of GCB DLBCL patients. [92] Moreover, promising results from a phase Ib trial evaluating addition of ibrutinib to frontline R-CHOP in CD20+ B cell NHL [93] have led to a phase III study of this regimen in non-GCB DLBCL, currently accruing. In lupus mouse models, ibrutinib has been shown to reduce circulating autoantibodies and suppress disease, [94] but the drug has yet to be studied in human subjects with AID.

4.3 Inhibitors of BAFF and APRIL

In 2011, the anti-BAFF monoclonal antibody belimumab became the first drug licensed for treatment of lupus in 50 years, with modest improvements in disease activity, prevention of worsened organ dysfunction, and ability to lessen concomitant corticosteroid use seen in two large randomized clinical trials. [95] Belimumab has also been shown to be effective in a randomized phase II trial of RA patients who had failed prior therapies, [96] and shows promise in SS as well, although randomized studies have yet to be reported in that disease. [97] Agents that mimic the target receptors of BAFF and APRIL, such as TACI, BAFF-R and BCMA, have also been studied in AID. Atacicept, a recombinant fusion protein that combines the constant region of Ig with the binding site of TACI to inhibit both BAFF and APRIL, progressed to phase II/III trials in SLE and RA but did not meet primary endpoints of efficacy in either of those study populations. [98, 99] Similarly, evaluation of atacicept in NHL was discontinued after a phase I study showed no tumor response. [100] Preclinical findings that neutralizing endogenous BAFF and APRIL by soluble TACI and BCMA decoy receptors attenuated NHL B cell survival and decreased NF- κ B activation [60] make this axis an intriguing potential target in DLBCL, but clinical studies of BAFF and APRIL inhibitors in this setting have so far been limited.

5. Conclusions

Genomic profiling and large case-control studies constitute an important step towards understanding the complex interplay of factors underlying lymphomagenesis and autoimmune disease. Identification of dysregulated molecular pathways common to these disease entities may provide insight into specific mechanisms by which DLBCL arises in AID, in addition to highlighting potential targets for treatment or even prevention of lymphoma in patients with conditions such as SLE, RA and SS. However, much more work is needed to better characterize this patient population in terms of genetic risk factors, biologic pathway dysregulation, and lymphoma outcomes before novel treatment strategies can be developed for this distinct patient population.

6. Expert Commentary

At the beginning of the 21st century, gene expression profiling showed that DLBCL may be divided into two main subtypes with disparate responses to frontline therapy. Subsequent work has focused on defining genetic aberrations and dysregulated signaling pathways that impact prognosis and may be targeted by small-molecule inhibitors and/or monoclonal antibodies. The recent identification of AID as a significant risk factor for DLBCL presents

new questions in terms of how autoimmunity influences lymphomagenesis and disease behavior. As the treatment paradigm in DLBCL shifts more towards subtype-based therapy, it will be increasingly important to identify whether those cases arising in the setting of pre-existing AID harbor inferior prognoses, and, if so, whether they also exhibit certain characteristic molecular abnormalities that may be targeted to overcome such a gap in clinical outcomes.

7. Five-Year View

Large case-control and genome-wide association studies have just begun to scratch the surface of the relationship between DLBCL and AID. A multidisciplinary approach involving hematologists, rheumatologists and epidemiologists will be important to better describe the link between these two entities. Coupling epidemiologic and genetic data, as in the study of the TNF α G308A SNV by Wang *et al.*, will yield further insight into the biologic and environmental underpinnings of lymphomagenesis in the setting of AID. In addition, B cell-targeting therapies used in AID should be investigated for activity in DLBCL, and vice versa. As the subset of DLBCL patients with AID is characterized in greater detail in terms of specific risk factors and molecular abnormalities, there may be opportunities for tailored therapy in this group, or even a preventive strategy for AID patients identified as high-risk who have yet to develop lymphoma.

References

1. Sant M, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010; 116(19):3724–34. [PubMed: 20664057]
2. Morton LM, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood*. 2006; 107(1):265–76. [PubMed: 16150940]
3. Cerhan JR, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014; 2014(48):15–25. [PubMed: 25174023]
4. Flowers CR, Armitage JO. A decade of progress in lymphoma: advances and continuing challenges. *Clin Lymphoma Myeloma Leuk*. 2010; 10(6):414–23. [PubMed: 21156459]
5. Sinha R, Nastoupil L, Flowers CR. Treatment Strategies for Patients with Diffuse Large B-Cell Lymphoma: Past, Present, and Future. *Blood Lymphat Cancer*. 2012; 2012(2):87–98. [PubMed: 23532092]
6. Alizadeh AA, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000; 403(6769):503–11. [PubMed: 10676951]
7. Rosenwald A, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002; 346(25):1937–47. [PubMed: 12075054]
8. Fu K, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. *J Clin Oncol*. 2008; 26(28):4587–94. [PubMed: 18662967]
9. Ekstrom Smedby K, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood*. 2008; 111(8):4029–38. [PubMed: 18263783]
10. Koff JL, et al. To Each Its Own: Linking the Biology and Epidemiology of NHL Subtypes. *Curr Hematol Malig Rep*. 2015; 10(3):244–55. [PubMed: 26104907]
11. Ferri C, et al. Hepatitis C virus syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. *World J Hepatol*. 2015; 7(3):327–43. [PubMed: 25848462]

12. Koshiol J, et al. Racial differences in chronic immune stimulatory conditions and risk of non-Hodgkin's lymphoma in veterans from the United States. *J Clin Oncol*. 2011; 29(4):378–85. [PubMed: 21172877]
13. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005; 165(20):2337–44. [PubMed: 16287762]
14. Lazarus MN, et al. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. *Rheumatology (Oxford)*. 2006; 45(8):1012–5. [PubMed: 16490754]
15. Voulgarelis M, et al. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. *Medicine (Baltimore)*. 2012; 91(1):1–9. [PubMed: 22198497]
16. Royer B, et al. Lymphomas in Patients With Sjögren's Syndrome Are Marginal Zone B-Cell Neoplasms, Arise in Diverse Extranodal and Nodal Sites, and Are Not Associated With Viruses. *Blood*. 1997; 90(2):766–775. [PubMed: 9226177]
17. Smedby KE, Baecklund E, Askling J. Malignant Lymphomas in Autoimmunity and Inflammation: A Review of Risks, Risk Factors, and Lymphoma Characteristics. *Cancer Epidemiology Biomarkers & Prevention*. 2006; 15(11):2069–2077.
18. Makri P, et al. TREX-1 Variants in Sjogren's Syndrome Related Lymphomagenesis [abstract]. *Arthritis & Rheumatology*. 2015; 67(S10):3369–3370.
19. Fragkioudaki S, et al. Contribution of MTHFR Gene Polymorphisms in Sjogren's Syndrome Related Lymphomagenesis [abstract]. *Arthritis & Rheumatology*. 2014; 66(S10):S915.
20. Bernatsky S, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. *Ann Rheum Dis*. 2005; 64(10):1507–9. [PubMed: 16162903]
21. Baecklund E, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum*. 2006; 54(3):692–701. [PubMed: 16508929]
22. Baecklund E, et al. Characteristics of diffuse large B cell lymphomas in rheumatoid arthritis. *Arthritis Rheum*. 2006; 54(12):3774–81. [PubMed: 17133544]
23. Kaiser R. Incidence of lymphoma in patients with rheumatoid arthritis: a systematic review of the literature. *Clin Lymphoma Myeloma*. 2008; 8(2):87–93. [PubMed: 18501101]
24. Batten M, et al. TNF deficiency fails to protect BAFF transgenic mice against autoimmunity and reveals a predisposition to B cell lymphoma. *J Immunol*. 2004; 172(2):812–22. [PubMed: 14707051]
25. Bongartz T, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *Jama*. 2006; 295(19):2275–85. [PubMed: 16705109]
26. Mariette X, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. *Ann Rheum Dis*. 2010; 69(2):400–8. [PubMed: 19828563]
27. Bernatsky S, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. *Ann Rheum Dis*. 2014; 73(1):138–42. [PubMed: 23303389]
28. Taccioli G, et al. Impairment of V(D)J recombination in double-strand break repair mutants. *Science*. 1993; 260(5105):207–210. [PubMed: 8469973]
29. Li Z, et al. The generation of antibody diversity through somatic hypermutation and class switch recombination. *Genes & Development*. 2004; 18(1):1–11. [PubMed: 14724175]
30. Goodnow CC. Multistep pathogenesis of autoimmune disease. *Cell*. 2007; 130(1):25–35. [PubMed: 17632054]
31. Nutt SL, et al. The genetic network controlling plasma cell differentiation. *Seminars in Immunology*. 2011; 23(5):341–349. [PubMed: 21924923]
32. Basso, K.; Dalla-Favera, R. Chapter 7 - BCL6: Master Regulator of the Germinal Center Reaction and Key Oncogene in B Cell Lymphomagenesis. In: Frederick, WA., editor. *Advances in Immunology*. Academic Press; 2010. p. 193-210.
33. Basso K, Dalla-Favera R. Roles of BCL6 in normal and transformed germinal center B cells. *Immunol Rev*. 2012; 247(1):172–83. [PubMed: 22500840]

34. Klein U, et al. Transcription factor IRF4 controls plasma cell differentiation and class-switch recombination. *Nat Immunol.* 2006; 7(7):773–82. [PubMed: 16767092]
35. Luo J, et al. Up-regulation of transcription factor Blimp1 in systemic lupus erythematosus. *Mol Immunol.* 2013; 56(4):574–82. [PubMed: 23911415]
36. Tarella C, et al. Lymphocyte transformation and autoimmune disorders. *Autoimmun Rev.* 2013; 12(8):802–13. [PubMed: 23219771]
37. Yamamoto K. Pathogenesis of Sjogren's syndrome. *Autoimmun Rev.* 2003; 2(1):13–8. [PubMed: 12848970]
38. Davis RE, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature.* 2010; 463(7277):88–92. [PubMed: 20054396]
39. Jost PJ, Ruland J. Aberrant NF- κ B signaling in lymphoma: mechanisms, consequences, and therapeutic implications. *Blood.* 2007; 109(7):2700–2707. [PubMed: 17119127]
40. Compagno M, et al. Mutations of multiple genes cause deregulation of NF-[kgr]B in diffuse large B-cell lymphoma. *Nature.* 2009; 459(7247):717–721. [PubMed: 19412164]
41. Zhang J, et al. Genetic heterogeneity of diffuse large B-cell lymphoma. *Proceedings of the National Academy of Sciences.* 2013; 110(4):1398–1403.
42. Lenz G, et al. Oncogenic CARD11 Mutations in Human Diffuse Large B Cell Lymphoma. *Science.* 2008; 319(5870):1676–1679. [PubMed: 18323416]
43. Vereecke L, Beyaert R, van Loo G. The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology. *Trends Immunol.* 2009; 30(8):383–91. [PubMed: 19643665]
44. Lessard CJ, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjogren's syndrome. *Nat Genet.* 2013; 45(11):1284–92. [PubMed: 24097067]
45. Gregersen PK, et al. REL, encoding a member of the NF-[kappa]B family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. *Nat Genet.* 2009; 41(7):820–823. [PubMed: 19503088]
46. Wang SS, et al. Associations of non-Hodgkin Lymphoma (NHL) risk with autoimmune conditions according to putative NHL loci. *Am J Epidemiol.* 2015; 181(6):406–21. [PubMed: 25713336]
47. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. *N Engl J Med.* 2013; 368(2):161–70. [PubMed: 23301733]
48. Shaffer AL 3rd, Young RM, Staudt LM. Pathogenesis of human B cell lymphomas. *Annu Rev Immunol.* 2012; 30:565–610. [PubMed: 22224767]
49. Cao HY, Zou P, Zhou H. Genetic association of interleukin-10 promoter polymorphisms and susceptibility to diffuse large B-cell lymphoma: a meta-analysis. *Gene.* 2013; 519(2):288–94. [PubMed: 23485354]
50. Sakurai D, et al. Preferential binding to Elk-1 by SLE-associated IL10 risk allele upregulates IL10 expression. *PLoS Genet.* 2013; 9(10):e1003870. [PubMed: 24130510]
51. Beebe AM, Cua DJ, de Waal Malefyt R. The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS). *Cytokine Growth Factor Rev.* 2002; 13(4–5):403–12. [PubMed: 12220553]
52. Cobb BL, et al. Genes and Sjogren's syndrome. *Rheum Dis Clin North Am.* 2008; 34(4):847–68. vii. [PubMed: 18984408]
53. Mackay F, et al. The BAFF/APRIL system: an important player in systemic rheumatic diseases. *Curr Dir Autoimmun.* 2005; 8:243–65. [PubMed: 15564724]
54. Nossent JC, et al. Polymorphism in the 5' regulatory region of the B-lymphocyte activating factor gene is associated with the Ro/La autoantibody response and serum BAFF levels in primary Sjogren's syndrome. *Rheumatology (Oxford).* 2008; 47(9):1311–6. [PubMed: 18617551]
55. Mackay F, Tangye SG. The role of the BAFF/APRIL system in B cell homeostasis and lymphoid cancers. *Curr Opin Pharmacol.* 2004; 4(4):347–54. [PubMed: 15251127]
56. Novak AJ, et al. Genetic variation in B-cell-activating factor is associated with an increased risk of developing B-cell non-Hodgkin lymphoma. *Cancer Res.* 2009; 69(10):4217–24. [PubMed: 19383901]

57. Litinskiy MB, et al. DCs induce CD40-independent immunoglobulin class switching through BLYS and APRIL. *Nat Immunol.* 2002; 3(9):822–9. [PubMed: 12154359]
58. Schwaller J, et al. Neutrophil-derived APRIL concentrated in tumor lesions by proteoglycans correlates with human B-cell lymphoma aggressiveness. *Blood.* 2007; 109(1):331–8. [PubMed: 17190854]
59. Lofstrom B, et al. Expression of APRIL in diffuse large B cell lymphomas from patients with systemic lupus erythematosus and rheumatoid arthritis. *J Rheumatol.* 2011; 38(9):1891–7. [PubMed: 21724695]
60. He B, et al. Lymphoma B cells evade apoptosis through the TNF family members BAFF/BLYS and APRIL. *J Immunol.* 2004; 172(5):3268–79. [PubMed: 14978135]
61. Friedberg JW. Double-hit diffuse large B-cell lymphoma. *J Clin Oncol.* 2012; 30(28):3439–43. [PubMed: 22949152]
62. Bouamar H, et al. A capture-sequencing strategy identifies IRF8, EBF1, and APRIL as novel IGH fusion partners in B-cell lymphoma. *Blood.* 2013; 122(5):726–33. [PubMed: 23775715]
63. Tamura T, et al. The IRF family transcription factors in immunity and oncogenesis. *Annu Rev Immunol.* 2008; 26:535–84. [PubMed: 18303999]
64. Martinez A, et al. Expression of the interferon regulatory factor 8/ICSBP-1 in human reactive lymphoid tissues and B-cell lymphomas: a novel germinal center marker. *Am J Surg Pathol.* 2008; 32(8):1190–200. [PubMed: 18580679]
65. Ronnblom L, Alm GV, Eloranta ML. The type I interferon system in the development of lupus. *Semin Immunol.* 2011; 23(2):113–21. [PubMed: 21292501]
66. Lessard CJ, et al. Identification of IRF8, TMEM39A, and IKZF3-ZBP2 as susceptibility loci for systemic lupus erythematosus in a large-scale multiracial replication study. *Am J Hum Genet.* 2012; 90(4):648–60. [PubMed: 22464253]
67. Cunninghame Graham DS, et al. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. *PLoS Genet.* 2011; 7(10):e1002341. [PubMed: 22046141]
68. Chrabot BS, et al. Genetic variation near IRF8 is associated with serologic and cytokine profiles in systemic lupus erythematosus and multiple sclerosis. *Genes Immun.* 2013; 14(8):471–8. [PubMed: 23965942]
69. Nowakowski GS, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. *J Clin Oncol.* 2015; 33(3):251–7. [PubMed: 25135992]
70. Petrich AM, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood.* 2014; 124(15):2354–61. [PubMed: 25161267]
71. Baecklund E, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. *Arthritis Rheum.* 2003; 48(6):1543–50. [PubMed: 12794821]
72. Mikuls TR, et al. Prospective study of survival outcomes in Non-Hodgkin's lymphoma patients with rheumatoid arthritis. *J Clin Oncol.* 2006; 24(10):1597–602. [PubMed: 16520462]
73. Voulgarelis M, et al. Long term remission of Sjogren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). *Ann Rheum Dis.* 2006; 65(8):1033–7. [PubMed: 16322082]
74. Voulgarelis M, et al. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. *Rheumatology (Oxford).* 2004; 43(8):1050–3. [PubMed: 15187246]
75. Gisselbrecht C, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010; 28(27):4184–90. [PubMed: 20660832]
76. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA Cancer J Clin.* 2010; 60(6):393–408. [PubMed: 21030533]
77. Pfreundschuh M, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011; 12(11):1013–22. [PubMed: 21940214]

78. Coiffier B, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002; 346(4):235–42. [PubMed: 11807147]
79. Habermann TM, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006; 24(19):3121–7. [PubMed: 16754935]
80. Lund FE. Cytokine-producing B lymphocytes-key regulators of immunity. *Curr Opin Immunol*. 2008; 20(3):332–8. [PubMed: 18417336]
81. Gurcan HM, et al. A review of the current use of rituximab in autoimmune diseases. *Int Immunopharmacol*. 2009; 9(1):10–25. [PubMed: 19000786]
82. Buch MH, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011; 70(6):909–20. [PubMed: 21378402]
83. Emery P, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis*. 2010; 69(9):1629–35. [PubMed: 20488885]
84. Haraoui B, et al. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior tumor necrosis factor inhibitor: the RESET Trial. *J Rheumatol*. 2011; 38(12):2548–56. [PubMed: 21965646]
85. Smith KG, et al. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum*. 2006; 54(9):2970–82. [PubMed: 16947528]
86. Tanaka Y, et al. A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. *Mod Rheumatol*. 2007; 17(3):191–7. [PubMed: 17564773]
87. Merrill JT, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum*. 2010; 62(1):222–33. [PubMed: 20039413]
88. Rovin BH, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012; 64(4):1215–26. [PubMed: 22231479]
89. Coca A, Sanz I. Updates on B-cell immunotherapies for systemic lupus erythematosus and Sjogren's syndrome. *Curr Opin Rheumatol*. 2012; 24(5):451–6. [PubMed: 22871954]
90. Meijer JM, et al. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2010; 62(4):960–8. [PubMed: 20131246]
91. Davis RE, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010; 463(7277):88–92. [PubMed: 20054396]
92. Wilson WH, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. 2015; 21(8):922–6.
93. Younes A, et al. Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naïve patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study. *Lancet Oncol*. 2014; 15(9):1019–26. [PubMed: 25042202]
94. Honigberg LA, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A*. 2010; 107(29):13075–80. [PubMed: 20615965]
95. Ramos-Casals M, et al. B-cell-depleting therapy in systemic lupus erythematosus. *Am J Med*. 2012; 125(4):327–36. [PubMed: 22444096]
96. Stohl W, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging Study. *J Rheumatol*. 2013; 40(5):579–89. [PubMed: 23547209]
97. De Vita S, et al. Efficacy and safety of belimumab given for 12 months in primary Sjogren's syndrome: the BELISS open-label phase II study. *Rheumatology (Oxford)*. 2015; 54(12):2249–56. [PubMed: 26242856]

98. Isenberg D, et al. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). *Ann Rheum Dis*. 2015; 74(11):2006–15. [PubMed: 24951103]
99. van Vollenhoven RF, et al. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. *Arthritis Rheum*. 2011; 63(7):1782–92. [PubMed: 21452294]
100. Ansell SM, et al. Phase I clinical study of atacicept in patients with relapsed and refractory B-cell non-Hodgkin's lymphoma. *Clin Cancer Res*. 2008; 14(4):1105–10. [PubMed: 18281543]

8. Key Issues

- Recent pooled analyses of large case-control studies have allowed unprecedented characterization of risk factors for specific non-Hodgkin lymphoma subtypes such as diffuse large B cell lymphoma (DLBCL).
- Autoimmune disease (AID), especially systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome, represents a major risk factor for developing DLBCL.
- It remains unclear whether this increased risk is driven by disease activity or immunosuppressive therapies used to treat AID, but several large studies suggest the former.
- Both DLBCL and AID are characterized by B cells that fail to respond to physiologic regulatory cues, resulting in unchecked proliferation.
- Genome-wide association studies and mutational analysis reveal several shared genetic abnormalities in DLBCL and AID.
- Molecular pathways of interest in this regard include B cell receptor dysregulation, NF- κ B activation, and increased signaling mediated by TNF α , IL-10, BAFF and APRIL.
- Therapies used to target B cells in DLBCL may also have activity in AID, and vice versa.
- DLBCL arising in the setting of AID may have distinct characteristics compared to *de novo* DLBCL, but this area remains understudied.

Figure 1. Molecular aberrancies in B cell signaling pathways observed in diffuse large B cell lymphoma and autoimmune diseases. Yellow starbursts indicate abnormalities in DLBCL. Pink starbursts indicate abnormalities in autoimmune diseases. Orange starbursts indicate abnormalities shared between DLBCL and autoimmune diseases. BAFF, B cell activating factor; BAFF-R, BAFF receptor; BTK, Bruton's tyrosine kinase; CARD11, caspase recruitment domain family, member 11; IL-10, interleukin 10; JAK2, Janus kinase 2; NF- κ B, nuclear factor kappa B; PKC β , protein kinase C beta; SNV, single nucleotide variant; STAT3, signal transducer and activator of transcription 3; TNF α , tumor necrosis factor alpha; TNF-R1, TNF receptor 1.

Table 1

Risk factors shared by diffuse large B-cell lymphoma and autoimmune diseases.

Risk Factor	AID	Hypothesized pathogenic effect
Hepatitis C infection	SS ⁹³	Sustained antigenic stimulation ³
A-1082G SNV in promoter of <i>IL-10</i> gene, with increased serum levels of IL-10⁴¹	SLE, ⁴³ SS ⁴⁴	Suppressed cytokine production in helper T cells, resulting in reduced immune-mediated destruction of malignant cells ⁴¹ Promotion of autoreactivity in SLE ⁴²
G308A SNV in <i>TNF</i> gene	SLE, RA, SS	Increased TNF α expression and activation of canonical NF- κ B pathway ³⁸
Increased serum levels of BAFF⁴⁸	SLE, RA, SS ^{45,46}	Costimulation of B cells and promotion of class switch recombination ⁴⁹ Activation of non-canonical NF- κ B pathway ⁹⁴
Increased IRF8 expression in B cells⁵⁶	SLE ⁶⁰	Induction of BCL6 and increased expression and rearrangement of Ig light chain gene in B cells ¹⁵ Increased production of type I interferon by dendritic cells ⁵⁷