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Genetic contributors and soluble mediators in prediction of autoimmune comorbidity

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ABSTRACT

Comorbidities including subclinical atherosclerosis, neuropsychological aberrations and lymphoproliferation represent a major burden among patients with systemic autoimmune diseases; they occur either as a result of intrinsic disease related characteristics including therapeutic interventions or traditional risk factors similar to those observed in general population. Soluble molecules recently shown to contribute to subclinical atherosclerosis in the context of systemic lupus erythematosus (SLE) include among others B-cell activating factor (BAFF), hyperhomocysteinemia, parathormone (PTH) levels and autoantibodies against oxidized lipids. Variations of the *5, 10- methylenetetrahydrofolate reductase (MTHFR)* gene -the main genetic determinant of hyperhomocystenemia in humans-as well the *interferon regulatory factor-8 (IRF8), FcγRIIA and BAFF* genes have been all linked to subclinical atherosclerosis in SLE. *BAFF* variants have been also found to confer increased risk for subclinical atherosclerosis and lymphoma development in Sjogren's syndrome (SS) patients. Other genes shown to be implicated in SS lymphoproliferation include genes involved a. in inflammatory responses such as the NFκB regulator *Tumor necrosis factor alpha-induced protein 3 (TNFAIP3)* and the *Leukocyte immunoglobulin-like receptor A3 (LILRA3)* immunoreceptor, b. B cell activation and signaling (*BAFF/BAFF-receptor*), c. type I IFN pathway such as *three-prime repair exonuclease 1 (TREX1)*, d. epigenetic processes including DNA methylation *(MTHFR* rs1801133, *677T allele)* and e. genomic instability *(MTHFR* rs1801131, *1298C allele)*. Emerging soluble biomarkers for SS related lymphoma include mediators of B cell growth and germinal center formation such as BAFF, FMS-like tyrosine kinase 3 ligand (Flt-3L) and CXCL13 as well as inflammatory contributors such as inteleukin (IL)-17, IL-18, ASC, LILRA3 and the extracellular lipoprotein-associated phospholipase A2 (Lp-PLA2). In regard to fatigue and neuropsychologic features in the setting of SS, contributing factors such as *BAFF* variants, antibodies against neuropeptides, proteins involved in nervous system function as well as inflammatory cytokines have been reported.

1. Introduction

Comorbidities in the setting of autoimmune disorders are increasingly recognized as a major problem with impact in morbidity and mortality. In particular, patients with Systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) are at increased risk for accelerated atherosclerosis and lymphoma development, with the first being a major issue in lupus and the second in SS patients [1]. Of note, the latter have the highest susceptibility for lymphoma development amongst all autoimmune diseases [2,3]. Although chronic inflammation has been proposed as a major contributor of autoimmune-related atherogenesis and lymphomagenesis, the underlying biology remains poorly understood [4]. Moreover, fatigue in SS patients seems to originate by interplay between neuropsychological issues and a complex network of cytokines and neuropeptides [5–7]. In the present review, we will focus on our previous and ongoing work regarding soluble and genetic contributors in subclinical atherosclerosis in the setting of systemic lupus erythematosus and SS. Furthermore, new data on SS related fatigue, neuropsychological issues as well as lymphoproliferation will be discussed.

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Table 1
Genetic contributors in SLE related subclinical atherosclerosis and CV morbidity.

Gene/Gene variation	Function	Gene locus	Author/Year/Ref#	Number of study participants (SLE vs HC)	OR [CI 95%]	Associations
STAT4/rs10181656	Transcription factor	chr2:191105153G > C[¥]	Svenungsson et al., 2010 [37]	424 vs 492 154 vs 194	2.3 [1.6–3.3] combined	Ischemic cerebrovascular disease
IRF8/rs925994, rs419030 and rs10514610	Transcription factor	chr16:85912411G > T[¥] chr16: 85933195C > T chr16:85908569G > A[¥]	Leonard et al., 2013 [35]	Cohort 1. 575 SLE Cohort 2. 239 SLE	3.6 [2.1–6.3] 1.8 (1.3–2.5) 3.8 (2.1–6.9)	Coronary heart disease, Carotid plaque, IMT Coronary heart disease Coronary heart disease
MTHFR/rs1801133	DNA methylation	chr1:11796321G > A (p.Ala222Val)	Giannelou et al., 2018 [34]	150 vs 561	5.2 [1.1–24.0 4.9 (1.2–20.6)	Carotid/Femoral Plaque Arterial wall thickening
BAFF/rs12583006	B cell survival and proliferation	chr13:108285104T > A[¥]	Theodorou et al., 2018 [27]	250 vs 200	4.4 [1.3–15.4]	Carotid/Femoral plaque
IL19/rs17581834	Anti-inflammatory cytokine	chr1:206802774T > C[¥]	Leonard et al., 2018 [38]	1045 vs 2711 1043 vs 2711	2.3 [1.5 to 3.4]	Stroke/myocardial infarction
SRP54-AS1/rs799454	Non-coding RNA class	chr14:34927973A > G[¥]	Leonard et al., 2018 [38]	1045 vs 2711 1043 vs 2711	1.7 [1.3 to 2.2]	Stroke/transient ischemic attack
FcγRIIA/rs1801274	Low affinity receptor of the Fc portion of IgG antibodies	chr1:161509955A > G (p.His131Arg)	Clancy et al., 2019 [39]	80 vs 30	4.4 [1.2–14.9]	Carotid plaque

SLE: Systemic Lupus Erythematosus, HC: healthy controls; STAT4: signal transducer and activator of transcription factor 4; IRF8: Interferon regulatory factor-8; MTHFR: methylene tetrahydrofolate reductase; BAFF: B cell activating factor; IL19: Interleukin 19; SRP54-AS1: signal recognition particle 54 – antisense 1 locus; FcγRIIA: Fc fragment of IgG receptor IIa; IMT: intima media thickness, [¥] Intron.

1.1. Subclinical atherosclerosis in SLE and SS: genetic and soluble contributors

SLE is a multisystem autoimmune disease with a strong female predilection. Cardiovascular (CV) morbidity and mortality is a frequent complication, particularly in females aged 35–44 years, whose risk of myocardial infarction is raised 50-fold [8,9]. The mechanisms leading to the development of subclinical atherosclerosis and vascular injury in SLE are not fully elucidated. Traditional CV factors such as hypertension, diabetes mellitus (DM), obesity and hyperhomocystenemia are more common in SLE patients than in the general population. However, they do not completely account for the increased CV risk, implying that other factors related to lupus such as disease duration, activity and chronicity, chronic inflammation, impairment of immunological status, therapy with corticosteroids as well as psychosocial features, such as anxiety [10,11] may be involved. Though accelerated atherosclerosis was first established in lupus and rheumatoid arthritis (RA), over the last 15 years heightened rates of subclinical atherosclerosis have been recognized as a significant burden in SS as well [12–17], identifying SS as an independent predictor for subclinical atherosclerosis [13,15].

Despite that exact pathogenesis of atherosclerosis in the setting of autoimmune diseases remains ill defined, an imbalance between endothelial damage caused by increased oxidative stress and immune mediated production of atheroprotective molecules seems to be a crucial event [18]. Briefly, increased oxidative stress results in the accumulation and oxidation of LDL particles (oxidized LDL/oxLDL) in the vascular intima. OxLDL is immunogenic, chemo-attracts monocytes that migrate and differentiate into macrophages, which by accumulation of oxLDL they transform into inflammatory foam cells forming the atherosclerotic lesion [19]. Subsequently, other immune cells including T and B cells, neutrophils and dendritic cells produce cytokines and chemokines leading to the initiation and perpetuation of an inflammatory response. Recent findings support the role of the cytokine B-cell activating factor (BAFF) in atherogenesis possibly through selective activation, survival and proliferation of B2 atherogenic cells (which produce anti-oxLDL autoantibodies of IgG isotype) over the atheroprotective IgM producing B1a cells, resulting in atherosclerotic disease [20,21].

In this context, IgG autoantibodies to oxLDL have been previously shown to be mediators of autoimmune atherogenesis [22], though some studies in the general population revealed an opposite role [23]. In our recent report, reduced anti-oxLDL levels were reported in SS and RA, but not in lupus patients compared to healthy controls (HC) implying a potential protective role. Interestingly, SS patients with high titers of antibodies to oxLDL were independently associated with reduced rates of carotid and/or femoral plaque formation [24]. Given the increasingly recognized role of B-cell activating factor (BAFF) in both autoimmunity [25] and atherosclerosis [26], in a prospective cohort of 250 SLE patients we have shown that patients with high serum BAFF levels (defined as the upper quartile level of the distribution) displayed increased rates of both plaque formation and arterial wall thickening [defined as intima media thickness (IMT) > 0.90 mm] compared to patients with low BAFF levels; this association remained significant after disease related features were taken into account [27]. Towards the same direction, BAFF mRNA expression was found to be significantly higher in the whole peripheral blood of SS patients with plaque formation compared to those without the presence of plaque [28].

In view of recent findings supporting genetic influences on serum BAFF levels [25,29], we screened our lupus cohort for five *BAFF* gene variants previously shown to be linked to lupus [30]. The presence of the AA genotype of the rs12583006 BAFF gene variant increased the susceptibility for both lupus and lupus related plaque formation, while the haplotype TTTAT (formed by rs1224141, rs12583006, rs9514828, rs1041569 and rs9514827 variants) was found to be protective for plaque formation among SLE patients [27]. Similarly, the TT genotype of the rs9514828 BAFF promoter variation was found to be significantly increased in SS patients with plaque formation independently of traditional CV risk factors [28].

Another molecule involved in CV heightened observed risk in both lupus and general population is homocysteine [31,32]. Hyperhomocysteinemia is strongly influenced by functional polymorphisms of the *MTHFR* gene encoding for the enzyme 5, 10- methylenetetrahydrofolate reductase [33]. In our recent work of 150 SLE patients, both hyperhomocysteinemia and *MTHFR* (rs1801133) 677 TT genotype were identified as independent contributors for plaque formation, following adjustment for traditional CV risk factors and disease related features [34].

Additional genetic aberrations associated with lupus related CV disease include variations of the *interferon regulatory factor 8* (*IRF8*) [35], the *mannose-binding lectin* [36], the *signal transducer and activator of transcription 4* (*STAT4*) [37] and recently the *interleukin (IL)-19* and *signal recognition particle 54-antisense 1* (*SRP54-AS1*) [38] as well as the

FcγRIIA genes [39]. A summary of genetic variants previously found to be associated with both subclinical atherosclerosis and CV events in lupus patients are depicted in Table 1 [27,34,35,37–39].

Recent findings support an association of subclinical atherosclerosis and impaired bone health in autoimmune patients including lupus [40–42] and SS [13], in accord with previous observations in general population [43]. Thus, SLE and SS patients with evidence of plaque formation were also shown to display heightened rates of osteoporosis as well [13,40], with an inverse correlation between femoral neck bone mean density (BMD) values and total IMT scores reported for lupus patients. A plausible scenario could suggest the mobilization of calcium from osteoporotic/osteopenic bone to vascular wall leading to vascular tissue calcification and subsequently plaque formation [13,44]. In this setting, molecules traditionally involved in bone metabolism such as vitamin D, parathormone (PTH) and osteoprotegerin (OPG) attracted major interest over the last years in the pathogenesis of CV disease as well [45–47], though recent data failed to demonstrate a protective role for vitamin D supplementation in the reduction of CV risk [48]. In our lupus cohort, no associations between vitamin D serum levels and surrogate markers of subclinical atherosclerosis were detected. Nevertheless, PTH serum levels were found to be increased in lupus patients with both arterial wall thickening and plaque formation [40]. In SS patients, reduced serum levels of the Wnt mediator Dickkopf-related protein 1 (DKK1) have been associated with both plaque formation and lower BMD levels [13]. These findings are in accord with previously published findings supporting the emerging role of Wnt signaling pathway in both atherosclerosis and osteoporosis [49–51]. A summary of soluble mediators involved in lupus related subclinical atherosclerosis over the last years are displayed in Table 2 [27,31,34,40,46,52–59].

1.2. Soluble and genetic mediators in lymphoma development in SS

Lymphoproliferation in the setting of autoimmunity has been early recognized [60–63]. In patients with SS, this association was first reported by Talal and Bunim in the early sixties [64], an observation confirmed later in a metaanalysis published in 2005, in which SS has been found to confer the highest susceptibility for lymphoma risk among all autoimmune disorders, with a standardized incidence ratio of 18.9 [2]. While the prevailing concept in SS related lymphoma development is the end result of a long lasting chronic polyclonal B cell activation, a growing body of data supports the distinct prognostic nature of SS, already present at time of SS diagnosis [65]. Thus, clinical features including salivary gland enlargement (SGE), lymphadenopathy, purpura [65], Raynaud's phenomenon [66] and tongue atrophy [67], diagnostic markers such as rheumatoid factor [66,68], autoantibodies against Ro/SSA and La/SSB [66], anticentromere antibodies [69], low complement C4 [65,70], mixed monoclonal cryoglobulinemia [71], increased β2-microglobulin levels along with increased free light chain κ/λ ratio levels [72] as well as histopathological features (focus score ≥3, germinal center formation) [73,74] could serve as reliable predictors for lymphoma development. Moreover, it has been also appreciated that patients with SS onset earlier in life display more aggressive clinical phenotypes [75]. Taken together, these data prompted us to explore the potential contribution of genetic contributors in the pathogenesis of SS related lymphoma.

Given that B cell activation and germinal center formation are key pathogenetic events in both SS and non-Hodgkin lymphoma (NHL), molecules implicated in these processes are candidate biomarkers [76–78]. Thus, serum BAFF levels [72,76,79,80] along with other B cell growth factors including FMS-like tyrosine kinase 3 ligand (Flt-3L) and chemokines involved in organization of ectopic lymphoid follicles, such as CXC chemokine ligand 13 (CXCL13) have been previously shown to be elevated in serum derived from SS patients complicated by lymphoma [81–83]. Increased frequency of the minor T allele of the rs9514828 BAFF variation was detected in the high risk for lymphoma

Table 2
Soluble mediators in lupus related subclinical atherosclerosis.

Mediator	Function	Author/Year/Ref#	Number of study participants SLE vs HC	Associations
BAFF	B cell survival and proliferation	Theodorou et al., 2018 [27]	250	Carotid/Femoral plaque and arterial wall thickening
Cardiac troponin T	Cardiac enzyme	Divard et al., 2017 [52]	63 vs 18	Carotid plaque
Endocan	Cell adhesion and inflammatory responses	Icli et al., 2016 [53]	44 vs 44	Carotid IMT, BMI, ESR*
Fas	Apoptosis	Wigren et al., 2018 [54]	484 vs 253	Carotid plaque
Homocysteine	Endothelial damage	Roman et al., 2007 [31]	158	Progression of carotid plaque
		Perna et al., 2010 [55]	125	Arterial stiffness
		McMahon et al., 2014 [56]	210 vs 100	Carotid plaque
		Giannelou et al., 2018 [34]	150 vs 30	Carotid plaque
MMP7	Tissue degradation	Wigren et al., 2018 [54]	484 vs 253	Carotid plaque
OPG	Vascular calcification	Kiani et al., 2017 [46]	166	Age-lack of independent association with carotid plaque or IMT
PCSK9	Reduced clearance of pathogenic lipids	Fang et al., 2018 [57]	90 vs 50	Carotid IMT, lupus nephritis, CRP
piHDL	Defective HDL function	McMahon et al., 2009 [58]	276	Carotid plaque and higher IMT values
		McMahon et al., 2014 [56]	210 vs 100	Carotid plaque
PTH	Bone metabolism	Gupta et al., 2018 [59]	201	No association with carotid IMT
		Giannelou et al., 2019 [40]	138	Association with carotid/femoral plaque and IMT
TNFR1	Apoptosis	Wigren et al., 2018 [54]	484 vs 253	Carotid plaque
TRAIL receptor 2	Apoptosis	Wigren et al., 2018 [54]	484 vs 253	Carotid plaque
TWEAK	Inflammation, angiogenesis, apoptosis	McMahon et al., 2014 [56]	210 vs 100	Carotid plaque

BAFF: B-cell activating factor, Endocan: endothelial-specific molecule 1, Fas: Fas cell surface death receptor, MMP7: Metalloproteinase 7, OPG: Osteoprotegerin, PCSK9: Proprotein convertase subtilizing/kexin type 9, piHDL: proinflammatory High Density Lipoprotein, PTH: parathyroid hormone, TNFR1: tumor necrosis factor receptor 1, TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand, TWEAK: Tumor Necrosis Factor (TNF)-Like Weak Inducer of Apoptosis.

development group, in contrast the minor A allele of the rs12583006 was more prevalent in the low risk group. Haplotypes in the 5′ regulatory region of *BAFF* gene (formed by rs1224141, rs12583006, rs9514828 and rs9514827 variants) could also discriminate SS patients at high risk for lymphoma development from SS low risk patients; patients with lymphoma display lower frequencies of the TACC and TTCT haplotypes compared to low risk SS and HC respectively, together with a higher frequency of the TTTC haplotype compared to the low risk SS [84]. Interestingly, an increased prevalence of the His159Tyr mutation of the *BAFF* receptor in patients with SS was also detected, particularly in those patients complicated by mucosa-associated lymphoid tissue (MALT) lymphoma whose disease onset occurred at a younger age, reaching 70%; activation of the alternate NF-κB pathway, as evidenced by increased nuclear factor kappa-light-chain-enhancer of activated B cells 2 (NFκB2) expression levels in B cells derived from SS patients bearing the His159Tyr mutation was demonstrated [76].

Uncontrolled inflammatory responses have been previously linked to lymphoma development particularly of MALT type [85–88]. As already mentioned, extensive lymphocytic infiltration [73] along with increased percentage of IL-18 producing macrophages [89] and heightened transcript levels of both interferon γ (IFNγ) [80] and inflammasome molecules [90] in minor salivary gland (MSG) tissues have been previously related to lymphoma development in the context of SS. In line with these findings, serum levels of IL-18 and apoptosis-associated speck-like protein (ASC) were found to be increased in high risk SS patients and SS-lymphoma subsets [90]. One of the products of tissue macrophages is extracellular lipoprotein-associated phospholipase A2 (Lp-PLA2), which is found in the circulation associated with lipoproteins, playing an important role in both CV [91] and malignant diseases [92], including B-cell NHL lymphoma [93]. In a recent study from our group, serum Lp-PLA2 activity was found to be increased in primary SS-lymphoma compared to both primary SS patients without lymphoma and HC. Lp-PLA2 activity was determined by two different techniques (measuring [3H] PAF degradation products in liquid scintillation counter and a commercially available ELISA kit) in two independent SS cohorts including SS-lymphoma patients [94].

In view of the implication of the A20 protein in controlling the NFκB pathway, several studies explored the contribution of a functional tumor necrosis factor, alpha-induced protein 3 (*TNFAIP3*) variant -the encoding gene for A20- in both inflammatory and malignant disorders [95–97]. In patients with SS of French [98,99], UK [99] and Greek origin [100], the prevalence of the coding rs2230926 *TNFAIP3* variant, has been previously found to be increased in SS-lymphoma patients [99,100], increasing the risk by approximately 2.5-fold. In the Greek SS cohort the presence of the variant was associated with higher serum IgM and LDH levels, higher transcripts of the anti-apoptotic Bcl-XL molecule in peripheral blood as well as lower leucocyte and neutrophil counts [100]. Of interest, approximately one-fifth of SS-lymphoma cases with younger age at disease onset (≤40 years) carried the rs2230926 variant, supporting the concept of increased mutational load in SS patients with lymphoma presenting earlier in life. Similarly, the wild type variant of the immunoreceptor *LILRA3* (Leukocyte immunoglobulin-like receptor A3) –previously related in chronic inflammatory disorders [101,102] was detected in all primary SS patients ≤40 years complicated by lymphoma in comparison to 81.8% in primary SS-non lymphoma patients and 83.2% in HC. As expected, LILRA3 protein serum levels were also found to be increased in this SS subset [103]. Another regulator of inflammation namely major histocompatibility complex P5 (*HCP5*) has been recently found to get involved in lymphoma development in the context of SS, in a Italian cohort, with the rs3099844 gene variation increasing lymphoma risk by approximately seven fold [104].

A defective immunosurveillant function in a setting of deregulated inflammatory responses has been postulated as a major mechanism for malignant transformation [105]. In salivary gland tissues derived from SS patients complicated by lymphoma, IFNα transcripts were found to be downregulated, implying a similar operating mechanism in SS related malignant transformation [80]. In order to explore potential genetic contributors for the dampened type I IFN responses observed in salivary glands from SS-lymphoma patients, genetic variants of the three-prime repair exonuclease 1 (*TREX1*) gene, previously found to increase susceptibility in lupus patients with neuropsychiatric manifestations [106] and also involved in type I IFN pathways [107], were tested in SS patients of Greek and Italian origin complicated or not by lymphoma [108]. While no differences in the rs3135941 and rs3135945 variants were detected between groups, the frequency of the rs11797 A minor allele was found to be remarkably reduced in SS-lymphoma patients of non-MALT type. Since the presence of the rs11797 AA genotype was found to be related with increased type I IFN inducible genes in MSG tissues, we postulate that genetically diminished type I IFN responses could offer an alternative explanation for SS related lymphomagenesis [108].

Finally, epigenetic alterations have been associated with NHL pathogenesis in general [109], as well as in the setting of SS with defective expression of miR200b-5p [110] and DNA methylating enzymes [111] in MSG tissues derived from SS patients with lymphoma. Variations of the *MTHFR* gene and particularly the rs1801133 (c.677C > T) TT genotype has been shown to display increased frequencies among primary SS patients complicated by non-MALT lymphoma in association with decreased methylation levels [112]. On the other hand, reduced prevalence of the rs11801131 (c.1298A > C) C minor allele in the primary SS non-MALT group compared to controls and SS patients without NHL was observed leading potentially to increased double-strand breaks, a marker of DNA damage. These findings imply defective DNA methylation and subsequent silencing of oncogenes together with genomic instability as additional operating mechanisms in SS related lymphomagenesis [113]. Genetic variations and potential soluble biomarkers associated with lymphoproliferative disease in the context of SS are summarized in Fig. 1 and Table 3 [72,76,79,80,82–84,90,94,100,103,104,108,112,114,115].

1.3. Fatigue and SS

Fatigue has been appreciated as a major burden in patients with SS compromising quality of life [5,116–119]. In a previous study from our group, approximately one third of SS patients was affected [116]. Despite significant efforts, biomarker discovery for SS related fatigue has been limited. Thus, markers of B cell activation, such as serum BAFF levels and autoantibodies against organ-specific and nonspecific antigens, as well as peripheral blood transcripts of the IFN-inducible gene IDO-1 -previously shown to be associated with depression and fatigue through induction of serotonin catabolism [120]- did not seem to contribute to increased sense of fatigue experienced by these patients [116]. While no association between fatigue scores and disease activity indices, low hemoglobin levels, impaired thyroid function, complication by lymphoma or medication use was detected; multivariate analysis revealed depression, neuroticism, and fibromyalgia as independent predictors of SS related fatigue [116]. Discrete personality spectrum and psychopathology features have been previously demonstrated in patients with primary SS [6]. A higher number of primary SS patients reported distinct personality traits (neuroticism, psychoticism and obsessiveness) and psychological distress compared to HCs, with autoantibodies against alpha-melanocyte-stimulating hormone (alpha-MSH), oxytocin and vasopressin being correlated with anxiety scores in these patients [6]. Despite that pro-inflammatory cytokines have been long considered as fatigue inducers, recent data confirmed an inverse relationship between serum TNFα and lymphotoxin (LT) α with fatigue scores in patients with SS [7]. In contrast, IL1β related molecules measured in cerebrospinal fluid (CSF) were found to be positively associated with fatigue levels in these patients [121]. In a recent work by Bodewes and colleagues [5] using a proteomic approach, 16 serum proteins were found to be differentially expressed between fatigued and non-fatigued SS patients including several neuropeptides, the

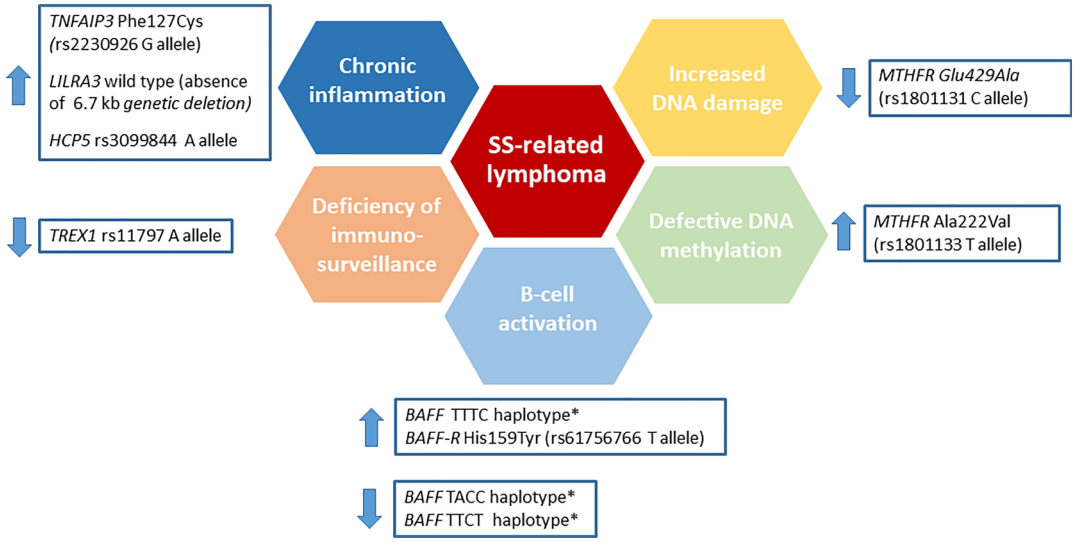

Fig. 1. Lymphomagenesis in the setting of Sjogren's syndrome-Genetic contributors and potential pathogenetic mechanisms involved. SS: Sjogren's syndrome; TNFAIP3: tumor necrosis factor-alpha induced protein 3; LILRA3: leukocyte immunoglobulin-like receptor subfamily A member 3; HCP5: major histocompatibility complex P5 gene; TREX-1: three prime repair exonuclease 1; BAFF: B cell activating factor; BAFF-R: B cell activating factor receptor; MTHFR: methylene tetrahydrofolate reductase, *contain alleles for rs1224141, rs12583006, rs9514828 and rs9514827 respectively.

proinflammatory mediator IL36a and complement components (upregulated); on the contrary, epidermal growth factor as well as an enzyme with potentially neurological effects namely formimidoyltransferase cyclodeaminase were found to be downregulated in fatigued SS patients. Finally, recent data revealed an association of severe fatigue in the setting of SS, with a reduced frequency of TT genotype of both rs9514828 and rs1224141 BAFF variations [122]. These associations remain to be confirmed in larger multicenter studies.

2. Conclusion

In conclusion, a comprehensive overview on genetic contributors and soluble biomarkers in comorbidities related to SLE and SS has been outlined revealing complex interactions between immune and/or neuroendocrine pathways in generation of fatigue and subclinical atherosclerosis. Deregulated inflammatory control, excessive B cell activation, impaired immune surveilling functions, as well as epigenetic alterations have been also shown to promote lymphomagenesis in the context of an otherwise benign autoimmune disease such as SS. We anticipate that through collaborative international efforts, novel etiopathogenetic pathways will be revealed and tailored therapeutic approaches will be established for SS patients.

Disclosures

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Table 3
Soluble mediators in Sjögren's syndrome related lymphoma.

Gene	Function	Author/Year/Ref#	Number of study participants (SS vs SS-L vs HC)	Association
B-cell activation				
BAFF	B-cell activation, survival and proliferation	Quartuccio et al., 2013 [79]	34 vs 42 vs 55	↑ in SS-L compared to SS and HC
		Gottenberg et al., 2013 [72]	377 vs 16	↑in SS-L compared to SS
		Papageorgiou et al., 2015 [76]	91 vs 32 vs 30	↑in SS-L compared to SS and HC
		Nezos et al., 2015 [80]	58 vs 22 vs 24	↑in SS-L compared to SS and all HC
Flt-3L	Growth of progenitor cells in bone marrow and blood	Tobon et al., 2013 [82]	369 vs 18 vs 50	↑in SS-L compared to SS and HC
		Papageorgiou et al., 2014 [76]	51 vs 29 vs 27	↑in SS-L compared to HC
Germinal cell formation				
CXCL13	Organization of B cells within follicles of lymphoid tissues	Nocturne et al., 2015 [83]	363 vs 22 vs 73*	↑in SS-L compared to SS and controls
Inflammation				
IL-18	Inflammasome activation	Vakrakou et al., 2018 [90]	36 vs 38 vs 27	↑in SS-L compared to SS and HC
IL-17	Proinflammatory cytokine		32 vs 33 vs 26	↑in SS-L compared to high risk SS and HC
ASC	Inflammasome activation		36 vs 38 vs 23	↑ in SS-L compared to SS and HC
TSLP	Immune tolerance/lymphocyte homeostasis	Gadolfo et,al. 2019 [115]	79 vs 12 vs 80	↑ in SS-L compared to SS and HC
Lp-PLA2	Monocyte derived phospholipase	Kotsifaki et al., 2019 [94]	48 vs 9 vs 40 25 vs 17 vs 10	↑ in SS-L compared to SS and HC
LILRA3	Immunostimulation	Argyriou et, al. 2019 [103]	24 vs 15 vs 9	↑in SS-lymphoma compared to HC**

SS: Sjögren's syndrome; SS-L: Sjögren's syndrome related lymphoma; HC: healthy controls; BAFF: B cell activating factor; Flt-3L: Fms-like tyrosine kinase 3 ligand; CXCL13: chemokine (C-X-C motif) ligand 13; IL-18: Interleukin 18, IL-17: Interleukin 17; Inflammasome Adaptor Protein Apoptosis-Associated Speck-Like Protein Containing CARD; TSLP: Thymic stromal lymphopoietin; LILRA3: leukocyte immunoglobulin-like receptor subfamily A member 3; lipoprotein-associated phospholipase A2, *sicca asthenia polyalgia syndrome, ** age of SS onset ≤ 40 years old.

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