HHS Public Access

Author manuscript

Curr Opin Rheumatol. Author manuscript; available in PMC 2015 April 27.

Published in final edited form as:

Curr Opin Rheumatol. 2013 July ; 25(4): 480–487. doi:10.1097/BOR.0b013e32836200d2.

Autoimmunity and Infection in Sjögren's Syndrome

Ann Igoe, MD[*,†] and **R. Hal Scofield, MD**[*,†,‡]

Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation

[†] Departments of Medicine and Pathology, University of Oklahoma Health Sciences Center

[‡] US Department of Veterans Affairs, Oklahoma City, Oklahoma, USA

Abstract

It is widely proposed that microbial factors may incite autoimmune disease. While this hypothesis is proven in a few illnesses such as rheumatic fever, there is no definitive evidence of an infectious environmental trigger in Sjögren's syndrome. However, there are circumstantial data with regard to viruses and several potential mechanisms of disease. These include antigen mimicry, polyclonal lymphocyte activation and infection mediated innate end-organ inflammation. In addition, hepatitis C virus infection clearly causes a Sjögren's-like illness.

Keywords

Sjögren's Syndrome; virus; autoimmunity; infection

Introduction

Sjögren's syndrome (SS) is named after Henrik Sjögren who in 1933 presented clinical and histological findings of 19 women who had symptoms of dry eyes and mouth [1] . SS is a systemic, multiorgan autoimmune disease with a chronic or progressive course and is characterized by, but not limited to, secretory dysfunction[2]** of salivary and lacrimal glands leading to sicca symptoms of dry eyes and dry mouth. SS is can be considered autoimmune epithelitis [3] and is either Primary (pSS) or Secondary (sSS). The latter where the disease is accompanied by another connective tissue disease, most commonly rheumatoid arthritis (RA) [4]*.

Induction of autoimmunity is perplexing and cryptic. The precise initiating event that results in autoimmune disease is unknown. Environmental and genetic factors have long been suggested to play a pivotal role and research in both fields has isolated many fragments of the paradox, which still remains mystifying. pSS affects approximately 0.1 – 0.4% of the general population with large female bias resulting in a female-to-male ratio of approximately 9:1 [5].With this in mind, genetic makeup is an intuitive source to hold accountable. Genetics is not fully responsible and it is the likely that the genetic

Correspondence to Hal Scofield, MD, Arthritis and Immunology Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, OK 73104 USA; phone: +1 405 271 7061, hal-scofield@omrf.ouhsc.edu.

Disclosure The authors do not have any conflict of interest.

predisposition and environmental factors together evoke autoimmune disease. Twin studies support this environmental ascendency where the concordance rate for autoimmune conditions is less than 50% in monozygotic twins therefore implying a non-genetic component [6][7]. Environmental or non-genetic factors encompass a vast array of moieties that are hypothesized to be antecedent in development of autoimmune disease, and in SS this mainly refers to infections.

Particular infections may mimic SS and are therefore SS-like illness[8] and, thus are postulated to be directly involved in pathogenesis and initiation of SS, while others may have a somewhat protective role[9] [10] . Infectious agents that may mimic SS include tuberculosis, leprosy, spirochetes, hepatitis A,B or C, parvovirus B19, Dengue fever, malaria, subacute bacterial endocarditis and HIV Certain viruses express tropism for salivary and lacrimal glandular tissue, especially the herpesvirudae family, which is a large family of DNA viruses that includes CMV, EBV, HHV-6,7,8[8]. Several lines of epidemiological, serological, and experimental evidence implicate retroviral infections – especially HTLV-1, HIVs, HIAP-I, and HRV-5 as triggering factors for the development of SS[11]**. This review will focus on the most significant viral agents that may have a role in the pathogenesis of SS.

Mechanisms

There are three main mechanisms by which infections might trigger autoimmune disease: antigen mimicry, polyclonal lymphocyte activation and increased immunogenicity of organ autoantigens secondary to infection mediated inflammation [12]. Some authorities hypothesize that molecular mimicry is the most important mechanism for virus induced autoimmunity [13]. Meanwhile, viruses affect exocrine tissue primarily through plasmacytoid dendritic cells (pDC) and toll-like-receptors (TLR). Firstly, dendritic cells are stimulated, which results in activation of the innate immune system via TLR pathways. TLR recognize conserved microbial molecular patterns and this recognition results in epithelial cells producing chemokines including type I interferon (IFN-1), and up-regulation of co-stimulatory adhesion molecules [14]. Activated epithelial cells can act as antigen presenting cells [15].

Activated IFN-1 pathway plays an important part in the autoimmune disease process of SS[16]** [17][18][19]**Induction of type I interferon propagates a multitude of biological functions including a protective role against viral and bacterial infection, immunomodulation and anti-proliferation [16]. pSS patients have up-regulated expression of IFN alpha in labial salivary glands, plasma and peripheral blood cells [17] and over-expression of type I interferon inducible genes in the peripheral blood and salivary glands of the patients. This gene expression, correlates positively to titers of anti-Ro60/SS-A and anti-La/SS-B autoantibodies [18]. Further, up-regulation of IFN regulated genes is associated with active disease[18][20][21] The main producers of type I IFN are the pDC, which produce 1000-fold more IFN alpha/beta compared to other cell types[21][22] .

EBV

Studies support Epstein Barr virus(EBV) involvement in SS pathogenesis and there have even been instances whereby primary EBV infections has been followed by SS [23] [24].Typically EBV infection of B lymphocytes results in latent infection that is characterized by three distinct processes - viral persistence, restricted viral gene expression, and the potential to reactivate to lytic replication. The last of these is responsible for new viral infection and induction of EBV-associated cellular changes. The latter may be a risk factor for both malignant transformation and initiation or perpetuation of glandular tissue damage leading to SS in genetically susceptible people. Data suggesting this possibility include the higher incidence of EBV reactivation in SS patients, higher expression of HLA-DR antigens on salivary epithelial cells, and increased levels of EBV antigens and DNA in salivary infiltrating lymphocytes[25][26][27]**. SS patients also have increased number of circulating B-cells that harbor EBV [28][29].

Activation of the aryl hydrocarbon receptor (AhR) may interact with latent EBV infection [27]**. This receptor has been highly conserved throughout evolution and is part of the basic-helix-loop helix transcription factor family. It is a cytosolic receptor that is normally inactive and bound to several co-chaperones [30]. AhR is activated by a diversity of endogenous and exogenous ligands. AhR activation can either increase or decrease inflammation. AhR ligands present a double edged sword. Exogenous activation of AhR has detrimental effects, while sustained activation of AhR by endogenous ligands is essential for proper cell functions[31]. In particular, cells of the immune system are affected where there is a role in the development, activation, proliferation and/or differentiation of leukocytes, including pronounced impact on DC [32] [33], regulatory T cell [34][35] and B cell [36] [37], cells of the T_H17 subset of $CD4^+$ helper T cells [34][38]. The prototypical exogenous ligand, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin), is a chemical carcinogen that is an extensive environmental pollutant with high affinity and stability owed to its 4 chlorine residues that prevent metabolic breakdown [39]. Some propose dioxin is a co-factor in the development of autoimmune diseases [38], as it contributes to the modulation of the activity of other transcription factors such as NF-kB [40]. Saliva from SS patients transactivate target genes of AhR, BZLF1 and CYP1A1, the former being the first gene to be transcribed during EBV replication [27]. CYP1a1 promoter and Zp130, which is a synthetic peptide related to Z Epstein-Barr replication activator (ZEBRA), was strongly activated by the saliva of SS patients in the presence of exogenous AhR expression compared to basal levels of the control[27]. These data indicate that an AhR ligand in the saliva of SS patients can stimulate BZLF1 transactivation [27]. The same study established a correlation between anti-La/SSB in the sera and AhR action in saliva of SS patients. Inoue et al hypothesize that EBV reactivation can be induced by dioxin and may be responsible for the immune response in salivary glands of SS patients.

CMV

In a cohort of 82 SS patients, Barzilai and colleagues found elevated titers of CMV IgM antibodies. This work also had similar findings in several autoimmune diseases,

however[41] thus, the immune response to CMV appears to be associated to autoimmune disease, but there are no clear connections to SS.

Mouse models may offer guidance in regards to a role of CMV in SS. Features of human SS including focal inflammation in the submandibular and lacrimal glands were demonstrated in female NZM2328 mice upon infection of sialotropic murine CMV (MCMV). MCMV DNA levels were detectable in the salivary gland and lacrimal glands 14-28 days after intra-peritoneal infection and interestingly correlated with acute inflammation in the submandibular gland. After latency, PCR was unable to detect the virus in the glands; however, a progressive loss in salivary gland function and focal dacryoadenitits was observed in the females during that latent infection [42]. M33 is the MCMV homologue of HCMV UL33 G-protein-coupled receptor (GPCR), which is important for salivary gland tropism and establishment of reactivation from latency [43-45]. When mice that are deficient for M33 or have an M33 mutation in a specific signaling domain are infected with recombinant viruses, the mice have significantly diminished MCMV infection of the salivary glands, indicating that M33 contributes to the efficient establishment or maintenance of long-term latent MCMV infection [43]. Common mechanism by which HCMV and MCMV confer complementation of salivary gland tropism is mediated predominantly by G protein signaling conserved with that of M33; in contrast, both G protein-dependent and independent pathways contribute to latency phenotypes [46]**.

Human Parvovirus B19

While HVB19 constituents may persist in salivary gland tissue without lymphocytic infiltration, there is no evidence associating this virus with SS[47][48]. Interestingly, one study reported that cytopenia in pSS correlated with serological evidence of past HPVB19 infection[49].

HBV

HBV is highly endemic in Taiwan with 17.3% of the adult population HBsAg-positive [50] . In Taiwan, the rate of HBV infection was significantly less frequent in pSS patients when compared to the general population. Further, pSS patients with chronic HBV had less pulmonary involvement when compared to pSS without HBV, indicating that HBV infection may reduce pulmonary involvement [10]*. Among SS patients a higher level of RF is also found in HBV carries [10,51], which may point to a more intense disease activity in patients with pSS and chronic HBV. However, there are no significant differences in the mortality rate or the presence of extraglandular manifestations between pSS patients with and without RF [10]. A Spanish study recorded a prevalence of chronic HBV infection in SS that is very similar to the prevalence in general population. Only 5 of 603 (0.83%) pSS patients were positive for HBsAg. In comparison to the close association between SS and HCV, chronic HBV infection is not associated with SS with a ratio SS-HBV/SS-HCV of 1:10 [52].

HCV

HCV is known to mimic SS [53] and a clear genetic association with HLA DQB1*02 has been documented in chronic HCV infection with sicca syndrome [54]. HCV “sicca-like”

symptoms tend to be milder compared to SS [55] and HCV-related SS has mild lymphocytic infiltrates that tend to locate in the pericapillary area rather than around the glandular ducts [56]. Only mild damage of the glandular tissue is reported in HCV-related SS [57][58].

Perhaps HCV could be a precipitator of autoimmune disease and result in pSS. There is a higher prevalence of SS in patients with HCV infection (25.9%) compared to patients with HBV (3.4%) [59].However, in this study the HCV group was much older and the former European criteria were used [60]. Unlike the present the American–European Consensus Criteria, these criteria did not mention HCV infection is an exclusion criteria [2]. The most commonly reported systemic autoimmune diseases in association with chronic HCV infection are SS (nearly half the cases), RA and SLE [61].

HCV expresses tropism for lacrimal and salivary epithelial cells and HCV RNA has been found both in saliva and salivary gland tissue [62] . Also, *in situ* hybridization studies have demonstrated that HCV is exclusively localized in the salivary epithelial cell cytoplasm [63]. However it has not necessarily been confirmed that the presence of HCV RNAs has an immune effect, either direct or indirect, in any salivary gland disorder [64].

Also linking HCV to SS are transgenic mice that carry HCV envelope genes E1 and E2. These mice develop SS-like symptoms manifesting as sialoadenitis [65]. Rosa and colleagues have hypothesized that the E2 glycoprotein, which is found on the surface of HCV, binds to CD81; thus, stimulating B cell proliferation [66].

HCV may provide chronic antigen stimulus that drives clonal expansion somatically mutated IgM memory B-cells [67], which of course have not undergone isotype switching. Some of these B-cells in HCV-infected patients are autoreactive [68]; and, therefore, may predispose to SS.

A correlation between Sjögren’s syndrome and mixed cryoglobulinemia has been repeatedly reported [69][70]. When patients with HCV-related SS were compared with to 60 pSS patients with negative HCV serology, the HCV seropositive patients demonstrated a higher prevalence of anti-gastric parietal cell antibodies, anti-mitochondrial antibodies, RF, cryoglobulinemia, and hypocomplementemia. The latter two are commonly found in HCV-infected patients, and are considered markers or predictors for the development of extra-hepatic manifestations of the disease, such as cutaneous vasculitis (cryoglobulinemic purpura), peripheral neuropathy, glomerulonephritis or sicca syndrome [71][72]. In HCV-related sialoadenitis, the coexistence of cryoglobulinemia may favor the development of lymphoproliferative diseases including B-cell non-Hodgkin’s lymphoma [73]. The biological background of cryoglobulinaemia is a different between SS and HCV infection. Of interest, levels of serum cryoglobulinemia and RF markedly decrease in SS who underwent bilateral subtotal parotidectomy [74]**.

Autoantibodies have a different pattern in HVC-related sialoadenitis and pSS. Antibodies to Ro and La are found in a much lower frequency in HCV-associated sialoadenitis compared pSS [75-78]*. Alpha-fodrin antibodies have recently been brought into the spotlight [79-81]. Potthoff, et al concluded that patients with chronic HCV infection show high titer of alpha-fodrin IgA and sicca symptoms, but neither symptom severity or frequency correlated with

alpha-fodrin antibodies [80]. There is also a higher prevalence of monoclonal gammopathy in HCV-related sialoadenitis than that in pSS [74]**. Detection of monoclonal gammopathy (IgMκ) might help to distinguish HCV related SS from pSS [82]*.

Doffoël-Hantz, et al proposed that HCV is implicated in the development of SS in a particular subset of patients for which the term SS "secondary to HCV" may be useful [83] [60]. Since sicca symptoms and focal sialoadenitis are not exclusive features of pSS, viral serology may allow one to confirm the presence of a causative agent.

Coxsackie

Coxsackie virus (CV) replication takes place in the submucosal lymph tissue and then disseminates to the reticuloendotheilas system. Further dissemination targeting organs occurs following a second viremia. RNA from two strains, CVB4 and CVA13, has been identified in MSG samples from pSS [84]; thus, implicating CV of a potential environmental trigger for SS.

Antibody cross-reactivity has been reported between 60 kD Ro and a CV protein. Protein 2B is a nonstructural small hydrophobic protein of 99 amino acids and is a product of P2 precursor molecule of the viral polyprotein. Functionally it is classified as a viroporin, which interacts with cell membranes, modifying permeability [85]. Ro60kD has a linear B-cell epitope spanning amino acids 216-232 (Ro216). The 222-229 residues share 87% amino acid homology with a region of protein 2B from CVA21 and CVA13. Stathopoulou, et al demonstrated a likely cross-reaction between antibodies to this linear B-cell epitope of Ro60kD and the homologous CV 2B protein in pSS patients. These investigators tested sera from patients with pSS, SLE, normal and diseased controls against the 2B peptides. 25% of SLE and 33.3% of pSS sera reacted against Ro216, whereas 28% of SLE and 37% of pSS sera recognized the viral peptides. The sera reacting with Ro216 were seemingly the same as those reacting with viral 2B peptides. Controls showed little reactivity (3.7% -10%) against either. Also, both the viral peptides reacted more strikingly with anti-Ro/La positive sera from pSS patients. Accordingly, with 17% of the anti-Ro/SSA positive sera recognizing the Ro216 sequence and 42% of the anti-Ro(SSA)/La(SSB) positive sera, while the 2B peptide was recognized by 28.5% of anti-Ro/SSA positive and 38% of anti-Ro(SSA)/La(SSB) positive sera. Purified anti-Ro216 promptly reacted with both peptides with inhibition experiments revealed the specificity of this reaction[86].

HTLV-1

HTLV-I infects 10 to 20 million people worldwide and is endemic in Southwestern Japan, South America, sub-Saharan Africa, and the Caribbean, along with foci in the Middle East and Australo-Melanesia [87][88]. The overall prevalence rates in Japan are estimated to be 0.66% and 1.02% in men and women, respectively [89]. Prevalence rises slowly with age, especially among women in all highly endemic areas [88]. Despite interesting data reviewed below, the worldwide prevalence of SS does not coincide with the regional distribution of this virus.

Several studies from both endemic and non-endemic areas have linked HTLV-1 to the pathogenesis of SS. Four Japanese studies have established the presence of HTLV-I proteins in the sera of SS patients and have shown direct affinity of this virus for labial salivary gland tissue. In SS patients that were also HTLV-I seropositive, viral loads within the labial salivary gland were found to be in the region of 8 to 9×10^3 higher than those in the peripheral blood mononuclear cells [90]. In an additional study conducted on 36 pSS patients, 13 were found to have antibodies towards HTLV-1[91] . HTLV-1 seroprevelance rate was found to be higher in SS (23%) compared to blood donors (3%). Also, the seropositive SS patient population had salivary IgA antibodies to HTLV-1 [92].

Tax is a HTLV-1 viral transcription factor that is essential for replication of the HTLV-1 genome and is required for HTLV-1 pathogenesis. As an oncoprotein, Tax transforms cells through various mechanisms, including the creation of chromosomal instability, the amplification of centrosomes, the abrogation of DNA repair, the activation of cyclin-dependent kinases, the silencing of p53 and spindle assembly checkpoints [93]. A French study with 11 SS patients showed anti-tax antibodies in approximately half of the patients implying that Tax oncogene may have a potential role in pathogenicity [94].

Sasaki et al researched the TCR Vβ gene usage by the infiltrating lymphocytes in the target organ and defined Vβ from HTLV-I positive SS compared to HTLV-1 seronegative SS. Usage among HTLV-1 seropositive SS patients was more restricted and was mostly Vβ5.2, Vβ6 and Vβ7. These workers suggested a small population of T cells expressing Vβ5.2,V β6 or Vβ7 expand in the periphery before activation in target organs [95]. Sasaki and colleagues also observed the most dominant junctional sequence Vβ7 transcript with the conserved amino acid motif “QDXG” was present in 5 of 6 HTLV-I seropositive and 2 of 5 seronegative SS, indicating the accumulation of HTLV-I infected T-cells expressing TCR with this conserved motif [95].

However, HTLV-1 may in fact aid in resistance toward salivary gland destruction; and therefore, preserving glandular function in SS patients. In a recent study involving 60 pSS patients, Nakamura, et al observed significantly fewer abnormalities determined by sialography in HTLV-I-seropositive SS patients in comparison with HTLV-I-seronegative SS patients. Also, these findings were substantiated by the results that none of HTLV-I-seropositive SS patients with focus score 0 had abnormal sialography findings. Thus, HTLV-I seropositivity may contribute to cell proliferation and survival resulting in more superior sialography results [9].

Sipsas, et al reviewed retroviral involvement such as HIV (HIV), human intracisternal A-type retroviral particle (HIAP-I) and human retrovirus-5(HRV-5) and concluded that these viral agents contribute to SS activation based on the presence of cross-reactive antibodies to retroviral Gag proteins, detection of retroviral antigens, isolation of retrovirus-like particles or novel retroviral sequences from salivary glands all within SS patients. Also, there are reports of improvement of sicca syndrome on commencement of HAART regime [11] **.

Conclusion

Sjögren's syndrome is a chronic inflammatory illness with no etiology identified. An easy and common hypothesis is that there is a viral etiological agent, which is a ubiquitous or near ubiquitous human infection. While a number of virus have been implicated as potential etiological agents and some viruses cause a Sjögren's-like illness, there are no conclusive data in regard to a causative role in the disease.

Acknowledgement

We acknowledge the support provided by NIH grants to RHS 1 P50 AR060804.

References

1. Theander E, Wollheim FA. Sjögren's Syndrome. Sjögren's Syndrome Practical Guidelines to Diagnosis and Therapy. 2012:11–4.

**2. Shiboski SC, Shiboski CH, Criswell LA, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: A data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance Cohort. Arthritis Care & Research. 2012; 64:475–87. – Up to date approach to classifying SS patients. [PubMed: 22563590]

3. Moutsopoulos HM. Sjögren's syndrome or autoimmune epithelitis? Clinical reviews in allergy & immunology. 2007; 32:199–200. [PubMed: 17992586]

*4. Haga H, Naderi Y, Moreno AM, et al. A study of the prevalence of sicca symptoms and secondary Sjo gren ' s syndrome in patients with rheumatoid arthritis , and its association to disease activity and treatment profile. International journal of rheumatic diseases. 2012; 15:284–8. – Study detailing Sicca symptoms in several countries, and demonstrates patients on biologicals tend to not have Sicca symptoms. [PubMed: 22709490]

5. Haugen AJ, Peen E, Hultén B, et al. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scandinavian journal of rheumatology. 2008; 37:30–4. [PubMed: 18189192]

6. Järvinen P, Aho K. Twin studies in rheumatic diseases. Seminars in Arthritis and Rheumatism. 1994; 24:19–28. [PubMed: 7985034]

7. Selmi C, Mayo MJ, Bach N, et al. Primary Biliary Cirrhosis in Monozygotic and Dizygotic Twins: Genetics, Epigenetics, and Environment. Gastroenterology. 2004; 5085:485–92. [PubMed: 15300581]

8. Fox RI, Fox CM. Sjögren's syndrome: Infections that may play a role in pathogenesis, mimic the disease, or complicate the patient's course. Indian Journal of Rheumatology. 2011; 6:13–25.

9. Nakamura H, Takagi Y, Kawakami A, et al. HTLV-I infection results in resistance toward salivary gland destruction of Sjögren's syndrome. Clinical and experimental rheumatology. 2008; 26:653–5. [PubMed: 18799099]

*10. Chen M-H, Hsiao L-T, Chen M-H, et al. Clinical significance of chronic hepatitis B virus infection in patients with primary Sjögren's syndrome. Clinical rheumatology. 2012; 31:309–15. – Discusses how HBV infection may protect individuals from pSS and reduce pulmonary involvement. [PubMed: 21809004]

**11. Sipsas NV, Gamaletsou MN, Moutsopoulos HM. Is Sjögren's syndrome a retroviral disease? Arthritis research & therapy. 2011; 13:212. [PubMed: 21489323]

12. Bach J-F. Infections and autoimmune diseases. Journal of autoimmunity. 2005; 25(Suppl):74–80. [PubMed: 16278064]

13. Coppieters KT, Wiberg A, Von Herrath MG. Viral infections and molecular mimicry in type 1 diabetes. APMIS?: acta pathologica, microbiologica, et immunologica Scandinavica. 2012; 120:941–9.

14. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annual review of immunology. 2003; 21:335–76.

15. Mitsias DI, Kapsogeorgou EK, Moutsopoulos HM. The role of epithelial cells in the initiation and perpetuation of autoimmune lesions: lessons from Sjogren's syndrome (autoimmune epithelitis). Lupus. 2006; 15:255–61. [PubMed: 16761498]

**16. Yao Y, Liu Z, Jallal B, et al. Type I Interferons in Sjögren's Syndrome. Autoimmunity reviews Published Online First. Nov 29.2012 doi:10.1016/j.autrev.2012.10.006 – Pathomechansim relating specfically to SS.

17. Zheng L, Zhang Z, Yu C, et al. Association between IFN-alpha and primary Sjogren's syndrome. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2009; 107:e12–8.

18. Emamian ES, Leon JM, Lessard CJ, et al. Peripheral blood gene expression profiling in Sjögren's syndrome. Genes and immunity. 2009; 10:285–96. [PubMed: 19404300]

**19. Rönnblom L, Eloranta M-L. The interferon signature in autoimmune diseases. Current opinion in rheumatology Published Online First:. Dec 15.2013 doi:10.1097/BOR.0b013e32835c7e32 – Describes how IFN can be used as a diagnostic tool, also explains different IFN pathways used by autoimmune diseases and where some converge.

20. Borden EC, Sen GC, Uze G, et al. Interferons at age 50: past, current and future impact on biomedicine. Nature reviews Drug discovery. 2007; 6:975–90.

21. Rönnblom L, Alm GV. A pivotal role for the natural interferon alpha-producing cells (plasmacytoid dendritic cells) in the pathogenesis of lupus. The Journal of experimental medicine. 2001; 194:F59–63. [PubMed: 11748288]

22. Siegal FP, Kadowaki N, Shodell M, et al. The nature of the principal type 1 interferon-producing cells in human blood. Science (New York, NY). 1999; 284:1835–7.

23. Gaston JS, Rowe M, Bacon P. Sjögren's syndrome after infection by Epstein-Barr virus. The Journal of rheumatology. 1990; 17:558–61. [PubMed: 2161461]

24. Horiuchi M, Yamano S, Inoue H, et al. Possible involvement of IL-12 expression by Epstein-Barr virus in Sjögren syndrome. Journal of clinical pathology. 1999; 52:833–7. [PubMed: 10690174]

25. Mariette X, Gozlan J, Clerc D, et al. Detection of Epstein-Barr virus DNA by in situ hybridization and polymerase chain reaction in salivary gland biopsy specimens from patients with Sjögren's syndrome. The American journal of medicine. 1991; 90:286–94. [PubMed: 1848394]

26. Fox RI, Luppi M, Kang HI, et al. Reactivation of Epstein-Barr virus in Sjögren's syndrome. Springer seminars in immunopathology. 1991; 13:217–31. [PubMed: 1664987]

**27. Inoue H, Mishima K, Yamamoto-Yoshida S, et al. Aryl hydrocarbon receptor-mediated induction of EBV reactivation as a risk factor for Sjögren's syndrome. Journal of immunology (Baltimore, Md: 1950). 2012; 188:4654–62. – Potential factor for EBV reactivation.

28. Tateishi M, Saito I, Yamamoto K, et al. Spontaneous production of Epstein-Barr virus by B lymphoblastoid cell lines obtained from patients with Sjögren's syndrome. Possible involvement of a novel strain of Epstein-Barr virus in disease pathogenesis. Arthritis and rheumatism. 1993; 36:827–35.

29. Vaughan JH, Valbracht JR, Nguyen MD, et al. Epstein-Barr virus-induced autoimmune responses. I. Immunoglobulin M autoantibodies to proteins mimicking and not mimicking Epstein-Barr virus nuclear antigen-1. The Journal of clinical investigation. 1995; 95:1306–15. [PubMed: 7533788]

30. Soshilov A, Denison MS. Ligand displaces heat shock protein 90 from overlapping binding sites within the aryl hydrocarbon receptor ligand-binding domain. The Journal of biological chemistry. 2011; 286:35275–82. [PubMed: 21856752]

31. Stejskalova L, Dvorak Z, Pavek P. Endogenous and exogenous ligands of aryl hydrocarbon receptor: current state of art. Current drug metabolism. 2011; 12:198–212. [PubMed: 21395538]

32. Simones T, Shepherd DM. Consequences of AhR activation in steady-state dendritic cells. Toxicological sciences?: an official journal of the Society of Toxicology. 2011; 119:293–307. [PubMed: 21097750]

33. Jin G-B, Moore AJ, Head JL, et al. Aryl hydrocarbon receptor activation reduces dendritic cell function during influenza virus infection. Toxicological sciences?: an official journal of the Society of Toxicology. 2010; 116:514–22. [PubMed: 20498003]

34. Quintana FJ, Basso AS, Iglesias AH, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature. 2008; 453:65–71. [PubMed: 18362915]

35. Funatake CJ, Marshall NB, Steppan LB, et al. Cutting edge: activation of the aryl hydrocarbon receptor by 2,3,7,8-tetrachlorodibenzo-p-dioxin generates a population of CD4+ CD25+ cells with characteristics of regulatory T cells. Journal of immunology (Baltimore, Md: 1950). 2005; 175:4184–8.

36. Allan LL, Sherr DH. Constitutive activation and environmental chemical induction of the aryl hydrocarbon receptor/transcription factor in activated human B lymphocytes. Molecular pharmacology. 2005; 67:1740–50. [PubMed: 15681594]

37. Lu H, Crawford RB, Kaplan BLF, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-mediated disruption of the CD40 ligand-induced activation of primary human B cells. Toxicology and applied pharmacology. 2011; 255:251–60. [PubMed: 21807014]

38. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008; 453:106–9. [PubMed: 18362914]

39. Veldhoen M, Duarte JH. The aryl hydrocarbon receptor: fine-tuning the immune-response. Current opinion in immunology. 2010; 22:747–52. [PubMed: 20926270]

40. Patel RD, Murray IA, Flaveny CA, et al. Ah receptor represses acute-phase response gene expression without binding to its cognate response element. Laboratory investigation; a journal of technical methods and pathology. 2009; 89:695–707.

41. Barzilai O, Sherer Y, Ram M, et al. Epstein-Barr virus and cytomegalovirus in autoimmune diseases: are they truly notorious? A preliminary report. Annals of the New York Academy of Sciences. 2007; 1108:567–77. [PubMed: 17894021]

42. Ohyama Y, Carroll VA, Deshmukh U, et al. Severe Focal Sialadenitis and Dacryoadenitis in NZM2328 Mice Induced by MCMV: A Novel Model for Human Sjogren's Syndrome. J Immunol. 2006; 177:7391–7. [PubMed: 17082658]

43. Cardin RD, Schaefer GC, Allen JR, et al. The M33 chemokine receptor homolog of murine cytomegalovirus exhibits a differential tissue-specific role during in vivo replication and latency. Journal of virology. 2009; 83:7590–601. [PubMed: 19439478]

44. Case R, Sharp E, Benned-Jensen T, et al. Functional analysis of the murine cytomegalovirus chemokine receptor homologue M33: ablation of constitutive signaling is associated with an attenuated phenotype in vivo. Journal of virology. 2008; 82:1884–98. [PubMed: 18057236]

45. Davis-Poynter NJ, Lynch DM, Vally H, et al. Identification and characterization of a G protein-coupled receptor homolog encoded by murine cytomegalovirus. Journal of virology. 1997; 71:1521–9. [PubMed: 8995678]

**46. Farrell HE, Abraham AM, Cardin RD, et al. Identification of common mechanisms by which human and mouse cytomegalovirus seven transmembrane receptor homologues contribute to in vivo phenotypes in a mouse model. Journal of virology Published Online First:. Jan 23.2013 doi: 10.1128/JVI.03406-12 – Describes common CMV receptors to human and mouse that may be implicated in SS.

47. De Stefano R, Manganelli S, Frati E, et al. No association between human parvovirus B19 infection and Sjögren's syndrome. Annals of the rheumatic diseases. 2003; 62:86–7. [PubMed: 12480682]

48. De Re V, De Vita S, Battistella V, et al. Absence of human parvovirus B19 DNA in myoepithelial sialadenitis of primary Sjögren's syndrome. Annals of the rheumatic diseases. 2002; 61:855–6. [PubMed: 12176821]

49. Ramos-Casals M, Cervera R, García-Carrasco M, et al. Cytopenia and past human parvovirus B19 infection in patients with primary Sjögren's syndrome. Seminars in arthritis and rheumatism. 2000; 29:373–8. [PubMed: 10924023]

50. Chen C-H, Yang P-M, Huang G-T, et al. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. Journal of the Formosan Medical Association = Taiwan yi zhi. 2007; 106:148–55. [PubMed: 17339159]

51. Watanabe K, Ohkubo Y, Funahashi Y, et al. An investigation on rheumatoid factor of different immunoglobulin classes in hepatitis B virus carriers. Clinical rheumatology. 1991; 10:31–7. [PubMed: 2065505]
52. Marcos M, Alvarez F, Brito-Zerón P, et al. Chronic hepatitis B virus infection in Sjögren's syndrome. Prevalence and clinical significance in 603 patients. Autoimmunity reviews. 2009; 8:616–20.
53. Ramos-Casals M, García-Carrasco M, Cervera R, et al. Hepatitis C virus infection mimicking primary Sjögren syndrome. A clinical and immunologic description of 35 cases. Medicine. 2001; 80:1–8.
54. Smyth CM, McKiernan SM, Hagan R, et al. Chronic hepatitis C infection and sicca syndrome: a clear association with HLA DQB1*02. European journal of gastroenterology & hepatology. 2007; 19:493–8. [PubMed: 17489060]
55. Loustaud-Ratti V, Riche A, Liozon E, et al. Prevalence and characteristics of Sjögren's syndrome or Sicca syndrome in chronic hepatitis C virus infection: a prospective study. The Journal of rheumatology. 2001; 28:2245–51. [PubMed: 11669164]
56. Scott CA, Avellini C, Desinan L, et al. Chronic lymphocytic sialoadenitis in HCV-related chronic liver disease: comparison of Sjögren's syndrome. Histopathology. 1997; 30:41–8. [PubMed: 9023556]
57. Freni MA, Artuso D, Gerken G, et al. Focal lymphocytic aggregates in chronic hepatitis C: occurrence, immunohistochemical characterization, and relation to markers of autoimmunity. Hepatology (Baltimore, Md). 1995; 22:389–94.
58. Vitali C, Sciuto M, Neri R, et al. Anti-hepatitis C virus antibodies in primary Sjögren's syndrome: false positive results are related to hyper-gamma-globulinaemia. Clinical and experimental rheumatology. 1992; 10:103–4. [PubMed: 1312919]
59. Nagao Y, Hanada S, Shishido S, et al. Incidence of Sjögren's syndrome in Japanese patients with hepatitis C virus infection. Journal of gastroenterology and hepatology. 2003; 18:258–66. [PubMed: 12603525]
60. Carrozzo M. Oral diseases associated with hepatitis C virus infection. Part 1. sialadenitis and salivary glands lymphoma. Oral diseases. 2008; 14:123–30.
61. Ramos-Casals M, Loustaud-Ratti V, De Vita S, et al. Sjögren syndrome associated with hepatitis C virus: a multicenter analysis of 137 cases. Medicine. 2005; 84:81–9. [PubMed: 15758837]
62. Toussirot E, Le Huédé G, Mougin C, et al. Presence of hepatitis C virus RNA in the salivary glands of patients with Sjögren's syndrome and hepatitis C virus infection. The Journal of rheumatology. 2002; 29:2382–5. [PubMed: 12415596]
63. Arrieta JJ, Rodríguez-Iñigo E, Ortiz-Movilla N, et al. In situ detection of hepatitis C virus RNA in salivary glands. The American journal of pathology. 2001; 158:259–64. [PubMed: 11141499]
64. Grossmann S, de MC, Teixeira R, de Oliveira GC, et al. Xerostomia, hyposalivation and sialadenitis in patients with chronic hepatitis C are not associated with the detection of HCV RNA in saliva or salivary glands. Journal of clinical pathology. 2010; 63:1002–7. [PubMed: 20924089]
65. Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94:233–6. [PubMed: 8990191]
66. Rosa D, Saletti G, De Gregorio E, et al. Activation of naïve B lymphocytes via CD81, a pathogenetic mechanism for hepatitis C virus-associated B lymphocyte disorders. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:18544–9. [PubMed: 16339892]
67. Machida K, Cheng KT-H, Pavio N, et al. Hepatitis C virus E2-CD81 interaction induces hypermutation of the immunoglobulin gene in B cells. Journal of virology. 2005; 79:8079–89. [PubMed: 15956553]
68. Roughan JE, Reardon KM, Cogburn KE, et al. Chronic hepatitis C virus infection breaks tolerance and drives polyclonal expansion of autoreactive B cells. Clinical and vaccine immunology?: CVI. 2012; 19:1027–37. [PubMed: 22623650]

69. Meltzer M, Franklin EC. Cryoglobulinemia--a study of twenty-nine patients. I. IgG and IgM cryoglobulins and factors affecting cryoprecipitability. The American journal of medicine. 1966; 40:828–36. [PubMed: 4956870]

70. Meltzer M, Franklin EC, Elias K, et al. Cryoglobulinemia--a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. The American journal of medicine. 1966; 40:837–56.

71. Himoto T, Masaki T. Extrahepatic manifestations and autoantibodies in patients with hepatitis C virus infection. Clinical & developmental immunology. 2012; 2012:871401. [PubMed: 22988469]

72. Ramos-Casals M, Font J. Extrahepatic manifestations in patients with chronic hepatitis C virus infection. Current opinion in rheumatology. 2005; 17:447–55. [PubMed: 15956842]

73. Ramos-Casals M, La Civita L, De Vita S, et al. Characterization of B cell lymphoma in patients with Sjögren's syndrome and hepatitis C virus infection. Arthritis and rheumatism. 2007; 57:161–70. [PubMed: 17266090]

**74. De Vita S, Quartuccio L, Salvin S, et al. Cryoglobulinaemia related to Sjogren's syndrome or HCV infection: differences based on the pattern of bone marrow involvement, lymphoma evolution and laboratory tests after parotidectomy. Rheumatology (Oxford, England). 2012; 51:627–33. – Differentiates the biologic background of SS-related cryoglobulinaemia as compared with cryoglobulinaemia linked to HCV infection.

75. Ramos-Casals M, García-Carrasco M, Cervera R, et al. Th1/Th2 cytokine imbalance in patients with Sjögren syndrome secondary to hepatitis C virus infection. Seminars in arthritis and rheumatism. 2002; 32:56–63. [PubMed: 12219321]

76. Jorgensen C, Legouffe MC, Perney P, et al. Sicca syndrome associated with hepatitis C virus infection. Arthritis and rheumatism. 1996; 39:1166–71. [PubMed: 8670326]

77. Ramos-Casals M, García-Carrasco M, Brito Zerón MP, et al. Viral etiopathogenesis of Sjögren's syndrome: role of the hepatitis C virus. Autoimmunity reviews. 2002; 1:238–43. [PubMed: 12849002]

78. Böckle BC, Baltaci M, Ratzinger G, et al. Hepatitis C and autoimmunity: a therapeutic challenge. Journal of internal medicine. 2012; 271:104–6. [PubMed: 21564352]

79. Ulbricht KU, Schmidt RE, Witte T. Antibodies against alpha-fodrin in Sjögren's syndrome. Autoimmunity reviews. 2003; 2:109–13. [PubMed: 12848967]

80. Potthoff A, Witte T, Rifai K, et al. Prevalence of alpha-fodrin antibodies in patients with chronic hepatitis C infection and Sjögren syndrome. Scandinavian journal of gastroenterology. 2009; 44:994–1003. [PubMed: 19462335]

81. Nordmark G, Rorsman F, Rönnblom L, et al. Autoantibodies to alpha-fodrin in primary Sjögren's syndrome and SLE detected by an in vitro transcription and translation assay. Clinical and experimental rheumatology. 2003; 21:49–56. [PubMed: 12673889]

*82. Brito-Zerón P, Retamozo S, Gandía M, et al. Monoclonal gammopathy related to Sjögren syndrome: a key marker of disease prognosis and outcomes. Journal of autoimmunity. 2012; 39:43–8. – Importance of using monoclonal gammopathy as a frequent immunological marker of primary SS. [PubMed: 22297146]

83. Doffoël-Hantz V, Loustaud-Ratti V, Ramos-Casals M, et al. Evolution of Sjögren syndrome associated with hepatitis C virus when chronic hepatitis C is treated by interferon or the association of interferon and ribavirin. La Revue de médecine interne / fondée . par la Société nationale francaise de médecine interne. 2005; 26:88–94. [PubMed: 15710254]

84. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjögren's syndrome. Arthritis and rheumatism. 2004; 50:2897–902. [PubMed: 15457458]

85. Agirre A, Barco A, Carrasco L, et al. Viroporin-mediated membrane permeabilization. Pore formation by nonstructural poliovirus 2B protein. The Journal of biological chemistry. 2002; 277:40434–41.

86. Stathopoulou EA, Routsias JG, Stea EA, et al. Cross-reaction between antibodies to the major epitope of Ro60 kD autoantigen and a homologous peptide of Coxsackie virus 2B protein. Clinical and experimental immunology. 2005; 141:148–54. [PubMed: 15958081]

87. De Thé G, Bomford R. An HTLV-I vaccine: why, how, for whom? AIDS research and human retroviruses. 1993; 9:381–6. [PubMed: 8318266]

88. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Frontiers in microbiology. 2012; 3:388. [PubMed: 23162541]

89. Satake M, Yamaguchi K, Tadokoro K. Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. Journal of medical virology. 2012; 84:327–35. [PubMed: 22170555]

90. Ohyama Y, Nakamura S, Hara H, et al. Accumulation of human T lymphotropic virus type I-infected T cells in the salivary glands of patients with human T lymphotropic virus type I-associated Sjögren's syndrome. Arthritis and rheumatism. 1998; 41:1972–8. [PubMed: 9811052]

91. Eguchi K, Matsuoka N, Ida H, et al. Primary Sjögren's syndrome with antibodies to HTLV-I: clinical and laboratory features. Annals of the rheumatic diseases. 1992; 51:769–76. [PubMed: 1352097]

92. Terada K, Katamine S, Eguchi K, et al. Prevalence of serum and salivary antibodies to HTLV-1 in Sjögren's syndrome. Lancet. 1994; 344:1116–9. [PubMed: 7934493]

93. Bogenberger JM, Laybourn PJ. Human T Lymphotropic Virus Type 1 protein Tax reduces histone levels. Retrovirology. 2008; 5:9. [PubMed: 18237376]

94. Coulderc LJ, Desgranges C, Coste J, et al. Antibodies to HTLV-I in Sjögren's syndrome. Lancet. 1995; 345:72. [PubMed: 7799738]

95. Sasaki M, Nakamura S, Ohyama Y, et al. Accumulation of common T cell clonotypes in the salivary glands of patients with human T lymphotropic virus type I-associated and idiopathic Sjögren's syndrome. Journal of immunology (Baltimore, Md: 1950). 2000; 164:2823–31.

Keypoints

- Certain infections may mimic SS and are therefore SS-like illness.
- Activated IFN-1 pathway plays an important part in the autoimmune disease process of SS.
- Dioxin has been proposed to be a co-factor in the development of autoimmune diseases as it contributes to the modulation of the activity of other transcription factors such as NF-kB.
- The most commonly reported systemic autoimmune diseases in association with chronic HCV infection is Sjogren's Sydrome.
- Autoantibodies have a different pattern in HVC-related sialoadenitis and pSS.

Purpose of Review

This review discusses recent developments concerning the potential viral pathomechanisms and involvement of viruses in Sjögren's Syndrome.

Recent Findings

Activated IFN-1 pathway plays an important part in the autoimmune disease process of SS therefore; several therapies aiming to reduce or inhibit the IFN-1 production and its effects may be a target for future treatment plans. Activation of the aryl hydrocarbon receptor (AhR) may interact with latent EBV infection which in turn may predispose to development of SS, it is estimated that the population is 95% positive for EBV serology.

Table 1

Viruses investigated as etiological agents in Sjögren's syndrome. The plus (+) signs indicate research that given virus has been implicated in the one of the molecular pathogenic mechanisms shown. A negative sign (−) indicates there is no evidence for a virus with the given mechanisms.

	Pathogenic Mechanisms		
	Molecular mimicry	**Polyclonal activation**	**Inflammation**
EBV	+	−	+
CMV	+	−	+
Parovirus B19	−	−	−
HBV	+	−	−
HCV	−	+	+
Coxackie	+	−	+
HTLV1	−	−	+