What is the evidence that mycobacteria are associated with the pathogenesis of Sjogren’s syndrome?

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ABSTRACT

Sjogren’s syndrome (SS) is a common, systemic autoimmune disorder primarily affecting the exocrine glands resulting in xerostomia and xerophthalmia. SS may also manifest with polyarthralgia, polyarthritis, polymyalgia, cutaneous/other organ vasculitis, interstitial lung disease, and/or various other disorders. The primary autoantibodies associated with SS and used as adjuncts to diagnosis are anti-Ro (SSA) and anti-La (SSB). The pathogenesis of SS is considered to involve genetic susceptibility and environmental triggers. An identified genetic susceptibility for SS lies in variants of the tumor necrosis factor alpha inducible protein 3 (TNFAIP3) gene, the product of which is known as A20. Deficiency or dysfunction of A20 is known to induce macrophage inflammatory response to mycobacteria, potentially increasing the repertoire of mycobacterial antigens available and predisposing to autoimmunity via the paradigm of molecular mimicry; i.e., providing a mechanistic link between genetic susceptibility to SS and exposure to environmental non-tuberculous mycobacteria (NTM). Mycobacterium avium ss. paratuberculosis (MAP) is an NTM that causes Johne’s disease, an enteritis of ruminant animals. Humans are broadly exposed to MAP or its antigens in the environment and in food products from infected animals. MAP has also been implicated as an environmental trigger for a number of autoimmune diseases via cross reactivity of its heat shock protein 65 (hsp65) with host-specific proteins. In the context of SS, mycobacterial hsp65 shares epitope homology with the Ro and La proteins. A recent study showed a strong association between SS and antibodies to mycobacterial hsp65. If and when this association is validated, it would be important to determine whether bacillus Calmette-Guerin (BCG) vaccination (known to be protective against NTM likely through epigenetic alteration of innate and adaptive immunity) and anti-mycobacterial drugs (to decrease mycobacterial antigenic load) may have a preventive or therapeutic role against SS. Evidence to support this concept is that BCG vaccination against certain autoimmune diseases is associated with a variety of systemic manifestations including arthralgia, arthritis, vasculitis, neuropathies, interstitial lung disease, bronchiectasis, intestinal disorders, and various hematologic manifestations including anemia of chronic disease, hemolytic anemia, lymphopenia, autoimmune neutropenia, and thrombocytopenia [1,3–5]. Lymphoma is also one of the more significant diseases associated with SS – most often manifesting as a

1. Introduction

Sjogren’s syndrome (SS) is a systemic autoimmune disorder known for its effects on the exocrine glands such as the salivary and lacrimal glands, resulting in xerostomia and xerophthalmia [1]. SS is one of the most common autoimmune diseases in adults, affecting up to 3.2 million individuals in the United States [2]. SS is also associated with a variety of systemic manifestations including arthralgia, arthritis, vasculitis, neuropathies, interstitial lung disease, bronchiectasis, intestinal disorders, and various hematologic manifestations including anemia of chronic disease, hemolytic anemia, lymphopenia, autoimmune neutropenia, and thrombocytopenia [1,3–5]. Lymphoma is also one of the more significant diseases associated with SS – most often manifesting as a
mucosa-associated lymphoid tissue lymphoma of the parotid gland – with a lifetime risk of about 10% [6–9]. When SS manifests without another concurrent autoimmune disease, it is referred to as primary SS whereas secondary SS is associated with one or more other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis [3,10,11].

The goal of this review is to provide evidence that exposure to mycobacterial antigens may be an important link between genetic susceptibility to and pathogenesis of SS. We further speculate that if the link between mycobacteria and SS can be further validated, the bacillus Calmette Guerin (BCG) vaccine and anti-mycobacterial drugs may help protect against and treat SS.

2. Evidence for the role of mycobacteria in autoimmune diseases

2.1. Genetic susceptibility to SS and mycobacterial infection

Deficiency of the protein A20, normally a negative regulator of tumor necrosis factor (TNF), is linked to inflammation and autoimmunity [12, 13]. A20 is encoded by tumor necrosis factor alpha-induced protein 3 (TNFAIP3) gene [14]. Interestingly, polymorphisms of the TNFAIP3 gene are associated with three common autoimmune diseases – primary SS, rheumatoid arthritis, and systemic lupus erythematosus – with the allu-

dation that A20 deficiency or dysfunction is associated with these implicated polymorphisms. Indeed, investigations of single nucleotide polymorphism (SNP) of TNFAIP3 showed that rs6920220 is associated with all three of these autoimmune diseases [15]. In another study, SNP rs2230926 of TNFAIP3 gene was associated with SS prevalence as well as non-Hodgkin’s lymphoma, a known complication of SS [16].

How could mutation of A20 predispose to autoimmunity in the context of mycobacteria? Defect or deficiency of A20 has been shown to decrease autophagy in CD4 (+) T cells, which could decrease survival of these adaptive immune cells that are important in host-defense against mycobacteria, predisposing to their colonization (Fig. 1) [17]. In contrast, A20 plays a role in dampening the innate immune response against mycobacteria such that A20-deficient macrophages are more effective in killing Mycobacterium tuberculosis [18]. This finding is supported by a study showing that alpha-1-antitrypsin inhibited A20 expression in human macrophages, resulting in greater autophagy (opposite to that seen with CD4 (+) T cells) and control of Mycobacterium intracellulare infection; i.e., with greater maturation of the autophago-

some (aka increased autophagosome-lysosome fusion), there is increased killing of mycobacteria that are in autophagosomes, resulting in mycobacterial peptides or lipids that are presented on either class II MHC or CD1, respectively, to activate T effector cells [19]. While B cells classically recognized antigens in their native form, they may also recognize membrane-bound antigens and become activated [20,21].

Hence, we reasoned that since a defect or deficiency of A20 would be expected to enhance autophagy in macrophages – a killing mechanism of mycobacteria – perhaps the macrophages of such individuals would be better able to process/kill mycobacteria, resulting in more abundant repertoire of mycobacterial antigens available to induce autoimmunity in SS through antigen presentation to either T cells or B cells [22,23] (Fig. 1). Thus, B cells can become activated by antigens presented by macrophages but also transfer antigens to macrophages (independent of MHC) to activate the latter, which can subsequently activate T cells [20]. In addition, bovine macrophages infected with Mycobacterium avium ss. paratuberculosis (MAP) – an NTM increasingly implicated in Crohn’s disease and other autoimmune diseases – induced long non-coding RNA’s which downregulated transcripts of TNFAIP3 [24], potentially further augmenting the availability of mycobacterial antigens. In contrast to that seen with MAP, murine bone marrow-derived macrophages infected with Mycobacterium fortuitum induced A20, which subsequently impaired the macrophage inflammatory response [25].

2.2. Autoantibodies SSA and SSB and the link to hsp65

The presence of autoantibodies is a hallmark of SS. Anti-SSA (Ro) and anti-SSB (La) autoantibodies are the main serological markers for the diagnosis of SS; these are directed against the Ro and La ribonucleo-


drotein complex. In two large cohorts, positive anti-SSA and anti-SSB serologies were present in 76% and 73%, respectively, of SS subjects [26].

Protective heat shock proteins (hsp) are found in all life forms. They play a critical role acting as chaperonins in protein folding [27] and are linked to the host immune response [28]. Hsp65 of mycobacteria is an immunodominant antigen in that during human mycobacterial infection, up to 40% of the T-cell response is directed against this single mycobacterial protein [29]. [30] The term “molecular mimicry” was introduced more than 50 years ago when it was posited that antigenic elements of a microorganism could mimic protein elements of its host [31]. This concept is based upon structural similarity between a pathogen protein and a host “self” protein and is used to explain the frequent association of infections with autoimmune diseases [30,32]. Indeed, mycobacterial hsp65 shares sequence homology with various human proteins [30]. The anti-hsp65 antibody testing is highly sensitive and reliably identifies individuals with abnormal immune responses to mycobacteria [29]. A recent study found that the seroprevalence of antibodies against mycobacterial hsp65 was 2.8% in a normal population, and 85% in a SS cohort [5]. In the same study, 68% of Crohn’s patients were found to have mycobacterial anti-hsp65 antibodies [28] (Fig. 2).
2.3. Human exposure to and infection with MAP and the link to autoimmune diseases

MAP is a slow-growing, acid-fast organism. In domestic ruminant animals, MAP causes a chronic fatal granulomatous enteritis known as Johne’s disease [35,36]. The United States Department of Agriculture noted that the herd-level prevalence of MAP infection in U.S. dairy herds has greatly increased, from 21.6% in 1996 to 91.1% in 2007 [37]. Newborn born and young calves are most susceptible to MAP infections [38–41]. Further complicating the control of Johne’s disease is that infected animals can remain clinically asymptomatic for years while shedding MAP in their feces and milk. An infectious dose can be as little as 2 g (0.07 ounce) of manure. A single “super-shredder” infected cow can produce up to 15 gallons a day of contaminated manure, equivalent to over 25,000 infectious doses per day [42].

MAP is transmitted to humans in a variety of ways. MAP is present in the environment as in surface water [43,44], municipal drinking water [45,46], and soil [43], and thus could be transmitted to humans directly from environmental sources. Furthermore, since viable MAP is recoverable from pasteurized milk [47,48] and from powder infant formula produced from pasteurized milk, it may be acquired through ingestion of dairy products [49,50].

The range of pathogenesis of MAP-related human disease is broad. MAP can initiate a granulomatous response and stimulate autoantibodies via molecular mimicry [51]. Another manner by which MAP may induce disease is by activating expression of antigens encoded by human endogenous retroviruses (HERV). While these traces of ancestral viral infections are usually genetically silent, they can be activated by a superimposed infection [52]. These HERV have been detected in a number of autoimmune diseases [52] including SS [53], multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis [51]. With regards to type 1 autoimmune diabetes mellitus, mycobacterial hsp65 shares homology with the pancreatic enzyme glutamic acid decarboxylase. Because an immune response against the persistent mycobacteria cross reacts with the pancreatic enzyme, insulin-producing islet cells are secondarily damaged [57]. In one study, reaction to mycobacterial hsp65 was detected in all newly diagnosed type 1 diabetic patients [58]. A disease without granulomas or autoantibodies in which MAP has been implicated is Parkinson’s disease, in which a consumptive exhaustion of autophagy caused by MAP is the postulated pathogenesis [59,60].

3. Countering mycobacteria with BCG and/or antimicrobial agents

3.1. BCG

Worldwide, BCG is the most common vaccine used. Its efficacy against tuberculosis (TB) resides mainly in its excellent protection against disseminated and meningeal TB in children [61]. While its efficacy against pulmonary TB has an overall rate ratio of ~0.50, it varies widely (with range of efficacy of 0–80% in different trials) depending on age at vaccination (better protection when given at neonatal and school ages), tuberculin skin test (TST) status (better protection when TST negative), and distance from the equator (better protection the further away the recipient lives from the equator) [61,62]. While BCG vaccine is currently given intradermally, oral BCG may be more effective in inducing mycobacteria-specific interferon-gamma responses while inhibiting delayed-type hypersensitivity reaction – the latter measured by a positive TST response to purified protein derivative (PPD); i.e., oral BCG may not only be more protective than intradermal BCG against mycobacterial infections but less likely to cause a false-positive TST [63]. Interestingly, a recent report indicated that BCG given intravenously to macaques provided much greater protection against TB [64]. There is increasing but largely epidemiologic evidence that BCG may also provide protection against NTM infections [65–70]. Thus, BCG has the potential to protect against NTM such as MAP and perhaps help prevent the initiation or exacerbation of autoimmune diseases that may be associated with them.

3.2. Anti-mycobacterial therapy

Treatment of NTM is challenging for several reasons including the relative and absolute resistance of NTM to many of the currently available antibiotics and the difficulty in tolerating prolonged multi-drug treatment regimens. For example, in the treatment of lung diseases due to Mycobacterium avium complex (MAC), comprised of several species with the most common ones being M. avium hominisuis, M. intracellulare, and M. chimaera, the standard treatment regimen is a combination of a newer generation macrolide such as clarithromycin or azithromycin, rifampycin and ethambutol; additional agents such as clofazimine and/or inhaled or intravenous amikacin may be added or substituted depending on severity of disease or drug susceptibility patterns. Yet-to-be-done, large, multi-center, prospective randomized studies to establish the best regimens will also be arduous because multiple NTM species are known to cause human disease, differences in virulence and response to treatment between different species and strains within a species will make unbiased randomization difficult, the need to distinguish relapse from a new infection, and the difficulty in adhering to the prescribed treatment due to intolerance, toxicity, and/or drug-drug interactions, often necessitating modification of therapeutic regimens. Thus, current treatment regimens for NTM infections are largely based on small case series, retrospective analyses, and expert opinions [71].

For all patients, whether or not they have autoimmune diseases, if NTM is isolated from a normally sterile site such as the blood [72], the decision to treat is easy as it essentially confirms a disease-causing infection. However, it remains to be seen whether treatment of culturable NTM from normally non-sterile sites such as stool, with the goal of decreasing the antigen load, could attenuate the manifestations of the autoimmune diseases. The challenges that could be anticipated to undertake such a study would be to determine: (i) where to culture for the NTM in those without infectious symptoms although stool analysis would be one potential source to recover MAP; (ii) in those with more than one NTM species are isolated, the decision to treat only one or more than one.

Fig. 2. Direct comparison of the blood levels of hsp65 antibody in patients with Crohn’s disease (n = 109) and Sjogren’s syndrome (n = 28) Used with permission from Dr. Zhang [28].

These findings support the century-long theory of the pathogenic link between Crohn’s disease and MAP [33] although this is not without controversy [34].
of the NTM isolated, (iii) length of therapy, and (iv) which clinical or laboratory biomarkers to determine response to treatment. Even in those with bona fide NTM disease, treatment is challenging because duration of multi-drug treatment is typically for 18 months or longer, and because NTM are ubiquitous environmental organisms, recurrence due to new infections are common. While MAP is a well-established cause of Johne’s disease, drug treatment is not feasible because the antibiotics required are not legal for use in food-producing animals and the duration and amount required for large animals would be prohibitively expensive. In vitro antimicrobial studies against MAP organisms show encouraging results with clarithromycin, rifabutin, and clofazimine. There is emerging evidence that targeting MAP with antibiotics in Crohn’s disease may be salubrious [73–75]. Consistent with their in vitro activity, the combination of clarithromycin, rifabutin and clofazimine, has shown efficacy as a primary treatment for Crohn’s disease [76]. Preliminary report from a multi-center, international open clinical trial of 331 participants with Crohn’s disease noted that adding anti-MAP therapy to standard therapy provided promising treatment effect [77–79].

4. Discussion

Since there is epipoetic homology between hsp65 with both SSA and SSB, it provides the mechanistic plausibility for the development of both anti-hsp65 and the anti-SSA and anti-SSB antibodies via the paradigm of molecular mimicry (Fig. 3a and b). While mycobacterial hsp65 may come from MAP or another mycobacteria, MAP is a leading candidate based on available data [80]. India is one country that has explored the concept of MAP “bio-load”; i.e., extensive fecal testing in one region showed that 34% of cattle, 36% of buffaloes, 23% of goats and 41% of sheep are infected with MAP [81]. In the same region, nearly 31% of 28,291 humans tested positive for MAP as well [81]. MAP has also been implicated in the pathogenesis of rheumatoid arthritis – which not uncommonly co-exist and has overlapping features with SS [82]. More specifically, supporting evidence for the link between mycobacteria and rheumatoid arthritis include the finding of mycobacterial antigens in the joints of rheumatoid arthritis patients and of increased level of anti-mycobacterial antibodies in their sera [82].

The finding of antibodies to mycobacterial hsp65 in a majority of SS patients gives a plausible basis for considering BCG vaccination and/or antimicrobial therapy to prevent development of, or possibly treat SS [23]. In the past 10 years, clinical trials of adult BCG vaccination have shown therapeutic benefits for an array of disease – including a variety of allergic and autoimmune disease such as type 1 diabetes mellitus and multiple sclerosis [83–91]. Hence, we have hypothesized that BCG may help ameliorate the development of other autoimmune diseases that have been linked to mycobacteria [92]. Shown in Fig. 4A is a world map of the relative incidence of autoimmune diseases, with the greatest incidence found in the United States, Canada, and western Europe, followed by Australia and South Africa. As seen in Fig. 4B, the countries with the least BCG utilization are also the ones with the greatest incidence of autoimmune diseases. Another potential mechanism of this hypothesized association is that individuals from wealthier countries may have less exposure to environmental microorganisms, resulting in greater prevalence of autoimmune diseases. Whether this inability to induce autoimmunity to one another mycobacteria may have minimal exposure to environmental bacteria in childhood, subsequent exposure may provide a trigger for onset of autoimmunity [93]. Conversely, in those who have such repeated exposures to environmental microorganism at a young age, we speculate that perhaps epigenetic changes in both their innate and adaptive immunity allowed tolerance and/or efficient control of these organisms. By introducing mycobacteria via BCG vaccination, humans might benefit immunologically. This concept is supported by a growing body of data in autoimmunity and data on the nonspecific immune benefit of BCG related to protection from diverse infections and early mortality [94]. While BCG is an attenuated strain of M. bovis, it does not appear to provoke autoimmunity [95]. Whether this inability to induce autoimmunity is due to the fact that M. bovis is in the MTB complex, is an attenuated bacterial strain, and/or another reason remains to be determined.

What is a potential mechanism by which BCG may be protective in this assortment of diseases? One paradigm is the induction of aerobic glycolysis (Warburg effect) by BCG. Aerobic glycolysis produces energy faster than the slower albeit more efficient mitochondrial oxidative phosphorylation. At the time of infection, pathogenic mycobacteria seem to locally usurp aerobic glycolysis to fuel its invasion of macrophages, playing a key role in their pathogenicity [96]. In turn, the host response is the “adaptation/resolution” process of broad aerobic glycolysis, boosting host immunity to counter the pathogen [96,97]. In other words, aerobic glycolysis is exploited by the mycobacteria in the early phase of invasion into macrophages but is also utilized by host innate immune cells to help control the infection [97,98]. In another example, the potential efficacy of BCG against Alzheimer’s disease is that BCG stimulation of aerobic glycolysis decreases amyloid-mediated neuronal death [99,100]. Despite the evidence that BCG provides benefit for a variety of diseases beyond TB, the lack of a known mechanism of action has been an obstacle to pursue the non-canonical use of BCG for these conditions [101]. However, more recent work has shown that BCG also has beneficial effects on infections other than those due to mycobacteria and that two immunological mechanisms have been proposed to mediate the protective effects of BCG: short term effects are likely mediated by epigenetic reprogramming of innate immune cells (“trained innate immunity” or “memory monocytes”) [102,103], while longer term effects are likely due to heterologous Th1/Th17 immunity [104]. While BCG-induced aerobic glycolysis may theoretically increase mycobacterial antigen load due to inhibition of oxidative stress → inhibition of NFκB induction of autophagy [10], BCG given prophylactically may also prime the immune system to efficiently kill pathogenic bacteria upon initial encounter, ultimately limiting the mycobacterial load. Another potential mechanism by which BCG may protect against the development of autoimmunity is through BCG induction of TNF, which is able to promote a targeted destruction of autoreactive T cells as well as induce T regulatory cells to suppress autoreactive T cells [105].
5. Conclusion

In conclusion, the unfolding knowledge of the epitope homology between SS-relevant autoantigens SSA/SSB and mycobacterial hsp65, the high prevalence of anti-hsp65 antibodies in SS patients, and the benefits of BCG in preventing NTM infections would suggest the rationale of a clinical trial to determine if BCG and/or anti-mycobacterial therapy can ameliorate SS.

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Both CTD and EDC wrote the manuscript.

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Declaration of competing interest

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