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Sjögren's Syndrome: An Immunological Perspective
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Sjögren's syndrome is an autoimmune disorder that develops when one's genetic predisposition combines with environmental or infectious factors. Further, there are *neural* and *hormonal* influences that influence the onset and severity of the disease.

The immune process may involve only the salivary and lacrimal glands (leading to dryness) or may involve additional organs, including nerve, muscle, joints, lung, kidney, gastrointestinal organs, and/or skin. There is a high frequency of associated fibromyalgia, a poorly understood condition that has symptoms of fatigue and vague cognitive changes. Although the pathogenesis of Sjögren's remains unclear, it involves the immune system in a manner that leads to an imbalance of inflammatory transmitters in the glands, tissues, and nerve fibers. Chapter 5 by Moser et al. outlines recent advances on specific genes associated with Sjögren's.

This chapter reviews the two basic portions of the immune system:

1. The *acquired* (or HLA-DR-dependent) immune system associated with autoantibody production

2. The *innate* (HLA-DR-independent) system responsible for many of the symptoms occurring in Sjögren's

We will also review how genetic factors interact with environmental factors to alter the hormonal and neural system and thus produce Sjögren's symptoms.

There are several important "take-home" points regarding the immune system and Sjögren's that will help us understand symptoms, current therapies, and approaches to develop new therapies:

- Biopsies of the salivary or lacrimal gland typically show that only about 50% of the ducts and acini are destroyed in Sjögren's patients, so one of the key questions is: *Why are the residual glands not functioning at optimal level?*

- Salivary and lacrimal functions, namely the production of tears and saliva, are part of a "functional" circuit that includes the central nervous system (midbrain and cortex of the brain), which in turn controls the blood vessels and glandular function;

- Saliva and tears are more than just water, as they contain a complex mixture of proteins, carbohydrates, and mucins to provide the lubrication required for movement of the mucosal membranes (including eyelids and tongue in the mouth).

- At the level of the salivary or lacrimal gland, as well as in the extra-glandular tissues, there is a complex interaction of immune cells that release a series of inflammatory factors that interfere with normal glandular function; type I interferon is an important part of this process.

- Sjögren's patients have more aggressive lymphocytes than in patients with other autoimmune disorders, which is reflected in an elevated frequency of lymphomas or infiltration into other organs such as nerves, lung, or kidney.

The Interaction of Genetic and Environmental Factors

Inherited genes are important, but not enough to explain why patients develop Sjögren's. In this chapter, we will often group certain results of studies of Sjögren's and systemic lupus erythematosus (SLE), since the genetic and nongenetic factors appear to have a great deal in common, and the data available for SLE are more extensive than those for Sjögren's at present. Indeed, the symptoms and pattern of autoantibodies are often overlapping, and the medications are frequently similar. However, the differences between Sjögren's and SLE will also be discussed below.

Physicians and patients have long recognized that simply having susceptibility genes is not enough to guarantee the emergence of clinical disease. The simplest example is the lack of concurrence of Sjögren's or SLE in identical twins:

- Each identical twin shares the same genome but has different exposure to environmental agents and slightly different ways in which their genes are activated (or rearranged) as they respond to infections and hormonal changes.

- If only genetic factors were required, then we would expect that if one twin develops Sjögren's, then the other twin would always develop Sjögren's as well.

- Although the second identical twin does have an increased risk for development of Sjögren's (the concordance rate), the observed frequency of Sjögren's (or SLE) in the other twin is only about 20% to 25%.

- So, roughly speaking, only about 20% of the disease can be considered strictly genetic (i.e., encoded by a person's genome), and the other 80% is due to some other factors such as environmental influence, including exposure to infections or hormonal changes.

Even though there is a great deal of enthusiasm surrounding genomic sequencing, we must remember that the best we will do in terms of prediction is what nature has provided us in the form of identical twins. We do not want to minimize the important role of new advances in genetics, however, and Chapter 5 outlines advances in identifying important genes and the interaction of genes (a field called proteomics).

To summarize, the study of genetics of Sjögren's has allowed the identification of different genes that vary from very important to those that play a weaker role, as assessed by a genetic measure called the *relative risk association*. Each individual will have some combination of these genes, and in the presence of the environmental trigger, an "immune mistake" will occur in which the body attacks some portion of glands or other tissues in a pattern characteristic for each Sjögren's patient.

Long before we ever started genetic studies, it was clear that one of the most important genes was gender, as 90% of Sjögren's patients are female. However, the specific genes on the X chromosome have been difficult to identify. One of the important genes identified in animal models was called the "Toll receptor," and this molecule helps link immune response to different

environmental antigens as discussed below. However, sex hormones also play an important role in modulating the effect of many other genes involved in inflammation. In those males who have Sjögren's, there is an increased frequency of an extra X chromosome (a condition called Klinefelter's syndrome). However, only a few males with Sjögren's have the extra chromosome, so that cannot be the whole story. Current research is trying to identify the specific mechanisms of hormonally responsive genes (particularly because of their role in progression of certain cancers), but this task has remained difficult to translate into useful therapies for Sjögren's or other autoimmune diseases.

The second strongest gene (or cluster of genes) is located on the sixth chromosome in a region that was first identified during the early days of organ transplantation. These genes are called human lymphocyte antigen (HLA) genes. When a person is typed for donation of an organ (such as liver or kidney), both the donor and recipient are tested for their HLA genes since a match will greatly decrease the chance of organ rejection. Subsequent studies have identified a series of additional genes on chromosome 6 that also contribute by encoding additional proteins, including one that was named "complement" (since it complemented the activity of antibodies) and other inflammatory mediators or receptors for those mediators. Thus, the take-home lesson here is that:

> Each SS patient has a series of genes, and when that genetically predisposed individual encounters certain environmental and hormonal stimulation, a "mistake" may be made that leads to the initiation and perpetuation of clinical symptoms of Sjögren's or SLE.

A schematic that shows the timeline is shown in Figure 6–1. The patient starts with the genetic tendency (i.e., female and perhaps HLA-DR3, discussed below). This predisposes the patient to make a particular set of autoantibodies, which we measure in blood tests such as the *anti-nuclear antibody* (ANA) and the antibody to *Sjögren's-associated antigen A* (SS-A), which we now recognize as two different proteins with molecular weight 60,000 and 52,000 respectively. Some patients make antibodies against only the 60,000 molecule, others against only the 52,000 molecule, but most patients make antibodies against both.

<Insert Figure 6–1>

In some patients, a second Sjögren's-associated antigen called SS-B, with molecular weight 45,000, is also found. These antigens are detected in clinical blood tests. The ability of patients to

make particular antibodies is closely correlated with the particular HLA-DR (and associated genes) that they have inherited. These antibodies may be present for many years prior to the onset of any clinical disease; indeed, many patients with these antibodies may never develop clinically significant disease. This is shown schematically in Figure 6–1.

The SS-A and SS-B are proteins that are derived from dying cells (a process called apoptosis). It has been hypothesized that some viruses damage particular cells in the salivary gland, leading to the release of the SS-A and SS-B proteins, and that immune response against "self antigens" becomes a self-perpetuating autoimmune response in genetically predisposed individuals. Later in this chapter we will discuss some of the environmental agents and "apoptotic" fragments that contribute to the immune process.

The (HLA-DR-Dependent) Acquired Immune System

The genome encodes two type of immune response. The part that involves "immune memory" and is associated with the antibodies characteristic of Sjögren's is called the *acquired* immune system. This is the part of the immune system first identified as being important in tissue transplantation. These histocompatibility genes are made of DNA and encode a series of proteins called HLA genes (Fig. 6–2). The HLA antigens were named in the order of their discovery—thus the first ones were called HLA-A, and then HLA-B, HLA-C, and finally HLA-D.

<Insert Figure 6–2>

The most important of these transplantation genes for the development of Sjögren's or SLE was found to be HLA-D. The genes encoded by the HLA-A and B have a slightly different structure than the structure of HLA-D (Fig. 6–2). In recognition of the importance of the HLA-D region and its control of autoantibody production, the acquired (transplantation-like) portion of the immune system is also called the HLA-DR-dependent part of the immune system.

The function of these histocompatibility genes is similar to a plate that holds food in an orientation that can be recognized by certain immune lymphocytes that "come to the table." In Figure 6–2, you can see that the histocompatibility molecule holds the small string of about 12 amino acids (called peptides) in a particular formation (shown by the red molecule held in a

groove). The stabilization of the peptide allows efficient recognition of the molecule by other immune cells. If the peptide correctly fits with the immune receptor (generally on the surface of the T cell or B cell, as discussed below), then the lymphocyte will be stimulated and will make an immune response. This ability to present (or not present) a peptide to the other immune cells is one of the key regulatory steps of the immune system.

Each individual inherits one copy of chromosome 6 from each parent and each contains one copy of HLA-DR. So the patient has two chances to be a responder (i.e., a binder of peptide), or a non-responder if neither of the histocompatibility antigens efficiently binds with the peptide. These histocompatibility genes are different in different individuals (like brown eyes or blue eyes) but have many more choices (as if we could have a hundred different types of eye color). Further, the distribution of these HLA-D antigens is quite different in distinct ethnic populations, and this may help explain the different frequency and clinical manifestation in different countries.

One of the surprising findings of the study of immunology is that a key role for the immune system is the "disposal" of fragments of dead cells that may die as a result of "natural causes" or after a viral infection. We create about a billion new cells per day and an equal number die a "normal death." The debris from these dead cells must be removed and "digested" so the protein and nucleic acid building blocks can be reused to form the new cells. Indeed, one of the immune system's most important functions is to dispose of cell debris.

One of the leading theories of autoimmune disease is that a mistake in processing of the fragments from dead cells is a key stimulus to autoimmune disease. Rather than simply disposing of the dead cell material, a mistake is made and the dead cell's material is identified as foreign and the immune system is activated (as if it were a foreign graft or invading virus). For example, in Sjögren's patients the characteristic Sjögren's antibody is anti-SS-A antibody, and immune responses against SS-A protein may have a role in perpetuating the damage to the glands and other tissues.

SS-A is a normal nuclear protein found in all cells, and its job is to "chaperone" another protein into the cell's cytoplasm. However, this protein (and its associated RNA molecule) is particularly difficult for the immune system to break down, and thus SS-A may accumulate after a cell dies.

This buildup may result in a stimulus to the immune system. Part of that reaction is the formation of antibodies to SS-A, which is a characteristic laboratory finding in many Sjögren's patients.

To summarize, the contribution of the "acquired immune system," autoimmunity is caused when self antigens cannot be properly removed by the immune system, and the residual protein is inappropriately bound to the HLA-D molecule (Fig. 6–3). This in turn stimulates a cascade of other immune factors that constitute the "acquired" immune system. This includes production of autoantibodies and the release of inflammatory factors that are measured when we try to assess the activity of the disease, such as the level of anemia, sedimentation rate, or attack of the immune system on organs other than the salivary and lacrimal glands. Many of the medicines now used in autoimmune disease were initially developed to prevent organ rejection in the "transplant" model. These include prednisone, hydroxychloroquine, methotrexate, and many others.

The (HLA-DR-Independent) Acquired Immune System or the "Innate" Immune System

We noted above that the acquired (HLA-DR) system was important but that it could not explain the entire story. In parallel with the search for an understanding of organ transplantation, other scientists were trying to understand the immune system's response to infectious organisms. Why do we get fevers, muscle and joint pains, and fatigue that we associate with feeling "flu-ish"? This led to recognition of a different part of the immune system that did not involve the HLA-DR system. It was called the "innate" (inborn) or the HLA-DR-independent immune response.

In autoimmune disorders such as Sjögren's or SLE, there is a close mutual stimulation of the innate and the acquired immune system. To assess disease activity and understand symptoms of Sjögren's, it is necessary to understand both arms of the immune system.

The acquired immune system is important, but it takes about 2 to 3 weeks after a foreign infection for this system to recognize the invader and make the appropriate T-cell, B-cell, and antibody responses. With most infections, we would have succumbed long before—assuming it was not an infection we recognized from a prior encounter and had an "acquired" immune memory.

Thus, studies of our response to infections such as pneumococcal infection led to recognition of a separate branch of the immune system called the innate (HLA-D-independent) system. The

acquired system (defined by HLA-D) and the innate system work closely together to defend us from external infections—but when they function together in excess, the result may be autoimmunity, such as Sjögren's or SLE.

The innate immune system provides our first line of defense to bacteria and viruses. It consists of a different set of cells, such as *macrophages* and *dendritic cells,* that are not dependent on HLA-D proteins for their response. Instead, it has evolved a series of receptors that can immediately recognize particular proteins, sugars, or nucleic acids that are common to many pathogens in the environment. Indeed, many of the symptoms such as fever or muscle aches that we feel in response to viruses or bacteria derive from the immediate release of inflammatory hormones from the cells of the innate immune system. A further consequence of stimulating the innate immune system is the stimulation of the acquired immune system described above. It is the perpetual mutual stimulation of the innate (HLA-D-independent) and the acquired (HLA-D-dependent) systems that characterizes autoimmune disorders such as Sjögren's and SLE.

The Relationship between Sjögren's and SLE

<Insert Figure 6–3>

The immunological features and clinical features of Sjögren's and SLE show a great deal of overlap. However, there are distinct differences that are important. Perhaps the easiest way to simplify this overlap is to consider SLE a disease where the "organ" damage is done by autoantibodies.

- This refers to the binding of an autoantibody to a self antigen, which is mistaken for a foreign protein.
- The autoantibody may be directed against an antigen (i.e., protein) located on the surface of a red blood cell (leading to hemolytic anemia), a platelet (leading to a condition called thrombocytopenia), or the skin (leading to certain types of rashes).

<Insert Box 6–1>

<Insert Box 6–2>

<Insert Box 6–3>

Also, autoantibodies may bind to circulating proteins or DNA to form "immune complexes," which can then lodge in the kidney (leading to glomerulonephritis) or in blood vessels (leading to vasculitis). The immune complex can bind an additional protein called "complement" and trigger an additional inflammatory cascade that is part of the innate immune system.

The pattern of antibodies found in SLE has a great deal of overlap with those found in Sjögren's. It is important to think of SLE as a series of different clinical syndromes that each has its characteristic autoantibodies (each associated with a distinct HLA-DR), and that one of the SLE subsets (characterized by HLA-DR3) has the closest overlap with Sjögren's. The HLA-DR3 subset of SLE has the antibody to SS-A, and these patients have Sjögren's-like symptoms, often termed "Sjögren's secondary to SLE."

In addition to immune complex features that characterize SLE in some Sjögren's patients, Sjögren's is also characterized by dryness of the eyes and mouth. This is due to the infiltration of the glands by lymphocytes (Fig. 6–4). Since the glands of most individuals do not have any lymphocytic infiltrates, we must consider Sjögren's a disease of "aggressive" lymphocytes where they get into tissues where they do not belong. This aggressive tendency can become very pronounced, where the salivary glands have become massively infiltrated and the patient may have developed a lymphoma (Fig. 6–5).

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The Immunology of Clinical Symptoms in Sjögren's

More commonly, we see only the results of glandular infiltration of the lacrimal and tear glands that results in dry eyes (Fig. 6–6) and dry mouth with associated dental problems (Fig. 6–7). The surprising feature of this severe dryness is that the glands are not totally destroyed by the lymphocytic infiltrates.

<Insert Figure 6–6 and 6–7>

Although we previously pointed out the lymphocytes that did form clusters in the gland, we now emphasize that about 50% of the glands remain visible. So one of the key questions in Sjögren's is: *Why are the residual glands not functioning at a high level?*

In other diseases, a kidney, liver, or lung may continue to function until the organ is over 90% damaged. Thus, we must conclude that in Sjögren's patients, the local release of inflammatory mediators within the gland causes the residual cells to be "paralyzed."

Studies in animal models indicate that the inflammatory mediators (such as type I interferon, tumor necrosis factor [TNF], and interferon gamma) greatly decrease the gland's ability to respond to neural stimulation. An example of a salivary gland biopsy with cells producing type 1 interferon is shown in Figure 6–8. Also in this figure, the right-hand panel shows the "gene expression signature" from the lip biopsy from different individuals.

<Insert Figure 6–8>

- The three columns on the left are from normals, the next three columns are from Sjögren's patients, and the three columns on the right side are from patients with dryness not due to Sjögren's.
- The pattern of colored bands indicates the strength of gene expression.
- In the middle columns (from the Sjögren's patients), the dark-green bands at the top of each column indicate a very high level of expression and show the characteristic pattern that is associated with response to type 1 interferon.

Thus, we see that different lip biopsies from Sjögren's patients all share a pattern of genes that are "upregulated" by type I interferon.

To re-emphasize this important point: One of the pivotal inflammatory molecules in both Sjögren's and SLE is type I interferon. This molecule is normally produced by the innate immune system in response to infection. It leads to low-grade fevers, fatigue, joint and muscle pain, and all of the symptoms we associate with having the flu. The presence of type I interferon leads to elevations of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) blood tests that we routinely measure in Sjögren's patients to assess activity. When the lymphocytes infiltrate the salivary or lacrimal gland, they paralyze the gland's response to normal stimuli. Thus, the gland

may be only 50% destroyed, but the residual glandular tissue is unable to secrete adequately due to the presence of inflammatory mediators such as type 1 interferon.

However, most of us get over flu symptoms in a day or two, so the key question is: What leads to the persistence of production of the type I interferon signal in the glands and other tissues? This appears to be the link between the *acquired* (HLA-DR) and *innate* (non-HLA-DR) systems.

Perhaps an additional factor in causing Sjögren's is the finding that certain genes appear to increase the sensitivity of type 1 interferon production and response. Sjögren's patients have increased frequency of two of these genes, called interferon response factor 5 (IRF5) and a molecule that is closely bound to the type 1 interferon receptor (Stat 4) (Box 6–4).

<Insert Box 6–4>

Extraglandular Manifestations of Sjögren's

Although Sjögren's is characterized by dry eyes and dry mouth, some patients have rash, muscle pains (myalgia), joint pains (arthralgia), nerve pain (neuropathy), and fatigue. The lymphocytes leave their site of origin (the bone marrow) and travel through the bloodstream to various organs that may be involved.

In addition to the glands, we mentioned that other tissues, such as lung, kidney, skin, and nerves, might have lymphocytic infiltration. For this to occur, the lymphocytes must travel through the bloodstream until they reach the target organ. The lymphocytes know when to take the "exit ramp" off the "highway" of the bloodstream due to particular molecules on both the lymphocyte (called addressins, since they encode the address of the target organ) and molecules on the local blood vessels (called vascular adhesion molecules). The additional genes that lead to susceptibility to Sjögren's (and its extra-glandular manifestations) play a key role in regulating this process of lymphocytes homing to the target organs.

Role of Antibodies Against SS-A and SS-B Antigens

The HLA-DR system encodes a tendency to make antibodies against the SS-A antigen, so a person born with the HLA-DR3 gene has a higher tendency to make the autoantibody. In salivary or

lacrimal gland tissue that is damaged by virus or some other process, the SS-A antigen stimulates the immune lymphocytes that produce the antibody, which in turn binds to a normal cell chaperone called hYRNA. Although this molecular biology is esoteric, it is fun to see the probable "smoking gun" that perpetuates the process of Sjögren's.

This immune complex is able to stimulate the production of type I interferon, which in turn stimulates the production of more antibody to SS-A. A vicious cycle leads to the clinical picture that we know as Sjögren's or SLE. Of course, a myriad of other genes and hormones play a role in modulating this process. How to interrupt this cycle without crippling the important infection-fighting capacity of the body is a goal of current research.

<Insert Figure 6–8>

Hormonal Influences

Estrogen activity may be involved in developing dry mouth and dry eye symptoms because of the following two factors:

1. Sjögren's affects women much more frequently than men.

2. The symptoms of dry mouth and dry eye are more prevalent in patients who are receiving hormone replacement therapy than those who are not.

Viruses, the Immune System, and Sjögren's

It is thought that some viral infections could have a role in the pathogenesis of Sjögren's by the following mechanism. After a virus or bacterium enters the body, an immune reaction is almost always activated. (Parasitic infections are less of a threat to us than they were to our forebears.) Thankfully, the infection is almost always defeated, and the person returns to normal health. Sometimes this initial response against the virus or bacterium becomes chronic because the body cannot clear the infection, and sometimes the immune response heads off in the direction of autoimmunity.

Examples of infections that can cause chronic problems include:

- Streptococci (a bacterium that can cause rheumatic fever)

- Human immunodeficiency virus (HIV)

- Hepatitis C virus (chronic hepatitis)

Indeed, hepatitis C virus can cause dry eye, dry mouth, and arthritis, all symptoms found in Sjögren's.

Epstein-Barr virus has been suggested as a possible activator or co-factor in the development of Sjögren's. Once we are infected with this virus, we remain infected for the rest of our lives, and nearly everyone is infected. The evidence for this virus being important in Sjögren's has not yet convinced most scientists, and it remains an idea that is not generally accepted.

Chronic **hepatitis C** can cause symptoms that are similar to Sjögren's (dry mouth, dry eye, and arthritis occurring in association with an enlarged parotid gland with lymphocytic infiltration). Anti-Ro and anti-La, which are present in the blood of Sjögren's patients, are typically absent in the blood of patients with chronic hepatitis C infection. Most experts in Sjögren's lean toward including hepatitis C as one of the differential diagnoses of dry eye–dry mouth syndrome, as other features distinguish it. Anti-Ro and anti-La are usually absent in hepatitis C patients, as are the usual pathologic findings of autoimmune Sjögren's.

Two **retroviruses**, HIV and human T-cell leukemia virus (HTLV-1), are known to be causes of a syndrome that presents with a clinical picture similar to that seen in Sjögren's. Those viruses affect males more than females, and the autoantibodies that define Sjögren's have not been found in the patients who carry those viruses. HLTV-1 may cause muscle deterioration and causes a condition with the unattractive name of tropical spastic paraparesis. This virus is endemic in some parts of the world.

The medical literature now has many, many reports describing the dry eye and mouth associated with HIV infection. Both Sjögren's and HIV infection have diffuse lymphocyte infiltration in the affected tissues. However, the kind of lymphocyte that dominates in HIV-infected patients tends to be different than those that dominate in Sjögren's. The characteristic autoantibodies, anti-Ro and anti-La, are typically not found in HIV-infected patients. There are other gene-related differences as well. Consequently, HIV-infected patients are not usually considered to have Sjögren's, but there is some disagreement among doctors on this point.

The Functional Circuit That Links Ocular/Oral Symptoms and Secretory Function

To understand the spectrum of disorders that contribute to dry eye and mouth, it is important to recognize that these symptoms result from an imbalance in a functional circuit that controls lacrimal and salivary function. The functional circuit can be considered to start at the mucosal membrane (either the ocular surface or buccal mucosal surface) where the patient has decreased aqueous secretions (Figs. 6–9) and 6–10). These highly innervated surfaces send unmyelinated nerves to specific regions of the midbrain, termed the lacrimatory and salvatory nuclei. This midbrain region sends signals to the cortex, where dryness is sensed, and receives input from cortical centers that reflect input such as depression or stress reactions associated with dryness. The clearest evidence of these cortical inputs is the classical Pavlovian response of salivation in response to other cortical stimuli.

<Insert Figure 6–9 and 6-10>

After the midbrain receives input from the mucosa and higher cortical centers, efferent (outgoing) nerves that innervate the glands using cholinergic neurotransmitters (especially acetylcholine and vasoactive intestinal peptide) and blood vessels using adrenergic (adrenalin-containing) neurotransmitters are activated. The presence of inflammatory infiltrates in the glands contributes to inadequate secretory response not only by destruction of glandular elements, but also by interfering with effective release of neurotransmitters by the nerves in the end organ and the response of the glandular cells at the level of post-receptor signaling. As a result, there is decreased activation of the receptors that subsequently produce the energy source for water transport.

> Thus, a key point in the pathogenesis of Sjögren's is the observation that the salivary and lacrimal glands are not totally destroyed and local immune-generated release of cytokines, autoantibodies, and other chemicals leads to dysfunction of the residual glands.

Although rheumatologists are talking about autoantibodies and acute phase reactants, the patient has complaints about dry, painful eyes and mouth.

In the initial stages of the disorder, patients are describing increased friction as the upper eyelid traverses the globe or the tongue moves over the buccal mucosa. For example, the upper eyelid normally traverses the globe on a carpet of lubricating tear film, composed of a mixture of aqueous and mucous secretions. When the aqueous tear or saliva component is deficient, the patient senses

increased friction. The friction between the upper lids can be great enough so the surface components of the conjunctiva adhere to the upper lid and are torn off by upper-lid motion. Defects of the surface mucin layer are detected by the retention of Rose Bengal (a characteristic test for keratoconjunctivitis sicca [dry eye]). The ocular surface becomes a site of chronic inflammation, similar to a wound. From these regions arise unmyelinated afferent (incoming) nerves, which eventually end in specific regions of the midbrain, including the lacrimatory/salvatory nuclei. Neural signals are subsequently sent to the cortex, where pain is sensed.

Fibromyalgia or "Central Sensitization"

In addition to dry eyes and dry mouth, some of the most disabling symptoms for Sjögren's patients are fatigue and vague cognitive dysfunction. These symptoms do not correlate closely with our normal laboratory tests such as ESR or CRP (which are products of the innate immune system). Indeed, the symptoms of fibromyalgia are reminiscent of the "flu" or "jet lag," but the patient does not quickly bounce back. Studies in animal models and using new-generation magnetic resonance techniques have suggested that subtle interplay of inflammatory products in particular portions of the brain influences the function of nerves responsible for alertness and muscle pain. Since these symptoms are also found in many patients with depression, it is not surprising that many medications useful in depression are also useful in fibromyalgia.

A further finding is that there is a poor correlation between the findings of patient's pain in the nerves and muscles (i.e., muscle tender points) and the results of biopsies of nerve and muscle. This is currently being attributed to the fact that the nerve fibers from the "periphery" must travel up to the spinal cord, where they are joined through structures called ganglia. The nerve signal then ascends the spinal cord to particular portions of the brain that sense pain. Equally important, the brain sends signals down the spinal cord that "dampen" pain receptors, and this is also an important target for certain medications. Medications used in fibromyalgia are also used in peripheral neuropathy associated with diabetic neuropathy, since they help stabilize the neurotransmission along this critical pathway that the patient ultimately senses as pain.

Thus, the concept of fibromyalgia has now been upgraded to "central pain sensitization" to reflect the importance of how pain signals are transmitted.

However, we cannot emphasize strongly enough that fibromyalgia is the "elephant in the room." Many therapeutic trials have failed to understand that patients' quality of life may depend more on how their brain senses the dryness than the millimeters of tears that are generated, or that overall functional status depends strongly on the muscle pain, nerve pain, and "energy" level, which are not reflected in other measurements of glandular or inflammatory activity.

Summing Up

Sjögren's syndrome results from the interaction of genetic and environmental factors. It is likely that multiple genes interact to predispose an individual to Sjögren's. However, even when all of the genes are present (as in identical twins), it is clear that other (presumed) environmental factors play a role, since less than 20% of identical twins are concordant for the disorder.

No single environmental agent has been identified, despite an intensive 50-year search. It is more likely that many different agents can stimulate the innate immune system, which is a primitive immune system, and thus prime the more sophisticated acquired immune system to perpetuate the autoimmune process. The molecules that define the innate system and the acquired immune system and that link the two systems are the subjects of intensive research. It is hoped that an understanding of these molecular events will lead to a new generation of therapies for patients.

<Insert Table 6–1>

For Further Reading

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Figure 6–1. Time course of autoimmune response.

1. Environmental stress is interpreted in context of genetic factors.
2. Antibodies precede disease.
3. Presence of antibody does not mean disease.

Figure 6–2. The histocompatibility antigens bind small peptides.

HLA-A or B
HLA-D

Figure 6–3. What is the relationship between SLE and SS?

Figure 6–4. Lymphocytic infiltrates in Sjögren's syndrome

Sjögren's Normal

Figure 6–5. MRI not used much for diagnosis of Sjögren's itself but is of value in investigating causes of persistent salivary gland swelling. However, with the increasing availability of scanners, and emerging evidence from Berlin and Japan, we may see this noninvasive technique being used more frequently for diagnostic purposes.

Figure 6–6. Dryness results in the clinical appearance of keratoconjunctivitis sicca characteristic of Sjögren's syndrome. The upper lid literally sticks to the surface epithelial surface and pulls surface mucin layers off. The Rose Bengal dye retention is like rainwater pooling in a street pothole. This test can be done at bedside and allows "triage" and rapid referral of patients to Ophthalmology.

Figure 6–7. Sjögren's syndrome: cervical dental caries.

Figure 6–8. Interferon (IFN) type I in salivary gland suggests a role in Sjögren's syndrome.

Arrows indicate cells in Sjögren's salivary gland biopsy with type I IFN.

Normal lip biopsies lack type I IFN gene signature.

Sjögren's salivary gland biopsy with type I IFN gene profile.

Figure 6–9. The vicious cycle of innate and acquired leads to IFN type I (links genetic and autoantibody response).

Figure 6–10. Normal tearing or salivation secretion requires a functional unit.

Table 6–1. **Important Components of the Immune System in Sjögren's**

1. White blood cells
a. Granulocytes—promote acute inflammation
b. Lymphocytes—promote chronic inflammation
i. T cells (memory cells)
ii. B cells (promote production of autoantibodies)
2. Proteins
a. Albumin—carrier proteins, decreased in chronic disease
b. Globulin—levels increased in inflammation
i. Alpha globulins
ii. Beta globulins
iii. Gamma globulins—IgG, IgM, IgD, IgA, and IgE
3. Important autoantibodies in Sjögren's
a. Anti-SSA, also known as anti-Ro
b. Anti-SSB, also known as anti-La
c. Rheumatoid factor
d. Antinuclear antibody
e. Anti-muscarinic receptor antibody

Box 6–1 **Sjögren's Syndrome at a Glance**

- An autoimmune disorder characterized by severely dry eyes and dry mouth due to lymphocytic infiltrates

- Prevalence for primary Sjögren's: 0.1% to 0.3% of adult females

- Female-to-male ratio is 9:1.

- Two peak ages of onset—in the 30s and in the 50s

- Many older patients diagnosed with "SLE" actually have Sjögren's.

- Pediatric Sjögren's may be part of spectrum of juvenile rheumatoid arthritis.

Box 6–2 **Sjögren's Syndrome at a Glance**

- Patients have a characteristic HLA-DR (extended haplotype): in Caucasians, it is extended DR3

- The genetic background is different in distinct ethnic groups (Chinese, Japanese, Greeks), but these groups have similar antibody profiles.

- The autoantibody profile is similar to subset of SLE.

Box 6–3

- Increased mortality risk, particularly due to lymphoproliferative complications

- Quality of life—equated with moderate angina

- "Disability" predominantly due to fatigue and cognitive "limitations"

    - Dry eyes limit work, especially at computer.

    - Dry mouth limits sleep and social interaction.

Box 6–4 Genetic Predisposition in Sjögren's to Type I Interferon

In genome-wide screens, association of IRF5 alleles and Stat 4 is associated with predisposition to development of Sjögren's.