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Defining a Mechanism for the Histopathological Changes Seen in Salivary Gland Biopsies of Patients with Sjögren's Syndrome: A Mini-Review

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Abstract

Insights into the role that inflammatory mediators such as lymphocytes and matrix metalloproteinases play in remodeling of the basement membranes of salivary gland cells in patients with Sjögren's syndrome has led to several observations revealing irregular thickening and thinning of the basement membrane. These observations have revealed that the underlying mechanism for these irregularities in thickness may partly be due to laminin degradation in the basement membrane seen coincidentally along with the intracellular accumulation of laminin in salivary gland ductal and acinar cells.

Introduction

Sjögren's syndrome is an autoimmune disorder that affects many organs within the human body. The pathophysiology of the disease involves the development of autoantibodies to self-antigens on tissues and organs. Manifestations include acute interstitial nephritis, neuropathies and lung and cardiac involvement as well. The most common symptom encountered clinically however is the drying of the eyes known as keratoconjunctivitis sicca which often presents along with xerostomia or dryness of the mouth.

Diagnosis of Sjögren's syndrome (SS) includes the Schirmer test which involves placing a tissue paper to the conjunctiva and measuring the degree of lacrimation on that tissue paper. Patients with SS, who produce minimal tears, respond to the test negatively. Serological studies are often performed in the clinical setting which detect auto-antibodies characteristic of this disease, with a certain degree of sensitivity and specificity. Equivocal results from the previously mentioned diagnostic tests often lead clinicians to perform lip biopsies, which allow for histopathological diagnoses based on salivary gland features on light microscopy.

In the laboratory setting, several studies have made attempts to detail the pathophysiological mechanism that is responsible for the histological changes seen in ductal and acinar cell of salivary gland biopsies. Gross histological descriptions have revealed the presence of lymphocytes, which are predominantly CD4+ T-helper cells, infiltrating the ductal and acinar cells. It is interesting to note that other autoimmune disease processes such as AIDS, polymyositis/ dermatomyositis and chronic thyroiditis produce a secondary SS with similar histology [1,2].

In AIDS, histopathology demonstrates infiltration of glands by CD8+ T-helper cells. It is unclear as to why this difference exists. Furthermore, many questions yet remain as to the mechanism of lymphocytic inflammation in periductal and perivascular sclerosis and fibrosis seen on light microscopy of acinar and ductal cells. It has been observed that the development of sclerosis and fibrosis leads to expansion of the salivary gland lesion and eventual glandular atrophy or acinar "drop-out".

Though numerous questions remain, several labs have qualitatively demonstrated specific changes in ductal and acinar cells as an initial attempt to develop an understanding of this complex disease process. In particular, the basement membranes of ductal and acinar cells taken from salivary glands demonstrate gross morphological changes. These changes describe a thickening of the basement membranes of salivary glands taken for biopsy [3-5]. Transmission electron microscopy (TEM) in the areas of irregular thickening demonstrate thickening of the lamina densa with high electron density [6]. In contrast, our previous studies have shown that within the basal lamina of biopsied minor salivary glands, the lamina lucida thins out rather. Our most recent publication quantified the difference in the thickness of basal laminae in ductal and acinar cells of salivary glands to determine definitively whether the changes in the basement membranes are due to thinning or thickening [7]. Our results showed no statistically significant difference in the thickness of basement membranes of ductal and acinar cells within minor salivary glands taken from lip biopsies between patients with SS and control patients. Significant discrepancies remain with regards to the exact morphological changes within the basal laminae of ductal and acinar cells from salivary glands in patients with SS. There may not be a categorical way of classifying basement membranes but rather understanding that significant variations exist with respect to salivary gland cells. In

other words, the disease process leads to irregularities of basement membrane size, not primarily a thickening or thinning.

The Role of Matrix Metalloproteinases and Laminin in Basement Membrane Irregularity

Laminin is the main component of the basement membrane. It anchors the basement membrane to the cell and as such maintains the polarity of the cell. Using immunohistochemistry, our previous studies demonstrated that ductal and acinar cells of minor salivary glands in patients with SS had an accumulation of laminin intracellularly [8]. Interestingly, results obtained by other laboratories regarding the pathophysiology of the inflammation taking place within ductal and acinar cells of SS patients were successful in suggesting the possible role that laminin plays in the irregularity seen in salivary glands of SS patients.

The mechanism states that lymphocytes infiltrating the salivary glands release cytokines which, in turn, induce the expression of matrix metalloproteases-9 and 3 (MMP-9 and 3), which are enzymes involved in the degradation of collagen within the basement membrane. It is therefore highly suggestive of the possible role of MMP's in degrading laminin within the basement membrane of ductal and acinar cells [9]. There is evidence to support this weak expression of laminin in the basement membrane of patients with SS [10]. It has also been demonstrated that the fragmented products of laminin that are produced due to degradation by MMPs also promote further MMP expression, possibly in a positive feedback loop [11]. As stated, our lab demonstrated an intracellular accumulation of laminin in salivary gland cells in patients with SS, which coincides with its degradation in the basement membrane [8]. Although this finding demonstrates an association, any mechanism with respect to the association between these two events remains to be elucidated. However, the role that MMPs play in the degradation of laminin and other extracellular matrix proteins within the basement membrane along with the subsequent disorganization of the basement membrane has been demonstrated [10-12]. In addition, since laminin is an inflammatory mediator, it may act as a stimulus for lymphocytic infiltration. Thus, it is possible that changes within the basement membrane, producing irregular areas of thickening or thinning, may be the result of laminin degradation.

Results of Quantitative Analysis

Our most recent publication on this topic measured basal laminae thickness in ductal and acinar cells of minor salivary gland biopsies in 12 patients with primary or secondary SS versus a control group of 14 patients [7]. Criteria for SS were clinical symptoms of dry eyes and dry mouth, arthritis and a history of at least one positive serum SS-A (Ro), SS-B (La), anti-nuclear antibody (ANA) or rheumatoid factor (RF) test. Patients receiving steroid therapy were excluded from the study. Both SS and control patients had the same frequency of thickness when the basal laminae of the two groups were 0.24 µm or less in thickness. However, basal laminae that were greater than 0.24 µm proved to be thicker in healthy patients more frequently than that of SS patients. This coincides partially with our previous results demonstrating a thinning of the lamina lucida in ductal and acinar cells in SS patients [8]. In acini, however, the basal laminae were thicker consistently for SS patient specimens *vs*. that of control group specimens, regardless of any parameter of thickness. Overall, our data revealed irregularities in basal laminae thickness when comparing acinar and ductal basal laminae in the two patient groups. Despite our observations, based on trends in the measurements, this previous study was unable to show a statistically significant difference in the thickness of the basal laminae between SS *vs*. control patient biopsy specimens.

Conclusion

Previous unpublished studies in our laboratory revealed a statistically significant narrowing of the basal lamina in acinar and ductal cells of SS patients *vs*. that of non-diseased controls. However, results of our most recent study do not support previous findings and, interestingly, contrast with other reports, which generally describe "thickening" of basal laminae in SS. The changes represent rather irregularities in the basement membrane due to a complex inflammatory process involving lymphocytes, released cytokines and matrix metalloproteinases, associated with intracellular laminin accumulation.

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