Impact of Androgen Therapy in Sjögren’s Syndrome: Hormonal Influence on Lymphocyte Populations and la Expression in Lacrimal Glands of MRL/Mp-lpr/lpr Mice

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Recent research has demonstrated that androgen treatment dramatically curtails lymphocyte infiltration in the lacrimal glands of a mouse model of Sjögren’s syndrome. The purpose of the current study was to determine whether this androgen action involves the selective suppression of specific lymphocyte populations or la expression in lacrimal tissue. Autoimmune female MRL/Mp-lpr/lpr mice were administered placebo- or testosterone-containing compounds for 0, 17, or 34 d. Then lacrimal glands were obtained and processed for immunohistochemical evaluation. Results demonstrated that in pretreatment mice, lacrimal lymphoid foci were composed predominantly of Thy 1.2+ cells, bearing L3T4 (helper T cell) or B220 surface antigens. In contrast, suppressor T cells (Lyt 2+) and surface IgM-bearing B cells represented minority populations in the immune infiltrates. Class II antigen (la) expression was observed on over 40% of the infiltrate lymphocytes and occasionally on epithelial cells close to the lymphoid focus. During the experimental time course, the extent of lymphocyte infiltration increased in glands of placebo-treated mice. This cellular accumulation was associated with an elevation in the frequency of B220+ cells, but not that of other lymphocyte subclasses. Testosterone administration induced a striking diminution in the area encompassed by all immune cell populations. Moreover, hormone therapy significantly reduced the frequency of B220+ cells in focal infiltrates. Overall, these findings demonstrate that androgen exposure stimulates a decrease in the quantity, but not necessarily the entire lymphocyte composition, of lymphoid aggregates in lacrimal glands of MRL/lpr mice. Invest Ophthalmol Vis Sci 33:2537-2545, 1992

The preocular tear film plays an essential role in the maintenance of corneal integrity, the protection against microbial challenge, and the preservation of visual acuity.1 These functions, in turn, are critically dependent upon the stability, tonicity, or composition of the tear film structure.1,2 Alteration, deficiency, or absence of the tear film may lead to intractable desiccation of the corneal epithelium, ulceration and perforation of the cornea, an increased incidence of infectious disease, and, ultimately, severe visual impairment and blindness.2,3 Throughout the world, innumerable people suffer from tear film dysfunctions, which are collectively diagnosed as keratoconjunctivitis sicca (KCS) or, simply, dry eye.1,2 By far, the greatest single cause of KCS worldwide, excluding those countries where trachoma remains epidemic, is Sjögren’s syndrome.2 This syndrome, which represents the second most common autoimmune disease,4,5 primarily afflicts females and is characterized in the eye by an insidious and progressive lymphocytic infiltration into the main and accessory lacrimal glands, an immune-mediated, extensive disruption of acinar and ductal tissues, and KCS.4,6-8 A current perception is that Sjögren’s syndrome may be clinically irreversible,4 an autoimmune disease to be controlled, yet not cured.8 As a result, the mainstay of therapy for management of this dry eye state is replacement with tear substitutes.3,9,10 Recently, however, research with female animal models of Sjögren’s syndrome has demonstrated that systemic androgen treatment may dramatically suppress autoimmune expression in lacrimal tissue after the onset of disease.11,12 These mouse models, which include the MRL/Mp-lpr/lpr [MRL/lpr] and NZB/NZW F1 strains, exhibit lacrimal autoimmune characteristics analogous to those of humans: Murine tissues harbor dense, multifocal lymphoid infiltrates
composed of T and B cells and display pronounced areas of acinar and ductal destruction. Testosterone administration to these mice induced a precipitous, time-dependent decrease in the number and size of lacrimal lymphoid foci, significantly curtailed the extent of lymphocyte infiltration, and appeared to ameliorate the immune-associated effects on acinar and ductal tissues. This hormonal influence may explain why three clinical, albeit uncontrolled, studies involving systemic androgen therapy of Sjögren’s syndrome patients resulted in an apparent reduction in ocular signs and symptoms and a stimulation of tear flow.

The underlying mechanism by which testosterone abrogates lacrimal lymphocyte infiltration in autoimmune models remains unclear. Theoretically, androgens could selectively diminish the accumulation of specific lymphocytes in lacrimal tissue, as has been observed in certain glands. Alternatively, testosterone could depress la expression on lacrimal cells, thereby decreasing inflammatory activity. la antigen levels are augmented in exocrine glands during autoimmune reactions and may be susceptible to androgen modulation. Clarification of the immune target involved in testosterone action in Sjögren’s syndrome could provide a potential site for therapeutic intervention. Therefore, the purpose of the present study was to determine whether androgens selectively alter the distribution of specific lymphocyte populations or la expression in lacrimal tissue of MRL/lpr mice.

Materials and Methods

Animals and Hormone Treatment

Female MRL/lpr mice (4–5 mo old; strain MRL/MpJ-lpr/lpr) were obtained from The Jackson Laboratory (Bar Harbor, ME) and maintained in constant temperature rooms with controlled light/dark intervals of 12 ho duration. After the onset of autoimmune disease, animals were treated with subcutaneous implants of placebo (cholesterol, methyl cellulose, lactose)-or testosterone (10 mg)-containing pellets (Innovative Research of America, Toledo, OH) in the subscapular area. This method of hormone administration, which ensured a continuous, physiologic release of androgen over a 3 wk period, resulted in the establishment of serum testosterone concentrations equivalent to those of an adult male mouse. To provide extended hormone exposure, new pellets were reimplanted 17 d after the initiation of treatment. These experiments adhered to the ARVO Resolution on the Use of Animals in Research.

Histologic Procedures

After hormone therapy, mice were killed and lacrimal glands were processed for immunohistochemical or morphologic evaluation. For immunohistochemistry, tissues (1 gland/mouse) were frozen in liquid nitrogen, transferred to Tissue-Tek OCT compound (Miles, Inc., Elkhart, IN), and cut into 6 μm sections at −20°C. Serial sections were placed on gelatin-coated glass slides, fixed in acetone for 10 min at 4°C, and blocked with a 1% “normal” rabbit serum and avidin D solution (Vector Laboratories, Burlingame, CA) for 20 min at room temperature prior to first antibody application. Primary antibodies (30 μl/section) and their optimal dilutions included: (1) purified rat monoclonal (IgG3μ) antibody to mouse Thy 1.2 (1/450 dilution), which reacts with mouse T cells (clone 30H12; Becton Dickinson, Mountain View, CA); (2) purified rat monoclonal (IgG3μ) antibody to mouse L3T4 (1/300 dilution), which identifies mouse helper T cells (clone GK 1.5; Becton Dickinson); (3) purified rat monoclonal (IgG3μ) antibody to Lyt 2 (1/100 dilution), which binds to mouse suppressor and cytotoxic T cells (clone 53-6.7; Becton Dickinson); (4) rat monoclonal (IgG3μ) antibody to mouse B220 antigen (1/500 dilution), which associates with mouse pre-B cells, B cells, plasma cells, and immature T cells (clone RA3-6B2; gift from Dr. R. L. Coffman, DNAX Research Institute of Molecular and Cellular Biology, Inc., Palo Alto, CA); (5) rat monoclonal (IgG3μ) antibody to mouse la (Class II; 1/600 dilution) antigen (clone M5/114; Boehringer Mannheim, Indianapolis, IN); and (6) purified F(ab')2 fragment of goat antimouse IgM μ chain (1/500 dilution), which detects surface IgM-bearing B cells (Jackson Laboratories, West Grove, PA).

After incubation with the first antibody for 60 min at room temperature in a humidified chamber, sections were exposed sequentially to an 0.3% hydrogen peroxide and biotin solution for 20 min and a secondary antibody (40 μl/section) for 35 min. Secondary antibodies included: biotinylated rabbit antirat IgG (Vector) and biotinylated rabbit antitoxon IgG F(ab')2 fragment, which were preincubated overnight with mouse liver acetone powder (Sigma Chemical Company, St. Louis, MO) at a concentration of 60 mg/ml in a 1% bovine serum albumin (BSA; Calbiochem-Behring, La Jolla, CA)/phosphate buffered saline (PBS; 0.01 mol/l sodium phosphate, 0.15 mol/l NaCl, pH 7.4) buffer prior to use; and commercially pre-adsorbed and biotinylated rabbit antirat IgG (Vector). After antibody treatment, sections were incubated with Vectastain Elite ABC reagent (Vector) for 40 min and developed for 5–10 min with an acetate buffer containing 3-amino-9-ethylcarbazole (Sigma),...
N, N-dimethylformamide, and hydrogen peroxide. Sections then were postfixed in 2% paraformaldehyde (Sigma) for 10 min, counterstained with Gill's hematoxylin formulation no. 1 (Fisher Diagnostics, Bedford, MA) for 30 sec, dipped in a lithium carbonate (Aldrich Chemical Co., Milwaukee, WI) solution (12.8 mg/ml cold double distilled water) for 1 sec, and preserved in Crystal Mount (Biomeda, Foster City, CA) by a 15 min incubation at 80°C. With few exceptions, the application of various reagents to sections was interspersed with air drying or rinsing of slides with PBS or warm water.

Antibody concentrations for these procedures, as well as incubation periods, were selected after extensive dilution and time course experiments. As positive controls, immunoperoxidase methods were verified by examining the distribution of Thy 1.2+, L3T4+, and Lyt 2+ cells in spleen sections from BALB/c mice, and by examining Ia antigen, surface IgM, and B220 staining in small intestinal, lacrimal, or mesenteric lymph node sections from C57Bl/6 or MRL/lpr mice. In addition, the topographic location of surface IgM+ B cells in lacrimal tissue was confirmed by using a purified rat monoclonal (IgG2a) antibody to mouse IgM (clone LO-MM-9; Zymed, San Francisco, CA). Negative controls for these studies included: (1) replacement of monoclonal antibodies with nonspecific, purified rat monoclonal IgG2a and IgG2b antibody preparations (Zymed) or (2) use of PBS instead of primary antibodies. The specificity of the anti-IgM reactivity was assessed by competition studies. Incubation of the antibody with purified mouse IgM, but not BSA/PBS or purified mouse IgG or IgA, resulted in the absence of staining in mesenteric lymph node and lacrimal gland sections.

For quantitative analysis of lymphocyte frequency, sections were evaluated with a Zeiss light microscope at 16× magnification. The percentage of cells positive for a specific surface marker, as identified by a peripheral brown outline of the cell membrane, was determined. This procedure involved covering a randomly selected, 'large' lymphoid focus with a micrometer disc that contained a 10 X 10 grid net (100 squares) encompassing an area of 0.3 mm². The percentage of each square (ie, 0, 25, 50, 75, and 100%) that harbored positive lymphocytes was recorded and then, after the entire lymphoid aggregate was examined, the overall frequency was calculated. Results were combined with those obtained from a separate (ie, tissue location) lymphoid focus on a nonadjacent section to permit computation of the average tissue frequency. The validity of this technique for the representative measurement of lymphocyte populations was demonstrated by analyzing the frequency of cell appearance in every lymphoid focus in two different sections from placebo- or testosterone-treated tissues. Final section results for Thy 1.2+, L3T4+, Lyt 2+, surface IgM+, B220+, and Ia+ cells essentially were the same as those found with the previously described method. Moreover, frequency determinations were highly reproducible, given that comparative data of two investigators were essentially identical.

To assess the percentage of specific lymphocyte infiltration in an entire section, cell frequency measurements were converted to decimal notation and multiplied by a tissue-related correction factor, which equaled the total lymphoid infiltrate area per section divided by the total section area. These latter morphometric calculations, unless otherwise indicated, were determined after extensive analysis of each contralateral lacrimal gland, as previously reported. Briefly, tissues (1 gland/mouse) were fixed overnight in 10% buffered formalin, dehydrated, and embedded in Historesin (LKB, Bromma, Sweden). Sections (3 μm) were cut from four different gland regions, all separated by successive distances of at least 30 μm, then stained with hematoxylin-cosin and examined with a Zeiss Videoplan II image analysis system to quantitatively measure the area of tissue sections (4 sections/tissue; 25× magnification) and lymphoid infiltrates (4 sections/tissue; 100× magnification). To compute the correction factor for a given mouse lacrimal gland, the areas of individual foci in a section were summed, divided by the total section area, and multiplied by 100, to yield the extent of lymphocyte infiltration (in percent units). Then, percentage infiltrate values from all four sections/tissue were averaged to provide a single numerical correction factor/gland. The rationale for using different fixation procedures for immunohistochemistry and morphometry was that lymphocyte surface markers were far better visualized on frozen sections, whereas determinations of total lymphocyte infiltration were more clearly resolved with plastic sections.

Photographs depicting immunoperoxidase staining of tissue sections were obtained with a Zeiss Axiovert 35 microscope (20× magnification) and Kodak (Rochester, New York) Ektachrome 50 tungsten film. Unless otherwise indicated, statistical analysis of data was performed by using Student's two-tailed t-test.

Results

To determine the influence of androgen exposure on specific lymphocyte populations and Ia expression in lacrimal glands of autoimmune animals, 4- to 5-month-old female MRL/lpr mice (n = 4–6/treatment
group) were given subcutaneous implants of placebo- or testosterone (10 mg)-containing pellets in the subscapular region. This hormone treatment, which resulted in the generation of physiologic serum testosterone levels,11 was continued for 17 or 34 d. Lacrimal glands were obtained after 0 (pretreatment), 17, and 34 d of androgen therapy and processed for immunohistochemical and morphometric analysis.

Pretreatment

As demonstrated in Figure 1, lymphoid foci in lacrimal glands of MRL/lpr mice were composed predominantly of Thy 1.2+ T cells. In pretreatment animals, these lymphocytes made up 76.7 ± 3.8% of the immune infiltrate and encompassed 8.7 ± 2.9% of the total tissue section area. The majority of these Thy 1.2+ cells were identified as L3T4+, helper T lymphocytes, and B220+ cells, which equaled 49.2 ± 3.5% and 34.3 ± 7.2%, respectively, of the cells in the inflammatory foci of pretreatment mouse glands. In contrast, suppressor T cells (Lyt 2+) represented a minority lymphocyte population, embodying only 12.0 ± 0.9% of the lymphoid aggregate and covering less than 1.5% of the section area. Similarly, surface IgM-bearing B cells appeared in limited frequency, averaging 8.8 ± 2.0% in foci of pretreatment glands. Regarding la expression, this antigen was observed on 40.9 ± 1.5% of the infiltrate lymphocytes and occasionally on epithelial cells close to the lymphocyte focus. However, distinct la+ staining could not be detected on epithelial cells distant from the lymphocyte infiltrate. B cells in focal infiltrates of the experimental groups was identical to frequencies measured in pretreatment and placebo-exposed controls.

Placebo Treatment

During the time course of this experimental study, the magnitude of B220+ cell infiltration increased dramatically in lacrimal glands of placebo-treated mice. Thus, from 0 to 34 d, the extent of B220+ cell accumulation had risen three fold (P < 0.05), so that these lymphocytes encompassed 10.5 ± 1.7% of the total section area (Fig. 2). Moreover, the proportional frequency of the B220+ cells in focal infiltrates rose significantly (P < 0.05, one tail) to equal 52.5 ± 3.2% of the lymphoid populations in lacrimal tissue (Fig. 3). This B220+ cell distribution in "placebo" lacrimal glands, although considerable, was comparatively far less than observed in mesenteric lymph nodes. In these peritoneal tissues, B220+ cells represented between 80 and 90% of the entire lymphocyte population (data not shown).

Regarding other cell types in the lacrimal glands of placebo-treated mice, the absolute frequency of Thy 1.2+, L3T4+, Lyt 2+, IgM+, and Ia+ lymphocytes in focal infiltrates did not vary significantly over the 34 d time period (Fig. 3). However, given that the magnitude of total lymphocyte infiltration approximately doubled in tissue sections during this interval (day 0 = 11.9 ± 4.6% of section area; day 34 = 21.57 ± 3.5% of section area), the relative area covered by Thy 1.2+, L3T4+, Lyt 2+, IgM+, and Ia+ cells also appeared to increase by up to a two-fold amount.

Hormone Treatment

Testosterone administration to MRL/lpr mice induced a striking decrease in the size of different immune cell populations. As shown in Figure 2, androgen exposure significantly (P < 0.05) reduced the section areas encompassed by Thy 1.2+, L3T4+, Lyt 2+, IgM+, B220+, and Ia+ cells, compared to those of placebo-treated controls. This effect, as previously described,11 was associated with an overall 4- to 12-fold drop in the extent of lymphocyte infiltration in tissue sections, relative to that of 17- and 34-day-treated "placebo" glands.

However, the proportional composition of lymphoid aggregates after hormone therapy was almost identical to frequencies measured in pretreatment and placebo tissues (Fig. 3). Thus, the absolute percentage of Thy 1.2+, L3T4+, Lyt 2+, IgM+, and Ia+ cells in focal infiltrates of the experimental groups was similar, regardless of treatment. In contrast, testosterone caused a significant (P < 0.05) reduction in the frequency of B220+ cells in infiltrates of 34 day-treated animals, compared to those of placebo-exposed controls.

These results demonstrate that androgen action stimulates a decrease in the quantity, but not necessarily the percentage distribution, of lymphocyte infiltrates in lacrimal glands of MRL/lpr mice.

Discussion

The present study demonstrated that lymphocytic infiltrates in lacrimal glands of female MRL/lpr mice expressed a high degree of la antigen staining and consisted primarily of L3T4+ helper T cells and B220-bearing lymphocytes. In contrast, immune foci contained only limited populations of Lyt 2+ suppressor T cells and surface IgM+ B cells. Most strikingly, the extent of lymphocyte infiltration in MRL/lpr lacrimal tissues was extremely susceptible to androgenic influence. Testosterone administration induced a profound decrease in the area encompassed by Thy 1.2+, L3T4+, Lyt 2+, IgM+, B220+, and Ia+ cells and significantly reduced the proportional frequency of B220+ cells.

Our assessment of the inflammatory cell distribution in lymphoid aggregates of adult MRL/lpr lacri-
Fig. 1. Immunohistochemical staining of Thy 1.2+ (A), L3T4+ (B), Lyt 2+ (C), B220+ (D), surface IgM+ (E), and Ia+ (F) positive lymphocytes in lacrimal tissue of an MRL/lpr mouse. Serial sections of a lacrimal gland from a placebo-treated (day 34) animal were processed for antigen-specific immunohistochemistry, as explained in Materials and Methods. As a negative control (G), the primary antibody was replaced with phosphate-buffered saline. Original photographs were taken with Kodak Ektachrome film at original magnification ×20.
Influence of testosterone treatment on the extent of specific lymphocyte infiltration in lacrimal tissues of MRL/lpr mice. Animals (n = 4 to 6 per group) were administered placebo- or testosterone (10 mg)-containing compounds. Lacrimal glands were obtained 17 or 34 d after hormone exposure. After immunohistochemical and morphometric analysis, as described in Materials and Methods, the region encompassed by immune cells, as a percentage of total section area, was determined. Because of the loss of a contralateral gland, the total infiltrate area of one androgen-treated tissue (day 17) was calculated by image analysis of the "frozen" sections. Bars equal the means ± standard errors of 4 to 6 values per group, with one exception: The slg(M) results from the day 17 placebo group were obtained from the tissues of three rats. *Significantly (P < 0.05) less than value of placebo control.

Regarding la expression, this antigen appeared associated with lymphocytes and epithelial cells adjacent to immune infiltrates. This topographic pattern is analogous to that identified in salivary glands of MRL/lpr mice23 and of human patients with Sjögren's syndrome.21 22 The presence of class II antigens on parenchymal cells proximal to lymphoid aggregates may be a result of local lymphokine (eg, interferon-gamma) secretion, which is known to induce la expression.22 However, we were unable to detect distinct la antigen expression on epithelial cells distant from lymphocyte infiltrates. This result does not coincide with recent findings on extensive, class II antigen distribution in autopsy specimens of human lacrimal tissue.31 Several possible explanations could account for this apparent discrepancy, including species and pathologic differences, dissimilarities in antibody affinity, and variations in tissue preservation.

The impact of testosterone administration on immune foci in lacrimal tissue of MRL/lpr animals was extraordinary. Androgen action elicited a precipitous decrease in the extent of Thy 1.2*, L3T4*, Lyt 2*, slg*, and Ia+ cells in lymphocyte infiltrates of pretreatment or placebo-exposed mice were analogous to those percentages detailed by Jabs et al.15 25 We also observed a significant accumulation of B220+ lymphocytes, which increased during the experimental period and occurred in frequencies similar to those found in MRL/lpr submandibular tissues.23 This B220+ subset most likely corresponds to pre-B cell, B cell, plasma cell, and immature T cell populations, but also may have included the so-called "double negative" cells. These latter cells express B and T (eg, Thy 1.2) cell surface attributes,26 may bear L3T4 antigens,27 and represent a unique lymphocyte subclass in MRL/lpr mice.24 Moreover, the "double negative" cells are predominantly rapidly dividing and immature B220+ T lymphocytes that possess markedly impaired potential for antigenic stimulation and lymphokine elaboration,28 29 and appear responsible for the pronounced lymphadenopathy characteristic of MRL/lpr mice.30 However, whether these "double negative" cells exist in B220+ populations of MRL/lpr lacrimal tissue remains to be determined.

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The impact of testosterone administration on immune foci in lacrimal tissue of MRL/lpr animals was extraordinary. Androgen action elicited a precipitous decrease in the extent of Thy 1.2*, L3T4*, Lyt 2*, slg*, B220* and Ia* cell infiltration. This effect, which occurred in concert with a considerable drop in the number and size of total lymphoid aggregates,14 also was associated with a significant diminution in the proportional frequency of B220+ cells. For several reasons, these findings, when compared to other observations,11 13 32 33 suggest that testosterone's antiinflammatory activity may be unique and lacrimal gland specific. First, the androgen-induced immunosuppression in lacrimal tissue does not extend to peripheral lymph nodes,32 indicating that this steroid hormone does not cause a generalized depression in lymphocyte migration to, or proliferation in, systemic or mucosal sites. Second, testosterone exposure reduces the magnitude of lymphocytic infiltration in submandibular glands of MRL/lpr mice,11 but the overall susceptibility of these focal infiltrates to androgens and pharmacologic agents appears quite different than that found in lacrimal tissue11 (Sato EH and Sullivan DA, unpublished data). In fact, salivary

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Infiltrates in MRL/lpr animals are distinctly less severe than those of lacrimal glands, suggesting that the underlying pathogenesis or progression of disease may vary between these tissues. Third, androgens exert significant control over immunologic functions in lacrimal glands, but not necessarily over those of salivary or systemic tissues. In a sense, androgen activity is reminiscent of cyclophosphamide’s influence on MRL/lpr salivary infiltrates. This drug, in a tissue-specific manner, reduced the extent of lymphoid infiltration and the number of B220+ cells (identified with the 14.8 monoclonal antibody), but did not alter the frequency of T cell subsets in the salivary gland.

Although androgens ameliorate autoimmune expression in lacrimal glands through a possible local effect, the precise mechanism underlying this hormone action remains elusive. It is unlikely that androgen effects are initiated through selective suppression of Ia expression, given that the frequency distribution of this antigen was not altered by hormone treatment. Furthermore, it is improbable that hormone action is mediated entirely through a direct influence on lymphocytes, considering the apparent scarcity of androgen receptors in immune cells. One possible explanation is that testosterone, which is known to markedly curtail certain inflammatory reactions, could suppress lymphocyte foci through the stimulation of epithelial cytokine synthesis and release. In support of this hypothesis, epithelial products have been demonstrated to regulate immunocyte dynamics. Moreover, such antiinflammatory cytokines might be anticipated to uniformly diminish lymphocyte accumulation or proliferation, which generally appears to be the result of androgen action. A potential cytokine candidate for the mediation of hormone effects could be secretory component (SC), the IgA antibody receptor. Recent research has shown that free SC, unbound to polymeric IgA, exerts significant antiinflammatory activity through the suppression of arachidonic acid release. Thus, considering that androgens induce the synthesis and secretion of free SC by lacrimal acinar cells and that free SC possibly could be discharged into the stroma during tissue inflammation or luminal obstruction, this glycoprotein theoretically could play a role in the hormone-associated abrogation of lymphocyte infiltration in lacrimal glands of MRL/lpr mice.

In summary, our results demonstrate that testosterone significantly diminishes the total population, but not necessarily the frequency, of T, B, and Ia+ cells in lacrimal tissue of MRL/lpr mice, an animal model of Sjögren’s syndrome. Furthermore, our findings indicate that this hormone action may be mediated through local effects. Yet to be determined is whether...
similar immunoendocrine activity occurs during the putative androgen suppression of ocular autoimmune disease in Sjögren’s syndrome patients.

Key words: Sjögren’s syndrome, lacrimal gland, testosterone, T and B lymphocytes, immunohistochemistry, MRL/Mp-lpr/lpr mouse

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References