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Effects of Aging in Dry Eye

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Abstract

Dry eye affects millions of people worldwide and causes eye well recognized risk factors for dry eye. Anatomical and inflammation-induced age-related changes affect all components of the lacrimal gland functional unit, inclusive of lacrimal gland, conjunctiva, meibomian gland and compromise ocular surface health. There is increased evidence that inflammation plays a role in dry eye. This review will summarize the current knowledge about aging and dry eye, inclusive of lessons learned from animal models and promising therapies.

Introduction

Tear dysfunction is one of the most common problems encountered by eye doctors. Tear dysfunction has a reported prevalence ranging from 2 to 14.2%.[1–3] It has been found to increase with age from the 4th to 8th decade of life and is more prevalent in women than men throughout this period.[4, 5] Tear dysfunction results from disease of one or more components of the lacrimal functional unit that consists of the tear producing glands and their neural connections. Many patients over the age of 40 with tear dysfunction have evidence of meibomian gland disease (MGD) as an underlying cause, particularly in patients with an unstable tear film, but normal tear production and tear volume. This review will focus on epidemiological aspects of aging, possible mechanisms for age-related dry eye and discuss some potential therapies along with lessons learned from animal models of aging.

1. Aging as a risk factor for Dry Eye

Aging is a significant risk factor for dry eye—Large epidemiological studies from the Women's Health Study and Physician's Health noted that dry eye prevalence increases in women and men every five years after the age of 50, with greater prevalence in women compared to men.[1, 3–8] Age and female sex have been found to be the greatest risk factors for dry eye. This is supported by the clinical findings of decreased tear production in women through the 6th decade of life.[9, 10] The corneal surface irregularity in dry eye degrades visual function by decreasing contrast sensitivity and functional visual acuity.[11, 12] The presence of dry eye was found to significantly impact the ability to perform daily activities such as reading, using a computer and driving.[13] Using time trade-off techniques, Schifman and others calculated that severe dry eye had the same impact on quality-of-life as moderate to

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severe angina.[14, 15] With an increasing aged population and with the increased life expectancy, it is expected that dry eye will continue to be one of the main reasons for ophthalmologic visits.[16] Therefore, better understanding specifically of age-related dry eye and therapies tailored to this specific population are much needed.

The lacrimal gland (LG) suffers significantly with aging. Various histopathologic changes were observed in the human main lacrimal gland such as acinar atrophy; periacinar fibrosis; periductal fibrosis; interlobular ductal dilatation; interlobular ductal proliferation; lymphocytic infiltration; and fatty infiltration.[17–20] Several histopathologic differences exist between the palpebral and orbital lobes. Diffuse fibrosis and diffuse atrophy in orbital lobes were more frequently observed in women than in men.[20, 21] Rodents are frequently used in aging research as their LG suffer aging-related changes similar to humans (see review by Rocha and colleagues).[22–25]

Age-related eyelid alterations include lid laxity, meibomian gland atrophy and orifice metaplasia, decrease in tear volume with increased tear break-up time and dry eye.[26–31] In the young healthy eyelid, the meibomian gland orifices are located anterior to the mucocutaneous junction that can be identified as Marx's line, a physiological line of staining with diagnostic dyes, such as fluorescein, lissamine green, and rose bengal. It has been reported that Marx's line migrate anteriorly with aging.[32] MG have androgen receptors and respond to androgen stimulation[31, 33–37] and MGD is more frequent in men than women.[28, 29, 38, 39] MGD may occur by itself or in association with aqueous-tear deficiency (ATD). The inflammatory cytokine milieu both in tears and the conjunctiva cells collected by impression cytology are different than ATD.[40–44] ATD patients have significant goblet cell loss, increased expression of IFN-γ and IL-17A compared to normal controls, but none of the aforementioned changes are present in MGD patients.[44]

Another frequent age-related disorder is conjunctivochalasis, a condition where the conjunctiva folds and becomes redundant and may obstruct the puncta and cause ocular discomfort. It is often associated with age[45–48] and it is discussed in more details in the companion article by Gumus and colleagues.

There is still controversy if aging leads to dry-eye or if dry eye is an age-related disease that has a totally different mechanism than aging per se.[49] For example, age as a risk factor for goblet cell loss remains controversial.[23, 50–54] It has becoming more apparent that similar to autoimmune dry eye, age-related dry eye has significant inflammation and a complex immune response that overtime leads to profound LG and ocular surface alterations (Figure 1).[22–25, 28, 51, 55–58]

2-Age-related co-morbidities and iatrogenic dry eye

Aging is often accompanied by co-morbidities such as cardiovascular diseases, type 2 diabetes, depression, glaucoma and other ocular diseases. Some of these co-morbidities themselves or the medications that are used to manage them, may have a deleterious secondary effect on the ocular surface. An example is diabetes mellitus that affects retina, LG and corneal nerves and it is frequently associated with dry eye.[59–61] Some of the age-related co-morbidities alters ocular surface homeostasis secondary to the systemic or ocular

therapies that are required to control the original morbidity and some of these medications may have secondary ocular drying effects. For example, anti-hypertensive, anti-histaminics and antidepressants are some of well-recognized classes of drugs that have a drying effect on the ocular surface.[3, 5–8, 56, 62] For a complete list of medications that have been noted to have a drying effect or to aggravate dry eye, please refer to review by Fraunfelder and colleagues[62, 63] and visit the National Eye Drug registry (http://www.eyedrugregistry.com/about.html).

Patients with glaucoma, a disease with greater incidence in elderly patients, often complain about ocular irritation.[64, 65] Although a direct effect of the compounds used to treat glaucoma cannot be excluded, benzalkonium chloride, a widely used eyedrop preservative due to its potent antibacterial action, has been recognized as toxic to the ocular surface. Benzalkonium chloride enhances drug penetration, partially due to secondary epithelial barrier breakage and toxicity to corneal epithelium.[65–68] Recent studies have shown that switching to a preservative –free solution improved ocular surface related-symptoms with no loss efficacy of anti-glaucoma drugs, promising relief to a great number of patients with secondary dry eye due to glaucoma eyedrops.[69–71]

3-Possible mechanisms leading to age-related dry eye

All organisms start to age as soon as they are born. While some age-related changes are celebrated as milestones, (i.e. first baby steps and words, first definitive tooth, first mustache shaving in boys; first child, etc), the decline in health status and vitality that often accompanies aging is a nuisance for many. There is also an economical burden to the society and caregivers as life expectancy increases as well as susceptibility to a great number of diseases, such as cancer, cardiovascular diseases, autoimmunity and frailty.

The immune system also undergoes aging, named immunosenescence, a decline in the immune function characterized by a decrease in naïve T cells, chronic inflammation, hyperimmunoglobulinemia, autoimmunity, poor response to vaccines, and increased susceptibility to infections.[72–75] A typical feature of aging is a chronic, low-grade inflammatory status, named inflammaging[76], characterized by a general increase in the production of proinflammatory cytokines. Increased serum inflammatory mediators have been found associated with Alzheimer’s disease, dementia, Parkinson’s disease and type 2 diabetes.[76–78] The changes in the immune system have profound consequences for survival and are reliable predictors of morbidity and mortality in the elderly.[75]

Other age-related cellular/metabolic theories regarding aging include increased oxidative stress, increased DNA damage, alteration of DNA repair, increased protein glycation, telomere shortening and decreased proteasome function to name a few.[79, 80] Although an extensive body of evidence has accumulated in these areas, the precise mechanism(s) that control aging are still poorly understood. Every cell ages, but not at the same rate; age-related changes may or may not accompany pathological aging and every person is unique and so its own aging. The same is true for aging-related dry eye.

There is increasing evidence that dry eye is accompanied by inflammation. In the last 20 years there was a shift on dry eye paradigm, from merely a disease of decreased tears to a

disease where inflammation and autoimmunity play an important role. Increased levels of inflammatory and T cell related mediators such as IL-1β, IL-6, TNF-α, IL-17, IFN-γ have been noted in conjunctiva and tear fluid of dry eye patients compared to control subjects.[12, 40, 44, 81–90] The activation of the local immune environment is another universal feature of dry eye, as increased expression of HLA-DR$^+$ cells are a frequent finding, which has been used as an indicator of therapeutic response in clinical trials.[81, 91–100] Other features of dry eye include increased production of matrix metalloproteinases (MMPs), increased levels of chemokines and proteins involved in oxidative stress, increased squamous metaplasia of the ocular surface epithelium, loss of goblet cells and increased endoplasmic reticulum stress.[12, 81, 83, 85, 96, 97, 101–117]

Dry eye is a chronic disease but acute exacerbations are frequent when performing activities such as driving, viewing a video display for long periods of time and shopping in stores with high flow AC. Dry eye patients live and work in controlled drafty and/or low humidity (desiccating stress) environmental conditions, and the irritation and ocular surface disease[118–122] they experience from this environment may decrease their productivity and quality of life.[123, 124] Exposure to desiccating environmental conditions has been shown to activate stress-sensing cells/pathways on the ocular surface, to stimulate ocular surface epithelial cells to synthesize and secrete of pro-inflammatory cytokines and MMPs that can be detected in the epithelial cells themselves.[42, 85] This acute stress related inflammation can sensitize corneal nociceptors and cause surface epithelial changes, such as breakdown of epithelial tight junctions resulting in corneal barrier dysfunction, clinically observed as increased uptake of fluorescein. The environmental changes related to dry eye are discussed in more details in the companion article by Calonge and colleagues.

4-Animal models of age-related dry eye

A variety of animal models have been described that have been used to study pathogenesis of dry eye. The desiccating stress dry eye model that uses a combination of low humidity, environmental stress, and pharmacological cholinergic blockade has become a standard model in the research field. It has been used in more than 65 publications since its first description.[125] This model recapitulates several features of human dry eye, inclusive of corneal barrier dysfunction, goblet cell loss and production of cytokines by the ocular surface epithelium.[126–144] The desiccating stress mostly uses the inbred C57BL/6 mouse strain, while Balb/c mice have also been used with slightly different disease kinetics.[142] Recent studies have shown that aged C57BL/6 mice are a valuable tool to study age-related dry eye, as these mice develop age-related MGD, corneal staining, goblet cell loss and conjunctival lymphocytic infiltration and dacryoadenitis.[23, 145, 146] Similarly to desiccated mice and human Sjögren Syndrome (SS) patients, there is an increase production of MMP-9 and T-cell related cytokines such as IL-17, IFN-γ, on the aged ocular surface and an influx of CD4$^+$ and CD8$^+$ T cells into the aged LG[23], suggesting that multiple inciting mechanism may converge to produce clinically significant dry eye independent of the initiating factor. Inflammation may be a common denominator in these situations. Lessons learned from animal models of dry eye are discussed in more details in the companion article by Stern and Pflugfelder. Pathogenic studies that utilized aged mice are summarized and briefly discussed in the next paragraphs.

a. **Female sex is a risk factor for dry eye**. Similar to the human studies[4, 147], female C57BL/6 mice develop greater corneal barrier disruption than age-matched male mice, although other features of dry eye such as low goblet cell density and LG infiltration were similar in both sexes.[23] This was accompanied by greater levels of IL-17A and IFN-γ compared to young mice. IL-17 stimulates MMPs- 3 and -9, which have been shown to break tight junction proteins and disrupt corneal barrier function.[85, 148–151] Dry eye affects quality of life[7, 14] and quality of vision, and decreases contrast sensitivity.[12, 13] We can speculate that greater corneal disease in female patients may bring more women to the eye clinic than men, although other factors such as sex hormones and their influences on the corneal disease cannot be excluded.

b. **Aged $CD4^+$ T cells are spontaneously autoreactive**. A common feature observed in SS subjects, SS animal models and desiccating stressed mice is increased infiltration of $CD4^+$ T cells in conjunctiva and LG biopsies.[152–157] This has also been observed in aged C57BL/6 mice.[23] Furthermore, adoptive transfer of aged $CD4^+$ T cells induced greater lymphocytic infiltration of the conjunctiva and LG and greater goblet cell loss than adoptive transfer of young donors, demonstrating that aged $CD4^+$T cells participate in age-related dry eye.[23] These studies indicate that aging promotes generation of autoreactive T cells; however, the precise mechanism of generation of these autoreactive T cells remains unknown as wells as the antigen. It is possible that a combination of factors such as aging of the immune system, lack of peripheral tolerance or accumulated exposure of an antigen over a life's period maybe at play. It is possible that all three could be acting synergistically.

c. **Interferon-γ participates in age-related goblet cell loss**. The conjunctiva is one of the goblet-cell richest tissues in all body, just trailing the intestinal tract. Goblet cells are very sensitive to the ocular environment and besides producing mucins, have been implicated in immunomodulation on the ocular surface.[158–161] The Th-2 signature cytokine IL-13 has an important role in goblet cell survival and homeostasis.[162, 163] IFN-γ, on the other hand, has been shown to negatively impact conjunctival goblet cells.[112, 130, 157, 164] This is true for both DS-induced or aged-induced upregulation of IFN-γ, as IFN-γKO mice are partially resistant to aged-related goblet cell loss.[23, 57, 157]

d. **Aged regulatory T cells are dysfunctional**. Using a variation of the nonobese diabetic mouse that does not develop diabetes, Coursey and colleagues demonstrated that dacryoadenitis in aged NOD.B10.H2b mice is accompanied by a significant increase in frequency of regulatory T cells (Tregs) in the LG, despite increased LG pathology compared to young mice of the same strain.[25] This is in agreement with reports about biopsies of salivary glands from SS patients where increased frequency of $Foxp3^+$ cells correlated with more severe disease.[165, 166] Despite being dysfunctional and unable to suppress T effector cells in vitro, these aged murine Tregs do not loose $Foxp3^+$ expression, but acquire the ability to produce IFN-γ and IL-17. Furthermore, adoptive transfer of aged T regs or aged T effectors resulted in similar higher inflammatory lacrimal

keratoconjunctivitis scores compared to young Tregs and T effectors, suggesting loss of in vivo suppression ability and acquisition of an effector phenotype.[25]

e. **Oxidative stress in aged LG impairs tear secretion**. Reactive oxygen species generated from normal metabolism must be counteracted by anti-oxidant defenses to prevent damage to lipids, DNA and mitochondria. Mice that have increased mitochondrial oxidative stress or decrease in anti-oxidative pathways with aging have altered LG homeostasis, leading to decreased LG tear volume and increased corneal staining.[167–170] In support of the animal studies, decreased expression of anti-oxidant enzymes and increased expression of oxidative stress markers have been noted in conjunctiva of SS patients.[108–111] Elevated tear concentration of hexanoyl-lysine, a lipid oxidative stress marker, correlated significantly with staining scores and inflammatory cell density in confocal microscopy study evaluating SS and controls.[108] Although it is unclear if oxidative stress occurs as a cause or consequence of dry eye, Deng and colleagues recently showed that hyperosmolarity can increase oxidative stress in cultured epithelial cells.[171]

f. **Aged meibomian glands become atrophic**. Histologic analysis of aged human eyelids have shown many morphological alterations including cystic dilatation of acini and/or ducts, atrophy of acini, thickening of acini basement membrane, granulation tissue, and lipogranulomatous inflammation.[26] Aged C57BL/6 mice also develop age-related MGD, characterized by a dropout in acini volume, and increased expression of cytokines, and increased meibocyte differentiation.[145, 146, 172, 173] It is postulated that a decrease in acini volume maybe secondary to loss of stem cells within the meibomian gland and not necessary to duct keratinization, as no increase in Keratin 10 nor SPRR1-a was noted in aged C57BL/6 MG.[145, 173] In elegant studies using immunofluorescent computed tomography and 3D reconstruction, no duct keratinization was observed in aged meibomian glands from C57BL/6 mice, further corroborating their findings.[145]

5. Treatment of age-related dry eye

There are only two FDA-approved drugs to treat dry eye. Cyclosporine, a T cell modulator, has been extensively used for more than a decade to treat all forms of dry eye.[92, 99, 106, 117, 174–177] Lifitegrast, a novel inhibitor of lymphocyte function-associated antigen-1 (LFA-1) which is involved in migration of T cells from the vessels, has just received approval to treat signs and symptoms of dry eye in July 2016. Results from the Phase 2 and 3 clinical trials showed promising results.[178–180] For reviews about current dry eye therapies please see the published reviews.[181–183] Other new therapies for dry eye are reviewed in the companion article by Gumus and Pflugfelder.

A non-pharmacological approach to improve dry eye is the use of supplements. Polyunsaturated fatty acids such as omega-6 (linolenic acid) and omega-3 (α-linolenic acid) have gained popularity as oral supplements in dry eye disease as they decrease inflammatory mediators and decrease activation of dendritic cells.[95, 184–188]

A more holistic approach to aging-dry eye has been proposed and it involves the use of calorie restriction (CR) and supplementation with vitamins and anti-oxidants.[189] Calorie restriction (CR) without malnutrition has emerged in the 21st century as a potential strategy to prevent age-related diseases. Although first published in 1935 by McCay and Colleagues,[190] CR has gained interest after studies showing prolonged life span, decreased cardiovascular diseases and incidence of tumors in rodents.[191–194] These results were duplicated in non-human primates,[195, 196] generating great interest of the scientific community in this aging intervention. A massive body of evidence has been accumulated since then, demonstrating that CR induces profound metabolic, hormonal and molecular changes. For a detailed review about CR inclusive of NIH-sponsored CALERIE (**C**omprehensive **A**ssessment of **L**ong-term **E**ffects of **R**educing **I**ntake of **E**nergy) clinical trial in humans, please see the review by Most and colleagues.[197] In ophthalmology, CR has been shown to substantially decrease infiltration of submandibular glands in aged autoimmune mice prone mice.[198] This was accompanied by a significant decrease in inflammatory mediators such as TNF-α and IL-6 while an increase in TGF-β1 was noted.[198] In aged rats, CR for 6 months significantly improved tear secretion, LG acinar morphology and decreased expression of lipid oxidation markers 8-hydroxy-2 deoxyguanosine (8-OHdG) and 4-hydroxynonenal (HNE) that relates to oxidative stress.[199]

Conclusions

Despite intensive research, the true nature of aging remains elusive. Not all organisms age well or will age at the same rate. However, aging involves complex biochemical, molecular, immune mechanisms that may be interacting. Inflammation on the ocular surface participates in age-related dry eye. Understanding the mechanisms of aging will enable early interventions and prevent end-stage organ atrophy and ocular surface disease.

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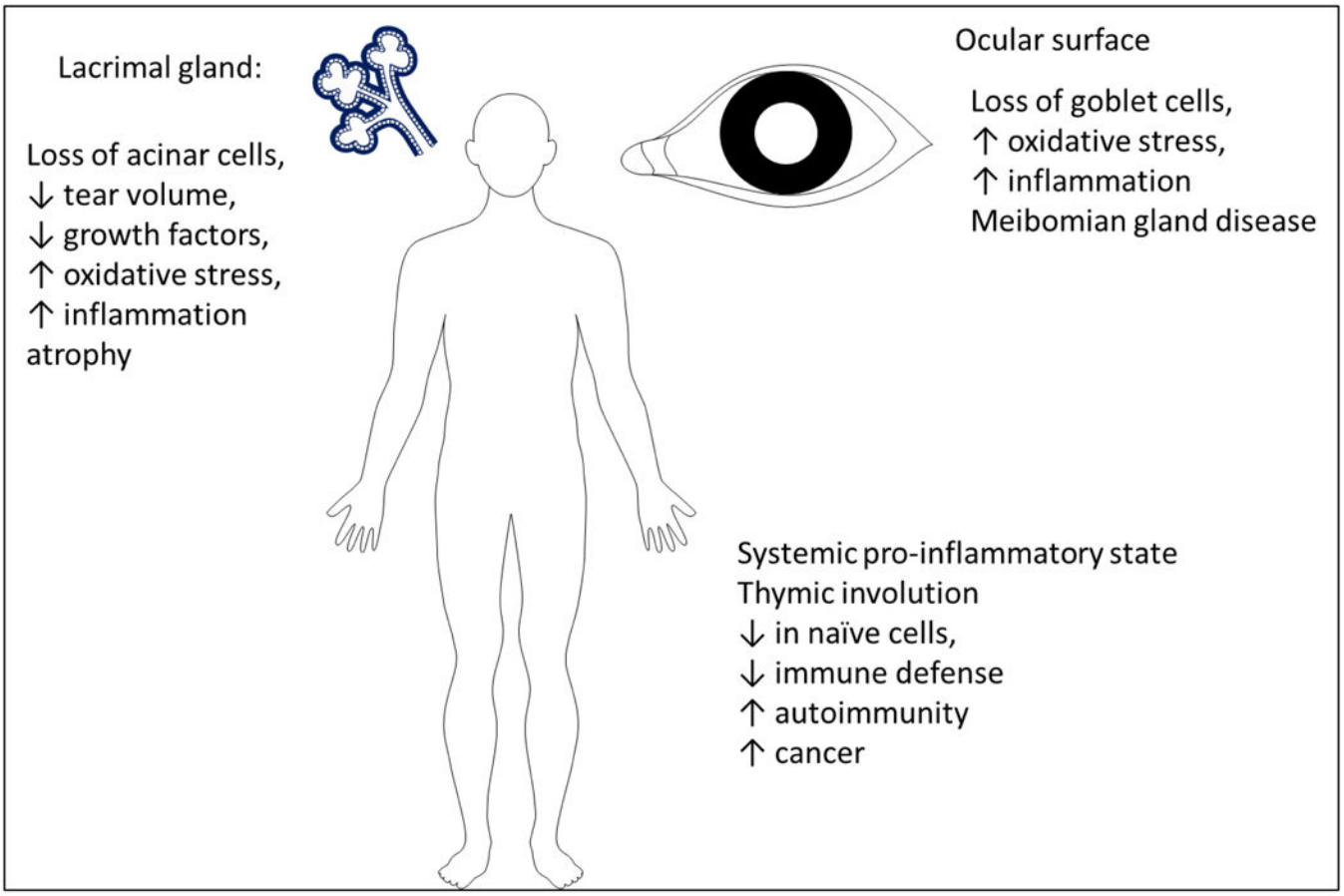

Figure 1.
Aging induces profound systemic changes but also changes the lacrimal gland functional unit.