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Aging and dry eye disease

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Abstract

Dry eye disease is a prevalent eye disorder that in particular affects the elderly population. One of the major causes of dry eye, meibomian gland dysfunction (MGD), shows increased prevalence with aging. MGD is caused by hyperkeratinization of the ductal epithelium of meibomian gland and reduced quantity and/or quality of meibum, the holocrine product that stabilizes and prevents the evaporation of the tear film. Of note, retinoids which are used in current anti-aging cosmetics may promote the development of MGD and dry eye disease. In this review, we will discuss the possible mechanisms of age-related MGD.

Keywords

aging; meibomian gland dysfunction (MGD); dry eye disease; FOXO; retinoic acid; androgens; stem cell; growth hormone; insulin-like growth factor-1 (IGF-1); insulin sensitivity

Introduction

The tear film plays an essential role in maintaining ocular surface integrity and health. It is structured in several layers that optimally maintain moisture on the ocular surface. The inner most is an underlying layer of glycocalyx that contains mucin, a highly glycosylated protein synthesized by the conjunctiva and cornea epithelial cells; a middle aqueous layer that is primarily secreted by lacrimal gland; and an overlying lipid layer that is released by the meibomian gland (Nichols and others 2011). The lipid layer prevents the evaporation of the tear film. Disruption or deficiency of the tear film causes increased sheer stress on the ocular surface that may lead to dry eye disease. If untreated, dry eye disease may result in perforation of the cornea, visual impairment and blindness (2007).

In the United States, it is estimated that 40 million people are affected by dry eye disease. Dry eye disease is classified into two types: aqueous-deficient and evaporative. The former is due to decreased tear secretion from the lacrimal gland, whereas the latter is caused primarily by meibomian gland dysfunction (MGD). One example of the aqueous -deficient dry eye is Sjögren's syndrome (SS), an autoimmune disease that affects approximately a million Americans. This disorder is associated with lymphocyte accumulation in lacrimal gland, an immune-mediated destruction and/or dysfunction of acinar and ductal epithelial

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cells, and a decline in aqueous tear output (2007). The second type, caused by MGD which also frequently occurs in SS, is believed to be the leading cause of dry eye disease worldwide (Nichols and others 2011). It is estimated that MGD is a contributing factor for over 2/3 of all dry eye cases (Shimazaki and others 1995). In one report, MGD accounted for 78% of dry eye patients (Horwath-Winter and others 2003). In Asian populations of adults older than 40yr, the prevalence of MGD is estimated to be 46.2-69.3%, although the prevalence is lower in caucasians of the same age group (Schaumberg and others 2011).

The evaporative dry eye, or MGD, is shown to have a strong positive correlation with aging (Den and others 2006; Hykin and Bron 1992; Schaumberg and others 2009; Schaumberg and others 2003; Sullivan and others 2006). In fact, aging is one of the major risk factors for MGD (Schaumberg and others 2011). Therefore the scope of this review will focus on MGD in aging research.

Meibomian gland biology

The meibomian gland is a large sebaceous gland located in the eyelids (Figure 1). It was named after Heinrich Meibom, the German physician and anatomist who described this gland in detail in 1666. As a sebaceous gland, meibomian gland synthesizes and releases a mixture of lipids and proteins called meibum onto the ocular surface to prevent evaporation of the tears. Unlike other sebaceous glands, the meibomian gland is richly innervated and is not associated with hair follicles.

A single meibomian gland is composed of multiple secretory acini that are arranged circularly around a central duct, with the acini being connected to the central duct via short ductules (Figure 2A). The acinus is composed of secretory meibocytes that differentiate and mature until they become loaded with lipids in a hypermature state, upon which they disintegrate and release the whole cell content (meibum) in a holocrine manner. Meibum is released into the central duct where it moves toward the orifice (opening) on the lid margin and eventually to the ocular surface. Due to their holocrine nature, meibomian gland cells have to undergo constant renewal. New meibocytes emerge from the acinar periphery and differentiate (mature) as they migrate to the lateral duct of the meibomian gland and the cell content, meibum, released to the tear film.

It is believed that MGD is primarily caused by hyperkeratinization of the ductal epithelium and reduced quantity and/or quality of meibum (Knop and others 2011). On the one hand, obstruction causes low delivery of meibum to the ocular surface, causing evaporative dry eye. On the other hand, the obstruction of the duct by hyperkeratinization and/or viscous meibum causes accumulation of meibum within the ductal system due to the continuous secretion from the acini. Persistent meibum accumulation results in a progressive increase in pressure and thus widening of the ductal system including the small connecting ductules. This results in acinar atrophy with a loss of meibocytes and eventually a squamous metaplasia that may result in full cornification of the epithelia of the ducts and acini (Knop and others 2011). A comparison of the structure of normal and obstructed human meibomian gland is shown in Figure 2 (Knop and others 2009a; Knop and others 2011). The consequence is reduced meibum secretion and gland dropout, increased evaporation and hyperosmolarity of the tears, increased sheer stress, onset of inflammation at the ocular surface and unstable visual acuity (Knop and others 2011).

MGD and aging in humans

As mentioned earlier, aging is a major risk factor for MGD. In a cross-sectional study involving 177 subjects aged 21-93yr, a significant association between abnormalities in the lid margin or meibomian glands and aging is observed (Den and others 2006). Another

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cross-sectional study of 80 subjects aged 5-87yr found that lid margin vascularity, cutaneous hyperkeratinization and meibomian gland orifice narrowing increased with age (Hykin and Bron 1992). Aging in men and women is associated with a significant increase in lower lid erythema, telangiectasia, keratinization, irregular posterior margins, orfice metaplasia and opaque secretions (Sullivan and others 2006). The number of active meibomian glands also decrease by half from 20 to 80yr (Norn 1987) and gland dropout is visible at old age (Arita and others 2008). Histology of 83 human meibomian gland samples from 17-87yr at autopsy reveals acini atrophy, cystic dilatation of acini and/or ducts and basement membrane thickening of acini (Obata 2002).

Tear film break up time (TBUT), a clinical measurement of the tear stability, decreases with old age (Arita and others 2008; Sullivan and others 2006). Aging is also associated with significant changes in the lipid profiles of human meibomian gland secretions (Sullivan and others 2006). One type of lipid, cholesteryl esters, is significantly increased in adults compared to infants and children (Shrestha and others 2011). However, the significance of this related to MGD is not clear because MGD patients secrete meibum that contains lower levels of cholesteryl esters (Shrestha and others 2011). In terms of meibomian gland cells, recently, it has been shown that aging meibomian glands have decreased meibocyte differentiation and cell cycling (Nien and others 2011).

MGD and aging in animal studies

There are very limited number of animal studies on MGD and aging. In one report, older mice (12 and 24 mo) showed less lipid content and acinar tissue atrophy compared to the young mice (2 and 6 mo) (Nien and others 2009). Further, the cellular location of peroxisome proliferator-activated receptor-γ (PPARγ) was altered, indicating altered lipid synthesis, and reduced Ki67 nuclear staining indicative of reduced cycling cells in the old mice (Nien and others 2009).

Potential mechanisms of increased MGD with aging

The mechanism of the age-related increase in MGD is not known. In fact, as discussed above, very few studies have been conducted on MGD in the context of aging at the mechanistic level. Interestingly, dry skin is often found in the elderly (White-Chu and Reddy 2011), suggesting a common aging phenomenon of meibomian gland and sebaceous gland. Based on available evidence in meibomian gland, sebaceous gland and a few other tissue types, several possible mechanisms are discussed below.

Androgens

Androgens promote the lipid synthesis activity in sebocytes and meibocytes. Androgen receptors are expressed in sebocytes as well as meibocytes (Luderschmidt and others 1983; Rocha and others 2000). Androgens have been shown to regulate meibomian gland gene expression and lipid production (Krenzer and others 2000; Schirra and others 2006; Schirra and others 2007; Schirra and others 2005; Steagall and others 2002; Sullivan and others 2000). In particular, androgens stimulate genes in the lipid synthesis pathways in mouse meibomian gland (Schirra and others 2007; Schirra and others 2005). One of these genes is sterol regulatory element binding protein (SREBP), the most important known transcription factor for lipogenesis (Rosignoli and others 2003). Another androgen target gene is stearoyl-CoA desaturase-1 (scd-1), which is up-regulated by androgens in mouse meibomian glands of both sexes (Schirra and others 2005; Sullivan and others 2009). Scd-1 is an important enzyme in fatty acid metabolism, and Scd-1 null mice have severe atrophies of sebaceous and meibomian glands (Miyazaki and others 2001). This shows that androgens promote crucial genes for normal meibomian glands. Consistent with this, anti-androgen treatment is

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associated with hyperkeratinization of the ductal epithelium, reduced meibum quality and MGD (Krenzer and others 2000; Sullivan and others 2002b). In complete androgen insensitivity syndrome (CAIS), significant alterations in polar and neutral lipids are found from meibomian gland secretions (Sullivan and others 2002a). Further, CAIS is associated with meibomian gland alterations and a significant increase in dry eye signs and symptoms, including significantly increased sensations of dryness, pain and light sensitivity, as well as a significant increase in telangiectasia, keratinization, lid erythema and orifice metaplasia of the meibomian glands, and a significant decrease in the tear meniscus and quality of meibomian gland secretions (Cermak and others 2003). Thus it is likely that age-related decline in androgens (Feldman and others 2002; Morley and others 1997) result in impaired lipid synthesis in meibomian gland cells, contributing to MGD at old age.

Stem cell

Stem cells in adults are responsible for tissue renewal. In the case of meibomian gland, stem cells are particularly important because meibocytes are continuously lost via holocrine secretion. The stem cells of the meibomian gland are not well characterized. It was reported in one study that stem cells of the meibomian glands are located at the circumference of each acinus (Olami and others 2001). However, another study showed that slow cycling stem cells were located in the ductal epithelial cells (Lavker and others 2003). Regarding sebaceous gland, stem cells are located in the central bulge (Taylor and others 2000), or interfollicular epidermis (Lo Celso and others 2008). It is also suggested that multiple classes of stem cells independent of bulge exist (Ghazizadeh and Taichman 2001). At least three independent stem cell populations are present in the skin (Blanpain and Fuchs 2009). Analogous to the epidermis and hair-associated sebaceous glands, it has been proposed that the meibomian gland also has three independent stem cell populations: the progenitor cells at the acinar periphery (committed to lipid-producing meibocytes), at the basement membrane of the ductal epithelium (committed to ductal cells with physiological incipient keratinization) and at the epidermis of the excretory duct (committed to fully cornified epidermis of the skin) (Knop and others 2011).

Although it is not confirmed that stem cell aging is responsible for aging at the organism level (Rando 2006), aging is characterized by a reduced tissue regenerative potential due to changes in tissue-specific stem cells (Conboy and others 2005). Stem cells do not necessarily decrease in number or their proliferative capacity, but rather their function to produce progenitor cells that differentiate properly according to the appropriate cues may decline with age (Sharpless and DePinho 2007). Indeed changes have been found in stem cells at old compared to young ages. For example, hematopoietic stem cells in old mice are less efficient at homing to and engrafting the bone marrow of irradiated recipients (Morrison and others 1996). In terms of stem cells of the skin, it is thought that impaired stem cell mobilization or reduced number of stem cells able to respond to proliferative signals contributes to skin aging (Zouboulis and others 2008). Thus it is possible that in the meibomian gland acinar region, the potential of the stem cells to regenerate new functional meibocytes is impaired at an advanced age, resulting in gland dropout and reduced quantity and/or quality of meibum. Studies in humans and mice support the notion of a reduced functional stem cell pool at old age (Nien and others 2011; Nien and others 2009).

Further, stem cells committed to meibomian gland ductal cells and fully cornified epidermis at the free lid margin as discussed above may also be influenced by old age. Being a ‘hair follicle without a hair shaft’, meibomian gland ductal cells contain keratohyalin granules, show an incipient keratinization and preserve a commitment to keratinization (Knop and others 2009b). Thus it is possible that these stem cells, either by intrinsic aging or responding to an aging environment, differentiate into hyperkeratinized cells, leading to cutaneous hyperkeratinization, abnormal lid margin and meibomian gland orifice narrowing

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commonly observed at old age (Den and others 2006; Hykin and Bron 1992; Sullivan and others 2006).

Growth hormone (GH)/Insuiln-like growth factor-1 (IGF-1)

GH, an important hormone regulating longitudinal body growth, stimulates the production of another hormone called IGF-1, which mediates some of GH's action for body growth. The GH/IGF-1 axis has been implicated in aging in animals as well as humans (Bartke 2011; Fontana and others 2010; Guevara-Aguirre and others 2011; List and others 2011; Shimokawa and others 2008). It is well known that an enhanced GH/IGF-1 axis causes premature aging in humans and mice (Chanson and Salenave 2008; Steger and others 1993; Wolf and others 1993) and conversely, diminished GH/IGF-1 axis as seen in GH receptor null mice results in increased lifespan (Coschigano and others 2003).

To date no study has been conducted on the effect of GH and IGF-1 on meibomian gland, although this gland may very well be regulated by both hormones, since both GH and IGF-1 receptor mRNAs are expressed in the mouse meibomian gland (Schirra and others 2005). GH/IGF-1 plays an important role in sebaceous gland development and growth (Deplewski and Rosenfield 2000), and acne peaks at puberty coinciding with the peak of GH/IGF-1 (Cara and others 1987). Further, acromegalic patients, who secrete excess GH due to pituitary adenomas, have increased acne (Burton and others 1972; Jabbour 2003). Specifically, GH induces the differentiation of sebocytes directly and also augments the androgen-induced sebocyte differentiation, whereas IGF-1 increases the sebocyte proliferation markedly (Deplewski and Rosenfield 1999). GH and IGF-1 levels decline during aging (HO and others 1987), possibly contributing to increased MGD as people age. This may seem paradoxical, given that increased GH/IGF-1 leads to premature aging (Chanson and Salenave 2008; Steger and others 1993; Wolf and others 1993). However, one major premise of this statement is the chronic hyperactive GH/IGF-1 axis as seen in acromegalic patients or GH transgenic mice, which is different from physiologically normal hormone levels that naturally decline as a function of age. In addition, aging at the organism level may not correlate completely with specific tissue aging.

Insulin sensitivity

Insulin sensitivity has a close relationship with aging. Insulin resistance is generally found at old age (Rowe and others 1983) and insulin sensitivity is a hallmark of increased longevity (Masternak and others 2009). Given that MGD and insulin resistance are both found at old age, could it be that insulin resistance contributes to MGD? To date no study has been conducted on the relationship between insulin sensitivity and MGD. Related to sebaceous gland, dry skin has been observed in morbidly obese people (Yosipovitch and others 2007), although it is not known whether this is due to reduced sebaceous gland activity or other dermatological issues. On the other hand, increased acne is associated with obesity-associated disorders including hyperandrogenism, and hirsutism and polycystic ovary syndrome (Yosipovitch and others 2007); however, these are complicated by the primary involvement of sex hormones. It will be interesting to see the clinical manifestations of sebaceous gland and meibomian gland activities in patients with obesity, insulin resistance or type II diabetes.

In the insulin sensitive state, insulin stimulation results in glucose uptake and synthesis of lipids as an energy reservoir. Insulin resistance is characterized with reduced response to insulin signaling, including lipogenesis. Insulin signaling activates a key transcription factor in lipogenesis, peroxisome proliferator-activated receptor-γ (PPARγ), which is required to promote adipocyte differentiation in vitro and in vivo (Rosen and others 1999). PPARγ also promotes sebaceous gland differentiation and lipogenesis as well as sebum secretion (Fu and

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others 2010; Rosenfield and others 2000; Trivedi and others 2006). In terms of meibomian gland, PPARγ coincides with mouse meibocyte differentiation and lipid synthesis (Nien and others 2010) during development, and altered PPARγ staining accompanied reduced lipid accumulation in both human and mouse meibomian glands with aging (Nien and others 2011; Nien and others 2009). These data show reduced PPARγ activity in the aged meibomian gland, which seems to be consistent with one aspect of insulin resistance. Research is needed to reveal a relationship between insulin resistance and MGD.

Converging signal: FOXOs

Recent advances have shown emerging cell signaling pathways in aging and age-related diseases such as cancer and diabetes. One of these pathways involves insulin/IGF-1 signaling dependent inhibition of forkhead box O1 (FoxO1). Insulin/IGF-1 activates a downstream signaling cascade of phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB, also known as AKT), leading to activation of FoxO transcription factors that activate or suppress an array of target genes (Figure 3).

FoxO transcription factors including FoxO1 (the most abundant isoform), FoxO3a, FoxO4 and FoxO6 regulate genes involved in cell cycle control, apoptosis, cell differentiation and stem cell homeostasis (Huang and Tindall 2007; van der Vos and Coffer 2011). The importance of these transcription factors may be apparent from genetic disruption of these genes in mice. FoxO1 null mice are embryonically lethal due to incomplete vascular development, whereas FoxO3a null mice show age-dependent female infertility and FoxO4 null mice appear normal (Hosaka and others 2004). FoxOs normally reside in the nucleus and function as transcription factors, but when stimulated by growth factors such as insulin and IGF-1, they become phosphorylated and translocate from the nucleus to the cytosol thereby losing their activity as transcription factors (Huang and Tindall 2007). On the other hand, deacetylation by silent mating type information regulation 2 homolog-1 (SIRT1) promotes the activity of FoxO1 in transcribing genes involved in cell cycle arrest (Brunet and others 2004).

During aging, insulin resistance and/or declined GH/IGF-1 axis as discussed above may result in reduced insulin/IGF-1 signaling, leading to activated FoxOs (Figure 3). FoxOs potentially regulate meibocytes via two ways: 1) inducing cell cycle arrest and apoptosis, and 2) inhibiting lipogenesis. FoxOs are known to induce apoptosis in various cell types (Essaghir and others 2009; Huang and Tindall 2007; Kops and others 2002; Sakoe and others 2010). FoxOs reduce DNA synthesis, induce G1/S cell cycle arrest, as well as regulate key genes in cell cycle (Essaghir and others 2009; Huang and Tindall 2007; Kops and others 2002; Sakoe and others 2010). FoxOs inhibit lipogenesis (Cheng and White 2011) and are known to regulate lipid metabolism via three pathways: PPARs, androgen receptor and SREBP. As noted above, PPARs are important regulators for lipogenesis for many cell types including the sebocytes (Makrantonaki and Zouboulis 2007). Agonists of PPAR isoforms (α, δ and γ) promote sebocyte differentiation. Of the three isoforms, PPARγ is the most important in lipogenesis of sebaceous gland. PPARγ heterodimerizes with retinoid X receptor (RXR) and binds to PPAR response elements (PPRE) in the promoters of target genes. FoxO1 inhibits PPARγ by blocking its activity and reducing its levels. For example, FoxO1 directly binds and represses PPARγ promoter and PPARγ function in primary rat adipocytes and Caenorhabditis elegans (Armoni and others 2006; Dowell and others 2003). In addition, FoxO1 down-regulates the expression of PPARγ by acting as a co-repressor at the promoter of PPARγ (Melnik 2011). Androgens promote lipid production as discussed earlier. FoxO1 reduces the expression of androgen receptor (Fan and others 2007; Ma and others 2009), interacts with androgen receptor and suppresses its target genes including SREBP. Further, FoxO1 directly suppresses the promoter of SREBP, leading to reduced lipid synthesis (Melnik 2011). However, the known effects of FoxO1 in

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apoptosis, cell cycle and lipid metabolism regulation are yet to be demonstrated in meibomian gland cells. Lastly, FoxO1 regulates stem cell homeostasis. Targeted disruption of FoxO1, FoxO3 and FoxO4 in the mouse hemotopoietic system resulted in increased short-term repopulation activity of the stem cells; however, in the long term, population of hematopoietic stem cells (HSC) were decreased, indicating that FoxOs are important in maintaining the HSC quiescence, thereby preserving their self-renewal capacity (Tothova and others 2007). It is therefore conceivable that if FoxO activity increases at old age, it will similarly keep stem cells in a quiescent state (Figure 3), even though FoxO activity is required at younger ages to prevent fast turnover and depletion of the stem cell pool. Thus FoxOs may show an antagonistic pleiotropic effect during aging.

Anti-aging treatment- potential influence on MGD and dry eye

It is of great interest for many to turn back the clock and look youthful, if only for the appearance. In the market of anti-aging products for skin, one touted active ingredient is retinoic acid (RA) and its derivatives (retinoids) (Levin and Momin 2010). Retinoids are thought to reduce hyperpigmentation and skin roughness by enhancing epidermal cell turnover, and reduce fine lines and wrinkles by stimulating glycosaminoglycan and collagen synthesis and inhibiting enzymes that degrade collagen (Sorg and others 2005). These effects are thought to be mediated by retinoic acid receptor (RAR) (Sorg and others 2005). Even though randomized, double blind, placebo-controlled clinical studies on the anti-aging efficacy of retinoids are scarce and lack statistical confirmation (Levin and Momin 2010),this does not thwart the fast growing market for RA-based anti-aging cosmetics. Anti-aging skin care products, of which retinoids-based products are a major component, showed an annual growth rate of 11.8% from 2002-2007 and 9.7% from 2007-2012, far exceeding all the other skin care products combined (Brandt and others 2011). Unfortunately one side effect of RA cream is dryness of the skin. In fact, 13-cis retinoic acid (13-cis RA), also known as isotretinoin or Accutane, was initially used to treat acne before it found its way into the anti-aging cosmetics. It is highly effective in reducing sebaceous gland size by inhibiting sebocyte proliferation, differentiation and sebum production (Zouboulis 2006). Not surprisingly, RA causes MGD and dry eye disease, given that meibomian gland is a sebaceous gland. RA causes keratinization and thickening of the meibomian gland ducts (Lambert and Smith 1989), degeneration and necrosis of the acinar cells (Kremer and others 1994), fibrosis of the periacinar tissue, and reduced lipid content in meibomian gland (Lambert and Smith 1989). Further, isotretinoin exposure is associated with tear film instability and hyperosmolarity, dry eye symptoms and blepharitis (Bozkurt and others 2002; Fraunfelder 2004; Karalezli and others 2009; Santodomingo-Rubido and others 2008). In effect, RA promotes MGD and evaporative dry eye disease (Knop and others 2011).

In the sebaceous gland, RA decreases basal sebocyte proliferation, prohibits sebocyte terminal differentiation, induces sebocyte apoptosis, and suppresses sebum production up to 90% (Nelson and others 2006). These effects appear to be mediated through receptor-dependent and –independent actions (Nelson and others 2006; Tsukada and others 2000) and alterations in gene expression (Nelson and others 2008). In addition, RA may suppress androgen receptors (Ubels and others 2003; Ubels and others 2002) and inhibit retinol dehydrogenase-4 in sebaceous glands (Karlsson and others 2003), which would diminish the local, intracrine production of dihydrotestosterone (DHT). Of interest, specific deletion of scd-1 in the mouse skin causes a robust elevation of retinol, RA and RA-induced genes in the skin (Flowers and others 2011). This indicates that not only does RA inhibit androgen action in the sebaceous gland, but disruption of an important androgen target gene also leads to enhanced RA activity, therefore androgens and RA have antagonistic actions in the sebaceous gland. By analogy, these actions of RA would similarly attenuate androgen activity in meibomian gland and lead to MGD.

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Another anti-aging agent that has attracted a lot of attention is resveratrol, a polyphenol found in red wine and a variety of fruits and plants, that has protective effects against age-related diseases in rodents (Baur and Sinclair 2006) and multiple potential health benefits in humans (Smoliga and others 2011). Recently it was used in a pilot study to treat acne, with positive results (Fabbrocini and others 2011). The mechanism of this is not yet known, but if the effect is mediated through the suppression of sebaceous gland, potentially a similar effect can be seen in meibomian gland.

Interestingly, RA is known to activate FoxO3a in several cell systems (Kim and others 2009; Sakoe and others 2010); and resveratrol also activates FoxO1in various cells (Chen and others 2010; Costa Cdos and others 2011; Niu and others 2011; Park and others 2010; Roy and others 2011), in part through activation of SIRT1 (Feige and others 2008), an NAD(+)-dependent deacetylase that has been recognized as a conserved regulator of aging (Satoh and others 2011). Therefore it is possible that RA and resveratrol exert their therapeutic effects on acne mediated by FoxOs in the sebaceous gland and meibomian gland (Figure 3), which in the meibomian gland could be a potential mechanism of RA-induced MGD and dry eye disease.

Conclusion

Dry eye disease is a prevalent eye disorder affecting many people worldwide. The evaporative subtype is primarily caused by MGD, with aging being a risk factor. MGD is a relatively new field in ophthalmological research (Nichols 2011) and hence not well-studied. Although the association of aging with MGD/dry eye disease has long been recognized, very few studies have been done to address the mechanism of age-related increase of MGD. Potentially relevant mechanisms include androgens, GH/IGF-1 axis, stem cell and insulin resistance, with one converging signal of FOXOs. One pertinent health problem is that certain anti-aging treatments may actually adversely affect MGD and lead to dry eye disease. Studies are needed to unravel the mechanism of age-related MGD in order to permit the development of safe and effective therapeutics.

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Highlights

- Dry eye disease caused by MGD is prevalent among the elderly population.
- Age-related MGD research in humans and animals are reviewed.
- Potentially relevant mechanisms for age-related MGD are discussed.
- Certain anti-aging reagents including retinoids may promote the development of MGD.
- Studies are needed to unravel the mechanism of age-related MGD.

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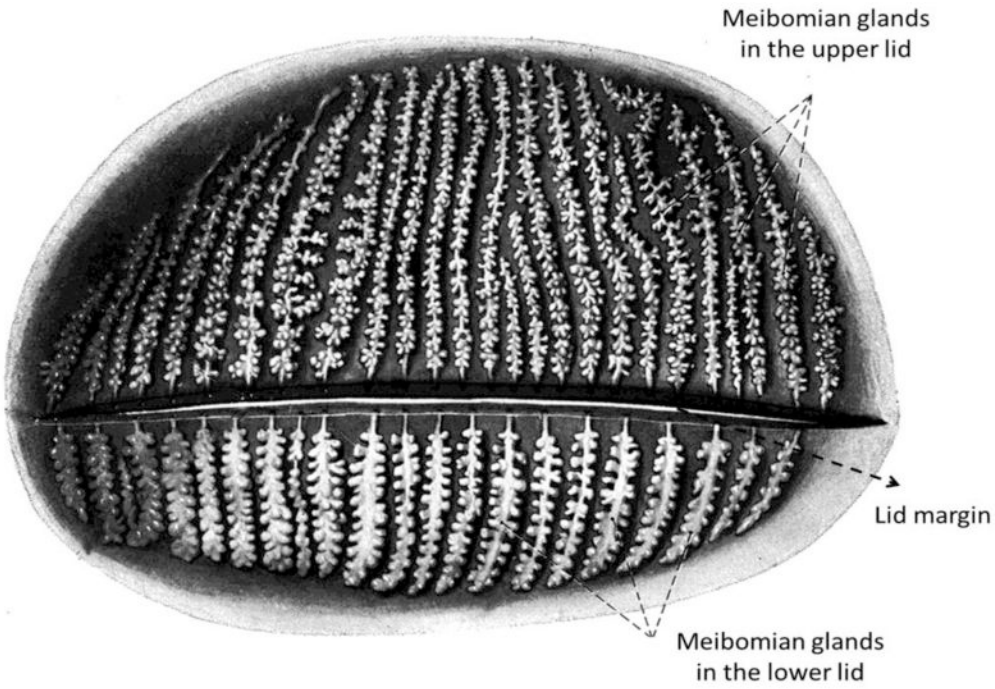

Figure 1.

Topography of the meibomian glands in the upper and lower eye lids. The drawing depicts a posterior view with the anterior part of the lid removed and the connective tissue made translucent so that the glands are exposed. Reproduced from Springer Science+Business Media: DER OPHTHALMOLOGE, Teil I: Anatomie, Embryologie und Histologie der Meibom-Drüsen, volume 106, 2009, page 872-983, Knop N, Knop E, Figure 3, which originated from Sobotta: Atlas der Anatomie des Menschen © Elsevier GmbH, Urban & Fischer Verlag München; with kind permission from Elsevier and Springer.

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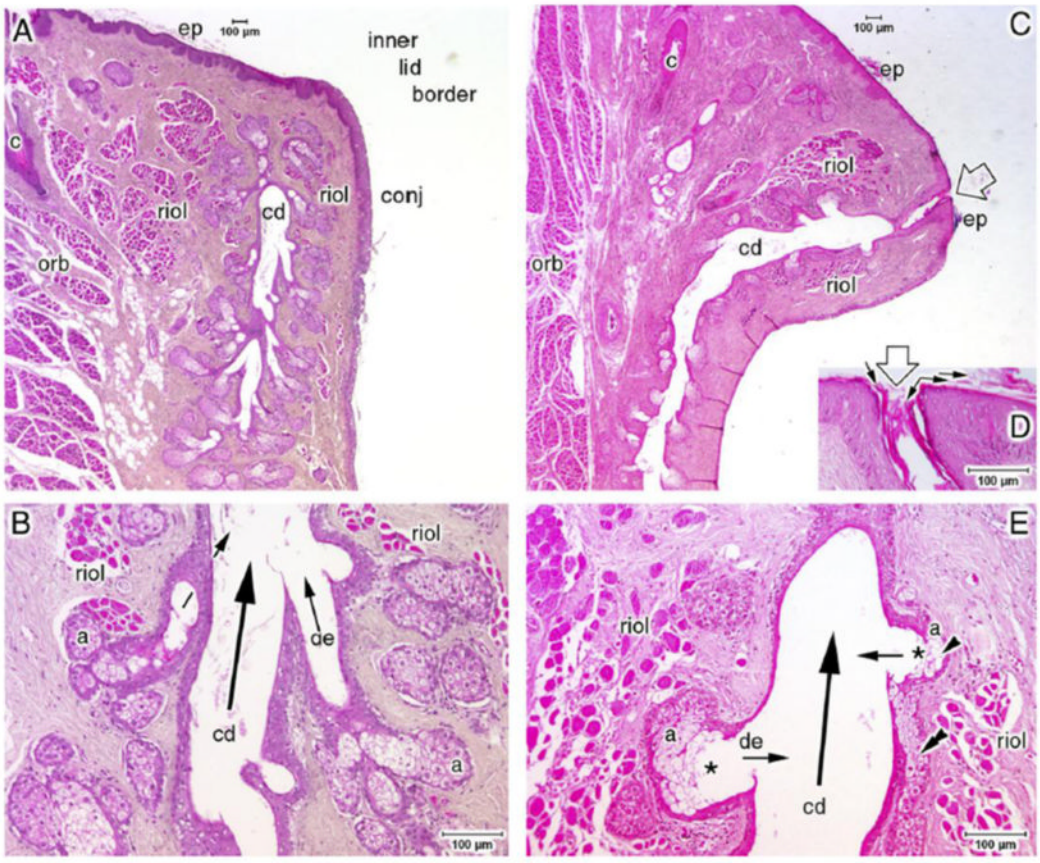

Figure 2.

Structural comparison of the meibomian gland in normal state and obstructive MGD. (A) A normal meibomian gland. This section is not cut through the orifice of the central duct (cd). (B) is a magnification of (A) showing the central duct (cd), the connecting ductules (de) and the acini (a). Normally, the ductule (de) is narrow and enters the central duct in an oblique direction. (C–E) Histology section of a meibomian gland with obstructive MGD. (C) The orifice is indicated by the open arrow. The central duct (cd) is partly dilated, with a thinner epithelium wall than in the normal gland. (D) The orifice is obstructed by keratin lamellae which are indicated by small arrows. (E) The ductules (de) are dilated and enter the central duct (cd) at right angles (small arrows). The secretory acini (a) are smaller than in a normal gland, the number of secretory meibocytes is reduced and only a few cell layers remain (arrowhead). Other abnormal structures include: asterisks indicate formations of lumens within the acini, and the double arrowhead indicates the apparent integration of meibocytes of a disrupted acinus into the wall of the central duct. Abbreviations: a, acini; c, ciliary; cd, central duct; conj, conjunctiva mucosa; de, connecting ductules; ep, epidermis; orb, orbicularis muscle; roil, Riolan's muscle. Light microscopic images of paraffin-embedded sections stained with hematoxylin and eosin (H&E); scale bars are shown in the images. Reprinted from Knop E, Knop N, Brewitt H et al. [Meibomian glands, Part III: meibomian gland dysfunction (MGD)—plaidoyer for a discrete disease entity and as an important cause of dry eye.] Meibom-Dru¨sen, Teil III: Meibomdru¨sen Dysfunktionen (MGD)—Pla¨doyer fu¨r ein igensta¨ndiges Krankheitsbild und wichtige Ursache fu¨r das Trockene Auge. Ophthalmologe. 2009;106:966–979, Figure 5, with kind permission of Springer Science and Business Media. The legend is adapted from (Knop and others 2011).

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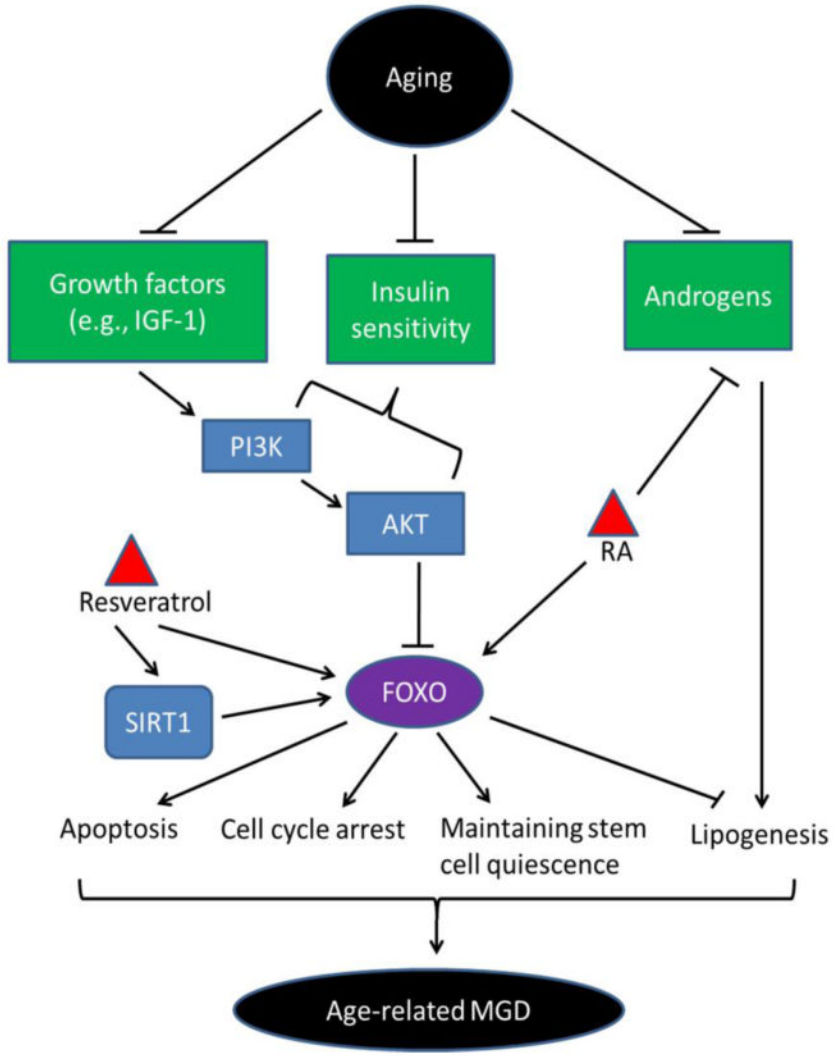

Figure 3.

Hypothetical signaling pathways in meibomian gland cells during aging. Levels of growth factors such as IGF-1 and androgens decline during aging, as well as insulin sensitivity, resulting in cell cycle arrest, apoptosis and reduced lipogenesis, possibly mediated via FOXOs. Increased FOXOs at old age may also keep stem cells in a quiescent state, resulting in less cell turnover of meibomian gland cells. Anti-aging agents such as RA and resveratrol also may influence FOXOs, leading to impaired meibomian gland function.