

Hormones and Dry Eye Disease

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Introduction

Dry eye disease (DED) is a very prevalent eye disorder, affecting 40 million people in the United States alone. The primary cause of DED is meibomian gland dysfunction (MGD) [1], which by itself is a disease entity. The meibomian gland is a large sebaceous gland located in the tarsal plate of the eye lids. It functions to synthesize and secrete lipids onto the ocular surface. These lipids make up the outer-most layer in the tear film and reduce tear evaporation. When the quantity or quality of the lipids is compromised such as occurs in MGD, tears evaporate more quickly, leading to increased DED, ocular surface discomfort, impaired vision and decreased quality of life.

Several risk factors for MGD have been identified, including aging, the female sex, androgen deficiency, rosacea, and medications such as isotretinoin (13-cis retinoic acid), antiandrogens and postmenapausal hormone replacement therapy [2]. In understanding why these factors are risk factors for MGD, one particularly interesting aspect is the hormonal regulation, as skin sebaceous glands are known to be heavily affected by hormones such as androgens, growth hormone (GH), insulin, insulin-like growth factor-1 (IGF-1), etc. [1]. These studies are made possible by a human sebaceous gland cell line. Recently, Dr. David A Sullivan's laboratory from Boston, Massachusetts has developed an immortalized human meibomian gland epithelial cell line using human telomerase reverse transcriptase. This cell line shows a normal karyotype, similar gene expression profiles to primary human meibomian gland epithelial cells, and can be induced to proliferate or differentiate under specific culture conditions [3-5]. This cell line has been sent to research laboratories all over the world for meibomian gland studies. In addition, we have created an in vitro MGD model using this cell line exposed to 13-cis retinoic acid, which induces cellular phenotypes and gene expression profiles characteristics of MGD. With the establishment of this cell line and the MGD model, we have started revealing the nature of the endocrine regulation of human meibomian gland and have identified possible interventions to counteract MGD. Here we will briefly summarize our recent findings related to hormones.

Isotretinoin

This is not a hormone per se, but it is often used systemically and is a risk factor for MGD. Isotretinoin, a vitamin A derivative, is used to treat severe acne; it is also a chemotherapeutic drug to treat cancer, and frequently found in anti-aging cosmetics due to its wrinklereducing effect. While quite effective in suppressing skin sebaceous gland growth, differentiation and lipid secretion, it also exerts a similar action on the meibomian gland, leading to dry eye. To understand the cellular and molecular mechanism of this action, we applied isotretinoin to immortalized human meibomian gland epithelial cells and analyzed the cellular phenotypes [6]. We discovered that isotretinoin inhibits cell proliferation, induces cell death, and significantly alters the expression of more than six thousand genes, including those involved in cell proliferation, cell death, differentiation, keratinisation and inflammation; further, isotretinoin also inhibits Akt signalling and increases the generation of interleukin-1 β and matrix metallopeptidase 9, both known to be associated with dry eye disease [7]. This demonstrates that vitamin A, even though an essential and beneficial factor for the health of the ocular surface, is toxic to the meibomian gland and induces dry eye at high doses. Therefore clinicians should monitor the dry eye side effect when treating acne or cancer using isotretinoin. Isotretinoin-exposed meibomian gland cells show characteristics of MGD, including cell atrophy and keratinisation, therefore we propose that this can be used as a model to study MGD pathophysiology and test treatments that may alleviate MGD *in vitro*.

Growth Hormone and IGF-1

The GH/IGF-1 axis promotes sebaceous gland proliferation and lipid secretion [8]. This leads to our hypothesis that GH and IGF-1 will similarly act on the meibomian gland. In support of this hypothesis, we have found that IGF-1 increases meibomian gland cell proliferation and lipid accumulation, and blocking the IGF-1 receptor diminishes these effects of IGF-1; however, GH does not produce an obvious phenotype in these cells [9]. We are actively seeking to identify the effect of GH on the meibomian gland in vivo and in co-culture models where the meibomian gland epithelial cells are cultured together with other supporting cell types that are present in vivo. The finding of IGF-1 receptor on the meibomian gland is clinically significant, as a cancer drug targeting IGF-1 receptor has already been found to lead to dry eye side effect in healthy human subjects [10]. Further, IGF-1 receptor is also considered a target for thyroid eye disease [11,12]. Therefore ophthalmologists should monitor meibomian gland health and dry eye disease when treating patients with IGF-1 receptor blockers.

And More

We are currently also working to elucidate the actions of steroid hormones such as androgens and estrogens, as well as insulin, a hormone that is dysregulated in diabetes. There are more than 50 hormones in the human body, and we are only begining to understand the endocrine regulation of the human meibomian gland. We welcome scientists all over the world to study the biology of this gland that plays such an essential role for ocular surface health.

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