

## The Importance of Lipids in Cutaneous Function

The skin is the largest organ of the body and has a very complex and heterogeneous structure. The innermost layer is the subcutaneous fat layer. Next is the dermis, which contains fibroblasts that produce collagen and elastic fibers. Localized within the dermis are specialized organelles including sebaceous glands, eccrine glands (sweat glands), and hair follicles. The nerves and blood vessels are also localized to the dermis. The outermost layer of the skin is the epidermis, a highly active lipid synthetic tissue, consisting of several distinct layers. The innermost layer of the epidermis is the basal layer, where cells are rapidly dividing. The spinous layer is in the mid-epidermis and represents cells that have undergone the initial steps of differentiation, while the stratum granulosum layer consists of cells that are further differentiated and have numerous lamellar bodies. The outer layer of the epidermis, the stratum corneum, consists of corneocytes (cells that have undergone terminal differentiation) and extracellular lipid membranes.

The skin has a large number of important functions. It provides an interface between a hostile external environment and the host. Thus the major function of the skin is to provide a barrier between the body and the outside environment. There are numerous barrier functions, and the skin has unique structures that provide for these various barriers. For example, the permeability barrier, which resides in the extracellular lipid membranes in the stratum corneum, prevents the loss of water and electrolytes. Additionally, it prevents the entry of toxic compounds. The skin surface is also, to a large extent, how we visualize other individuals, and thus the skin has not only biological functions but social functions. The cosmetic industry is built upon the aim of making the skin more attractive. Furthermore, skin diseases are very common. For example, atopic dermatitis affects 10-20% of children, acne affects almost all adolescents, and psoriasis affects 2% of the adult population.

While the skin is a vital organ, studies of lipid metabolism in the skin have not been in the mainstream of lipid research. However, now that molecular geneticists have shown a primary role for permeability barrier abnormalities as the cause of atopic dermatitis and perhaps other common cutaneous diseases, increasing attention is focusing on the factors that regulate and maintain permeability barrier function. Additionally, the key role of sebaceous gland lipids in acne, the marked dysfunction of sebaceous glands in genetically engineered mice with a deficiency of

enzymes required for fatty acid and triglyceride metabolism, and mutations in lipid enzymes as the etiology of many of the types of ichthyosis (skin changes resembling fish-scales) have also heightened interest in cutaneous lipid metabolism. Therefore, I think it is timely that a thematic review series provide an up-to-date discussion on lipid metabolism in the skin and hopefully interest other investigators to study this complex but essential organ.

I will lead off this series with a review of the role of epidermal lipids in permeability barrier function. For terrestrial life it is essential to have a functional permeability barrier that prevents the loss of water and electrolytes. This permeability barrier is comprised of extracellular lipid-enriched membranes in the stratum corneum that contain ceramides, cholesterol, and free fatty acids. I will review how these lipids are synthesized and the regulation of their synthesis in response to barrier perturbations.

Dr. Diane Thiboutot and colleagues will review lipid metabolism in sebaceous glands, which secrete a variety of different lipids including squalene, wax esters, and triglycerides onto the surface of the skin. Acne is dependent on lipid production by sebaceous glands, and strategies that reduce sebaceous gland lipid secretion could be useful in the treatment of acne. Additionally, the role of sebaceous gland lipids in skin hydration will be discussed.

Dr. Phillip Wertz and colleagues will review the role of skin lipids in preventing infections, one of the key barrier properties of skin. Although largely attributed to antimicrobial peptides, such as the  $\beta$ -defensins and cathelicidins, skin lipids, produced by both the epidermis and sebaceous glands, also play a key role in preventing infection, i.e., they are active participants in the innate immune system.

Dr. Peter Elias and colleagues will review the role of lipids in regulating desquamation. The epidermis is a rapidly dividing tissue that is constantly renewing itself. It is essential that the production of new keratinocytes is balanced by the shedding of corneocytes from the skin surface. Either failure to desquamate and/or overproduction of corneocytes results in thickening of the stratum corneum and thus ichthyosis. The appearance of the skin resembles fish scales, and the term ichthyosis is derived from the Greek word *ichthys* which means fish. A number of genetic abnormalities in lipid metabolism have been shown to cause ichthyosis, and these disorders have provided insights into the role of lipids in regulating cohesion and desquamation in normal skin.

Dr. Walter Holleran and colleagues will review sphingolipid metabolism in the epidermis. It is now recognized that the epidermis produces both large quantities and a great diversity of sphingolipids and that these sphingo-

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lipids play key roles in the formation of the extracellular lamellar membranes in the stratum corneum that account for the permeability barrier. Additionally, unique sphingolipids also play an essential role in the formation of the cornified lipid envelope that links the corneocyte with the extracellular lamellar membranes.

Finally, Dr Matthias Schmuth and colleagues will review the role of PPARs and LXRs in skin biology. The skin in general, and the epidermis and sebaceous glands in particular, are important sites of lipid synthesis, and therefore it is not surprising that the nuclear hormone receptors that are activated by lipids (liposensors) are present in the

skin and regulate a wide variety of skin functions. The role of PPARs and LXR in regulating sebaceous gland and epidermal function will be discussed in that review.

Together, this series of articles should provide an up-to-date review of cutaneous lipid metabolism. Hopefully, the reader will develop a greater appreciation for the key role of lipids in skin biology, and perhaps he/she will be attracted to applying his/her expertise to further elucidate the key roles of lipid metabolism in skin biology and disease.

Kenneth R. Feingold  
Associate Editor