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Review

Role of lipids in the formation and maintenance of the cutaneous permeability barrier☆

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ABSTRACT

The major function of the skin is to form a barrier between the internal milieu and the hostile external environment. A permeability barrier that prevents the loss of water and electrolytes is essential for life on land. The permeability barrier is mediated primarily by lipid enriched lamellar membranes that are localized to the extracellular spaces of the stratum corneum. These lipid enriched membranes have a unique structure and contain approximately 50% ceramides, 25% cholesterol, and 15% free fatty acids with very little phospholipid. Lamellar bodies, which are formed during the differentiation of keratinocytes, play a key role in delivering the lipids from the stratum granulosum cells into the extracellular spaces of the stratum corneum. Lamellar bodies contain predominantly glucosylceramides, phospholipids, and cholesterol and following the exocytosis of lamellar lipids into the extracellular space of the stratum corneum these precursor lipids are converted by beta glucocerebrosidase and phospholipases into the ceramides and fatty acids, which comprise the lamellar membranes. The lipids required for lamellar body formation are derived from de novo synthesis by keratinocytes and from extra-cutaneous sources. The lipid synthetic pathways and the regulation of these pathways are described in this review. In addition, the pathways for the uptake of extra-cutaneous lipids into keratinocytes are discussed. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

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1. Introduction

The skin is a large and complex organ that is very heterogeneous in terms of cells of mesenchymal and epithelial origin. In this special issue of the BBA — Molecular and Cell Biology of Lipids we are focusing on lipid metabolism in the epidermis, particularly as it relates to the permeability and antimicrobial barrier functions of the skin. It is important to recognize that other components of the skin, such as sebaceous glands, hair follicles, and fibroblasts, also synthesize and utilize lipids, often for specific and unique reasons. Therefore, in studying lipid metabolism in the skin, it is very important to isolate the specific components of the skin that are of interest. Accordingly, studies of the whole skin can be very difficult to interpret.

2. Barrier function of the skin

The major function of the skin is to form a barrier between the internal milieu of the host and the hostile external environment [1]. The skin must protect the organism from chemicals, ultraviolet light, mechanical insults, and pathogenic microorganisms. Most importantly, the skin must provide an efficient permeability barrier that prevents the loss of water and electrolytes [1]. Without a permeability barrier life on land would be impossible. By preventing the loss of fluid and electrolytes and blocking the entry of toxic compounds and allergens, lipids are essential in providing this permeability barrier [1,2]. Additionally, lipids also have antimicrobial properties, which contribute to the barrier to pathogenic microorganisms [3]. As part of this special issue the role of lipids in host defense is discussed in detail by Fischer and colleagues [4].

When the skin barrier is markedly perturbed, which occurs with severe burns or in premature infants, there is great difficulty in maintaining fluid and electrolyte balance and a high risk of infection [5,6]. As will be discussed in great detail in several articles in this special issue, a number of genetic disorders in lipid metabolism also lead to abnormalities in permeability barrier function. More subtle functional abnormalities in the permeability barrier function occur in neonates, the elderly, and in association with common skin diseases including psoriasis

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and atopic dermatitis [7–9]. As part of this special issue the role of lipids in the permeability barrier abnormality in atopic dermatitis will be discussed in detail by Elias [10].

3. Localization of permeability barrier function

The permeability barrier localizes primarily to the outermost layer of the epidermis, the stratum corneum (the epidermis consists of 4 layers — the undifferentiated basal layer, where cell proliferation occurs, the stratum spinosum where differentiation begins, the further differentiated stratum granulosum, and the outermost, acellular layers of the stratum corneum) [1]. The stratum corneum consists of keratinocytes (corneocytes) that have undergone terminal differentiation with degradation of the nucleus, loss of DNA, and formation of a unique cornified envelope that serves as a platform for a neutral lipid enriched extracellular matrix. This extracellular hydrophobic lipid matrix provides the barrier to the movement of water and electrolytes. Pioneering studies by Gray and colleagues that have been confirmed by numerous other laboratories have shown that this expanded lipid matrix, accounting for about 10% of the tissue mass of the stratum corneum, has a unique lamellar organization and composition with approximately 50% of the lipid mass ceramides, 25% cholesterol, and 15% free fatty acids with very little phospholipid [2,11,12]. As part of this special issue the composition and organization of lipids in the stratum corneum will be discussed in detail by van Smeden and colleagues [13]. The ceramides in the stratum corneum are unusual and very diverse with a high percentage of very long chain N-acyl fatty acids. Additionally, linoleate is present in a subgroup of acylceramides, which anchor adjacent bilayers together into multilayers of broad membrane sheets. In essential fatty acid deficiency, oleate replaces linoleate resulting in an abnormal appearance of the extracellular lipid membranes and perturbed permeability barrier function, indicating that essential fatty acids are required for the formation of a normal stratum corneum [14–17]. In this special issue Elias and colleagues discuss the role of linoleate in greater detail [18]. The free fatty acids in the stratum corneum are predominantly straight chained and greater than 20 carbons in length [11]. Cholesterol is the major sterol in the stratum corneum, but compared with other tissues the stratum corneum contains an abundance of cholesterol sulfate, which plays an important role in regulating stratum corneum cohesion and desquamation [19,20]. In this special issue Elias and colleagues discuss the formation, metabolism, and function of cholesterol sulfate [21].

4. Role of lamellar bodies

Lamellar bodies play a key role in delivering the polar precursor lipids from stratum granulosum keratinocytes into the extracellular spaces of the stratum corneum. Lamellar bodies are ovoid, 0.2 × 0.3 μm membrane bilayer-encircled secretory organelles in the epidermis that have a unique structure and chemical composition [22]. These organelles are formed as keratinocytes differentiate, and are first seen in the upper stratum spinosum layer of the epidermis with increasing numbers in the cytosol of the stratum granulosum cells. Lamellar bodies contain cholesterol, phospholipids, glucosylceramides and sphingomyelin [22] (see Fig. 1). Of note, in addition to lipids, lamellar bodies also contain enzymes such as beta glucocerebrosidase, acidic sphingomyelinase, and secretory phospholipase A2, as well as neutral and acidic lipases, chemotryptic enzymes (kallikreins 7 and 8), cathepsins (cathepsin D), protease inhibitors, caveolin-1, and corneodesmosin [22–24]. Moreover, antimicrobial peptides, such as beta-defensin 2 and the cathelicidin LL-37, also are localized to lamellar bodies [22]. It is likely that numerous other proteins are associated with lamellar bodies and mass spectrometry of enriched-lamellar body fractions have demonstrated the presence of a large number of proteins in various classes (proteases, protease inhibitors, secreted proteins, lysosomal proteins, calcium binding proteins, membrane proteins, Rab-associated proteins, membrane trafficking proteins, annexins, ion pumps, transporters and channels, receptors, and signal transduction proteins) [25]. It is important to recognize that our ability to isolate purified lamellar bodies is limited and therefore it is difficult to be sure that

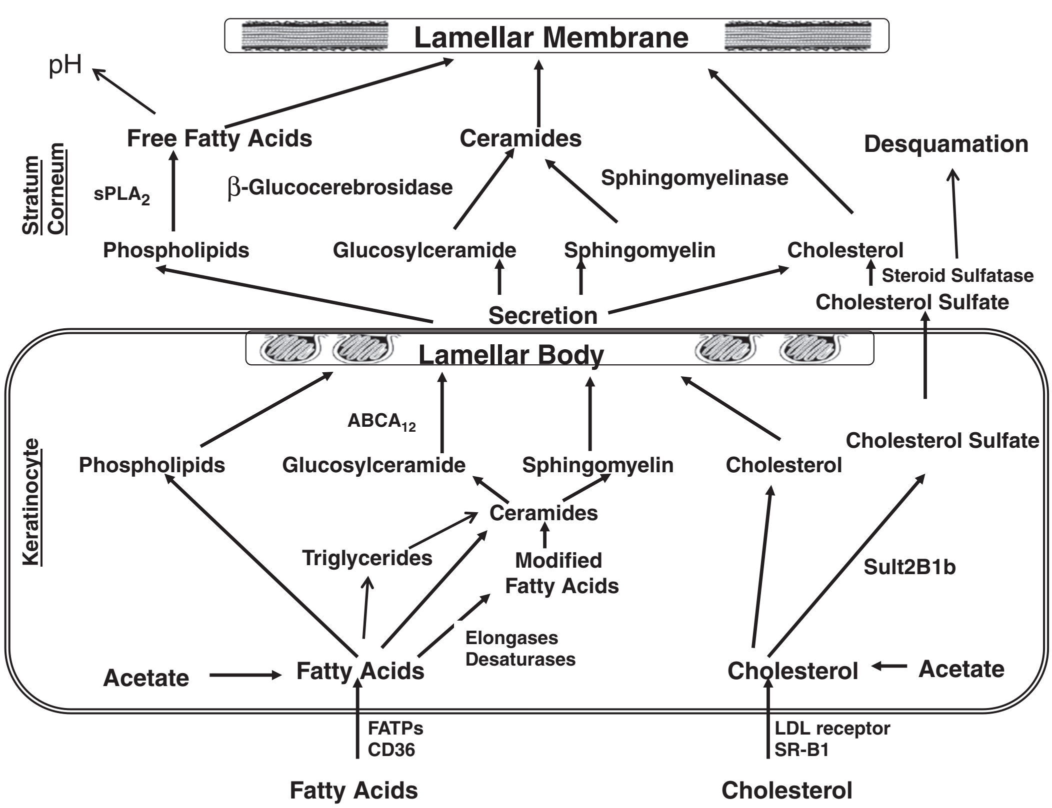

Fig. 1. Pathways for the formation of the extracellular lamellar lipid membranes that provide for the permeability barrier (figure modified from figure in reference 2).