

Chapter 47

Skin as an Organ of Protection

Ehrhardt Proksch & Jens-Michael Jensen

REFERENCES

1. Madison KC: Barrier function of the skin: "la raison d'être" of the epidermis. *J Invest Dermatol* **121**(2):231, 2003
2. Saint-Leger D et al: SC lipids in skin xerosis. *Dermatologica* **178**(3):151, 1989
3. Schneider MR, Paus R: Sebocytes, multifaceted epithelial cells: Lipid production and holocrine secretion. *Int J Biochem Cell Biol* **42**(2):181-185, 2010
4. Fluhr JW et al: Glycerol regulates SC hydration in sebaceous gland deficient (asebia) mice. *J Invest Dermatol* **120**(5):728, 2003
5. Winsor T, Burch GE: Differential roles of layers of human epigastric skin on diffusion rate of water. *Arch Intern Med* **74**:428, 1944
6. Blank IH: Further observations on factors which influence the water content of the stratum corneum. *J Invest Dermatol* **45**:249, 1953
7. Oren A et al: In human epidermis, beta-defensin 2 is packaged in lamellar bodies. *Exp Mol Pathol* **74**(2):180, 2003
8. Bouwstra JA, Pilgrim K, Ponc M: Structure of the skin barrier. In: *Skin Barrier*, edited by PM Elias, KR Feingold. New York, Taylor and Francis, 2006, p. 65
9. Gray GM, Yardley HJ: Different populations of pig epidermal cells: Isolation and lipid composition. *J Lipid Res* **16**(6):441, 1975
10. Elias PM: Epidermal lipids, barrier function, and desquamation. *J Invest Dermatol* **80**:44s, 1983
11. Downing DT et al: Skin lipids: An update. *J Invest Dermatol* **88**(3):2s, 1987
12. Wertz PW: Biochemistry of human stratum corneum lipids. In: *Skin Barrier*, edited by PM Elias, KR Feingold. New York, Taylor and Francis, 2006, p. 33
13. Proksch E, Elias PM, Feingold KR: Regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity in murine epidermis. Modulation of enzyme content and activation state by barrier requirements. *J Clin Invest* **85**(3):874, 1990
14. Mao-Qiang M, Elias PM, Feingold KR: Fatty acids are required for epidermal permeability barrier function. *J Clin Invest* **92**(2):791, 1993
15. Proksch E et al: Barrier function regulates epidermal lipid and DNA synthesis. *Br J Dermatol* **128**(5):473, 1993
16. Proksch, E: Biosynthesis of fatty acids in skin and their role in epidermal barrier function, in *Progress in Inflammation Research*. In: *Fatty Acids and Inflammatory Skin Diseases*, edited by JM Schroeder. Basel, Birkhauser Verlag, 1999, p. 1
17. Proksch E, Feingold KR, Elias PM: Epidermal HMG CoA reductase activity in essential fatty acid deficiency: Barrier requirements rather than eicosanoid generation regulate cholesterol synthesis. *J Invest Dermatol* **99**(2):216-220, 1992
18. Uchida Y, Hamanaka S: Stratum corneum ceramides: Function, origins, and therapeutic implications. In: *Skin Barrier*, edited by PM Elias, KR Feingold. New York, Taylor and Francis, 2006, p. 43
19. Holleran WM et al: Processing of epidermal glucosylceramides is required for optimal mammalian cutaneous permeability barrier function. *J Clin Invest* **91**(4):1656, 1993
20. Jensen JM et al: Roles for tumor necrosis factor receptor p55 and sphingomyelinase in repairing the cutaneous permeability barrier. *J Clin Invest* **104**(12):1761, 1999
21. Uchida Y et al: Epidermal sphingomyelins are precursors for selected stratum corneum ceramides. *J Lipid Res* **41**(12):2071, 2000
22. Man MQ et al: Basis for improved permeability barrier homeostasis induced by PPAR and LXR activators: Liposensors stimulate lipid synthesis, lamellar body secretion, and post-secretory lipid processing. *J Invest Dermatol* **126**(2):386, 2006
23. Schurer NY: Implementation of fatty acid carriers to skin irritation and the epidermal barrier. *Contact Dermatitis* **47**(4):199, 2002
24. Jiang YJ et al: Ceramide stimulates ABCA12 expression via peroxisome proliferator-activated receptor δ in human keratinocytes. *J Biol Chem* **284**(28):18942-18952, 2009

25. Roop D: Defects in the barrier. *Science* **267**:474, 1995
26. Nemes Z, Steinert PM: Bricks and mortar of the epidermal barrier. *Exp Mol Med* **31**(1):5, 1999
27. Webb A, Li A, Kaur P: Location and phenotype of human adult keratinocyte stem cells of the skin. *Differentiation* **72**(8):387, 2004
28. Williams ML: Ichthyosis: Mechanisms of disease. *Pediatr Dermatol* **9**(4):365, 1992
29. Pullmann H, Lennartz KJ, Steigleder GK: Disturbance of DNA-Synthesis in early psoriasis. *Arch Dermatol Res* **258**(2):211, 1977
30. Candi E, Schmidt R, Melino G: The cornified envelope: A model of cell death in the skin. *Nat Rev Mol Cell Biol* **6**(4):328, 2005
31. Marekov LN, Steinert PM: Ceramides are bound to structural proteins of the human foreskin epidermal cornified cell envelope. *J Biol Chem* **273**(28):17763, 1998
32. Swartzendruber DC et al: Evidence that the corneocyte has a chemically bound lipid envelope. *J Invest Dermatol* **88**(6):709, 1987
33. Proksch E et al: Barrier function regulates epidermal DNA synthesis. *J Clin Invest* **87**(5):1668, 1991
34. Grubauer G, Elias PM, Feingold KR: Transepidermal water loss: The signal for recovery of barrier structure and function. *J Lipid Res* **30**(3):323, 1989
35. Ekanayake-Mudiyanselage S et al: Expression of epidermal keratins and the cornified envelope protein involucrin is influenced by permeability barrier disruption. *J Invest Dermatol* **111**(3):517, 1998
36. Porter RM et al: Gene targeting at the mouse cytokeratin 10 locus: Severe skin fragility and changes of cytokeratin expression in the epidermis. *J Cell Biol* **132**(5):925, 1996
37. Jensen JM et al: Impaired cutaneous permeability barrier function, skin hydration, and sphingomyelinase activity in keratin 10 deficient mice. *J Invest Dermatol* **115**(4):708, 2000
38. Reichelt J et al: Normal ultrastructure, but altered stratum corneum lipid and protein composition in a mouse model for epidermolytic hyperkeratosis. *J Invest Dermatol* **113**(3):329, 1999
39. Presland RB et al: Barrier function in transgenic mice overexpressing K16, involucrin, and filaggrin in the suprabasal epidermis. *J Invest Dermatol* **123**(3):603, 2004
40. Djian P, Easley K, Green H: Targeted ablation of the murine involucrin gene. *J Cell Biol* **151**(2):381, 2000
41. Mildner M et al: Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model. *J Invest Dermatol* 2010 May 6. [Epub ahead of print] PubMed PMID: 20445547.
42. Ishida-Yamamoto A, Iizuka H: Structural organization of cornified cell envelopes and alterations in inherited skin disorders. *Exp Dermatol* **7**(1):1, 1998
43. Koch PJ et al: Lessons from loricrin-deficient mice: Compensatory mechanisms maintaining skin barrier function in the absence of a major cornified envelope protein. *J Cell Biol* **151**(2):389, 2000
44. Jensen JM, Proksch E, Elias PM: The stratum corneum of the epidermis in atopic dermatitis. In: *Skin Barrier*, edited by PM Elias, KR Feingold. New York, Taylor and Francis, 2006, p. 569
45. Elias PM, Fritsch P, Epstein EH: Staphylococcal scalded skin syndrome. Clinical features, pathogenesis, and recent microbiological and biochemical developments. *Arch Dermatol* **113**(2):207, 1977
46. Honari S: Topical therapies and antimicrobials in the management of burn wounds. *Crit Care Nurs Clin North Am* **16**(1):1, 2004
47. Furuse M et al: Claudin-based tight junctions are crucial for the mammalian epidermal barrier: A lesson from claudin-1-deficient mice. *J Cell Biol* **156**(6):1099, 2002
48. Turksen K, Troy TC: Permeability barrier dysfunction in transgenic mice overexpressing claudin 6. *Development* **129**(7):1775, 2002
49. Brandner JM, Proksch E: Epidermal barrier function: Role of tight junctions. In: *Skin Barrier*, edited by PM Elias, KR Feingold. New York, Taylor and Francis, 2006, p. 191
50. Trautmann A et al: The differential fate of cadherins during T-cell-induced keratinocyte apoptosis leads to spongiosis in eczematous dermatitis. *J Invest Dermatol* **117**(4):927, 2001
51. Maretzky T et al: ADAM10 mediates E-cadherin shedding and regulates epithelial cell-cell adhesion, migration, and beta-catenin translocation. *Proc Natl Acad Sci U S A* **102**(26):9182, 2005
52. Elias PM et al: Desmoglein isoform distribution affects stratum corneum structure and function. *J Cell Biol* **153**(2):243, 2001
53. Tunggal JA et al: E-cadherin is essential for in vivo epidermal barrier function by regulating tight junctions. *EMBO J* **24**(6):1146, 2005

54. Maretzky T et al: ADAM10-mediated E-cadherin release is regulated by proinflammatory cytokines and modulates keratinocyte cohesion in eczematous dermatitis. *J Invest Dermatol* **128**(7):1737-1746, 2008
55. Djalilian AR et al: Connexin 26 regulates epidermal barrier and wound remodeling and promotes psoriasiform response. *J Clin Invest* **116**(5), 2006
56. Matsuki M et al: Defective stratum corneum and early neonatal death in mice lacking the gene for transglutaminase 1 (keratinocyte transglutaminase). *Proc Natl Acad Sci U S A* **95**(3):1044, 1998
57. Huber M et al: Mutations of keratinocyte transglutaminase in lamellar ichthyosis. *Science* **267**(5197):525, 1995
58. Egberts F et al: Cathepsin D is involved in the regulation of transglutaminase 1 and epidermal differentiation. *J Cell Sci* **117**(11):2295, 2004
59. Zeeuwen PL et al: The cystatin M/E-cathepsin L balance is essential for tissue homeostasis in epidermis, hair follicles, and cornea. *FASEB J* 2010 May 21. [Epub ahead of print] PubMed PMID: 20495178.
60. Cheng T et al: The cystatin M/E-controlled pathway of skin barrier formation: Expression of its key components in psoriasis and atopic dermatitis. *Br J Dermatol* **161**(2):253-264, 2009
61. Descargues P et al: Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. *Nat Genet* **37**(1):56, 2005
62. Briot A et al: Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. *J Exp Med* **206**(5):1135-1147, 2009
63. Martin P: Wound healing—Aiming for perfect skin regeneration. *Science* **276**(5309):75, 1997
64. Wood LC et al: Barrier disruption stimulates interleukin-1 alpha expression and release from a pre-formed pool in murine epidermis. *J Invest Dermatol* **106**(3):397, 1996
65. Wood LC et al: Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. *J Clin Invest* **90**(2):482, 1992
66. Wang XP et al: The interleukin-6 cytokine system regulates epidermal permeability barrier homeostasis. *J Invest Dermatol* **123**(1):124, 2004
67. Menon GK, Grayson S, Elias PM: Ionic calcium reservoirs in mammalian epidermis: Ultrastructural localization by ion-capture cytochemistry. *J Invest Dermatol* **84**(6):508, 1985
68. Menon GK, Elias PM: Ultrastructural localization of calcium in psoriatic and normal human epidermis. *Arch Dermatol* **127**(1):57, 1991
69. Lee SH et al: Calcium and potassium are important regulators of barrier homeostasis in murine epidermis. *J Clin Invest* **89**(2):530, 1992
70. Hitomi K: Transglutaminases in skin epidermis. *Eur J Dermatol* **15**(5):313, 2005
71. Lavrijsen AP et al: Barrier function parameters in various keratinization disorders: Transepidermal water loss and vascular response to hexyl nicotinate. *Br J Dermatol* **129**(5):547, 1993
72. Verboomen H et al: Functional difference between SERCA2a and SERCA2b Ca²⁺ pumps and their modulation by phospholamban. *Biochem J* **286**:591, 1992
73. Foggia L, Hovnanian A: Calcium pump disorders of the skin. *Am J Med Genet C Semin Med Genet* **131**(1):20, 2004
74. Hu Z et al: Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. *Nat Genet* **24**(1):61, 2000
75. Denda M: New methodology to improve epidermal barrier homeostasis In: *Dry Skin and Moisturizers*, edited by M Loden, HI Maibach. New York, Taylor and Francis, 2006, p. 155
76. Gunathilake R et al: Epidermal barrier dysfunction in non-atopic HIV: Evidence for an “inside-to-outside” pathogenesis. *J Invest Dermatol* **130**(4):1185-1188, 2010
77. Berger CL, Edelson R: The life cycle of cutaneous T cell lymphoma reveals opportunities for targeted drug therapy. *Curr Cancer Drug Targets* **4**(7):609, 2004
78. Leung DY: New insights into the complex gene-environment interactions evolving into atopic dermatitis. *J Allergy Clin Immunol* **118**(1):37, 2006
79. Elias PM, Feingold KR: Does the tail wag the dog? Role of the barrier in the pathogenesis of inflammatory dermatoses and therapeutic implications. *Arch Dermatol* **137**(8):1079, 2001
80. Proksch E, Jensen JM, Elias PM: Skin lipids and epidermal differentiation in atopic dermatitis. *Clin Dermatol* **21**(2):134, 2003
81. Proksch E, Foelster-Holst R, Jensen JM: Skin barrier function, epidermal proliferation and differentiation in eczema. *J Dermatol Sci* **43**(3):159-169, 2006
82. Proksch E et al: Role of the epidermal barrier in atopic dermatitis. *J Dtsch Dermatol Ges* **7**(10):899-910, 2009

83. Palmer CN et al: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* **38**:441, 2006
84. Ruether A et al: Filaggrin loss-of-function variant contributes to atopic dermatitis risk in the population of Northern Germany. *Br J Dermatol* **155**:1093-1094, 2006
85. Weidinger S et al: Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* **118**:214, 2006
86. Irvine AD, McLean WH: Breaking the(un)sound barrier: Filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol* **126**:1200, 2006
87. Akiyama M: FLG mutations in ichthyosis vulgaris and atopic eczema: Spectrum of mutations and population genetics. *Br J Dermatol* **162**(3):472-477, 2010
88. Scott IR, Harding CR: Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol* **115**:84, 1986
89. Wu Z et al: Highly complex peptide aggregates of the S100 fused-type protein hornerin are present in human skin. *J Invest Dermatol* **129**(6):1446-1458, 2009
90. Walley AJ et al: Gene polymorphism in Netherton and common atopic disease. *Nat Genet* **29**:175, 2001
91. Macheleidt O, Kaiser HW, Sandhoff K: Deficiency of epidermal protein-bound omega-hydroxyceramides in atopic dermatitis. *J Invest Dermatol* **119**(1):166, 2002
92. Fartasch M, Bassukas ID, Diepgen TL: Disturbed extruding mechanism of lamellar bodies in dry non-eczematous skin of atopics. *Br J Dermatol* **127**(3):221, 1992
93. Grice K, Sattar H, Baker H: The cutaneous barrier to salts and water in psoriasis and in normal skin. *Br J Dermatol* **88**(5):459, 1973
94. Motta S et al: Abnormality of water barrier function in psoriasis. Role of ceramide fractions. *Arch Dermatol* **130**(4):452, 1994
95. Fartasch M: Epidermal barrier in disorders of the skin. *Microsc Res Tech* **38**(4):361, 1997
96. Segre JA: Epidermal barrier formation and recovery in skin disorders. *J Clin Invest* **116**(5):1150, 2006
97. Epstein EH Jr, Leventhal ME: Steroid sulfatase of human leukocytes and epidermis and the diagnosis of recessive X-linked ichthyosis. *J Clin Invest* **67**(5):1257, 1981
98. Bouwstra JA et al: Cholesterol sulfate and calcium affect stratum corneum lipid organization over a wide temperature range. *J Lipid Res* **40**(12):2303, 1999
99. Thauvin-Robinet C et al: Unique survival in chondrodysplasia-hermaphroditism syndrome. *Am J Med Genet A* **132**(3):335, 2005
100. Smith FJ et al: Loss-of function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* **38**:337-342, 2006
101. Jensen JM et al: Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol* **123**(5):1124-1133, 2009. Erratum in: *J Allergy Clin Immunol* **124**(5):1038, 2009
102. Ghadially R, Halkier-Sørensen L, Elias PM: Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol* **26**:387, 1992
103. Loden M, Andersson AC, Lindberg M: Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm). *Br J Dermatol* **140**:264, 1999
104. Tabata N et al: Biophysical assessment of persistent effects of moisturizers after their daily applications: Evaluation of corneotherapy. *Dermatology* **200**:308, 2000
105. Chamlin SL et al: Ceramide-dominant, barrier repair lipids improve childhood atopic dermatitis. *Arch Dermatol* **137**:1110, 2001
106. Berardesca E et al: Evaluation of efficacy of a skin lipid mixture in patients with irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis: A multicenter study. *Contact Dermatitis* **45**:280, 2001