

# Expression Profiles of Stratum Corneum Lipid Metabolism Pathways Associated with Intrinsic and Extrinsic Aging

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## INTRODUCTION

Skin aging has been described as a cumulative process resulting from unrepaired damage as well as age-related physiological changes. The damaging factors which accelerate skin aging can be divided into intrinsic factors, such as free radicals, and extrinsic factors, with sun exposure being the most important. Within the current study we examined the effects of both intrinsic and photoaging on the expression of stratum corneum lipid metabolism pathways.

## OBJECTIVE

The goal of the current work was to evaluate the effects of both intrinsic and extrinsic aging on the gene expression profiles of pathways involved in stratum corneum lipid metabolism.

## BACKGROUND

The major lipids of the human Stratum Corneum (SC) are ceramides, cholesterol, and fatty acids, comprising approximately 50%, 25%, and 10% of the total lipid mass, respectively<sup>1</sup>. These mature SC lipids are generated from precursor lipids<sup>2,3</sup> which are synthesized, packaged into lamellar bodies (LB), and then released into the SC extracellular space following LB fusion with the plasma membrane of granular keratinocytes<sup>4</sup>. Subsequent lipid processing yields the mature SC lipids [Figure 1]<sup>2,3</sup>.

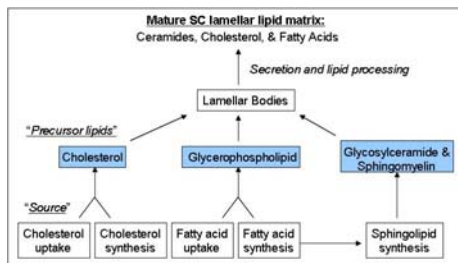


Figure 1. Summary of the *in vivo* pathways to form mature SC lamellar lipids.

## METHODS

A study was conducted with ten younger (18-20 years old) and ten older (60-67 years old) female subjects. Full thickness biopsies were sampled from sun-protected skin, the buttocks, to study intrinsic aging, and from the outer forearm to study the combined effects of photoaging and intrinsic aging. Older subjects were required to have moderate to severe forearm photo-damage. Total RNA from each sample was purified, labeled and hybridized to Affymetrix U133 plus 2 GeneChips. Following statistical analysis, bioinformatics focused on SC lipid metabolism genes.

## RESULTS

Figure 2 illustrates the gross appearance of skin samples analyzed, demonstrating that both intrinsically and photoaged skin show increased uneven texture and discoloration. Figures 3, 4 and 5 highlight the biochemical pathways by which SC cholesterol, fatty acids, and ceramides are produced. The key intermediates are given in yellow, while the enzymes responsible for their formation are given in red. Tables I, II, and III highlight the expression of these genes in both intrinsic and photoaging.



Figure 2. Representative images depicting the gross appearance of buttock (left panel) and forearm (right panel) samples used to analyze intrinsic and extrinsic aging, respectively.

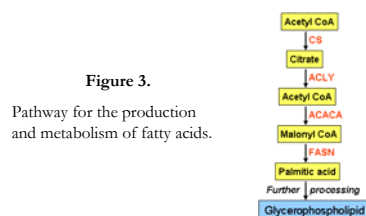


Figure 3.

Pathway for the production and metabolism of fatty acids.

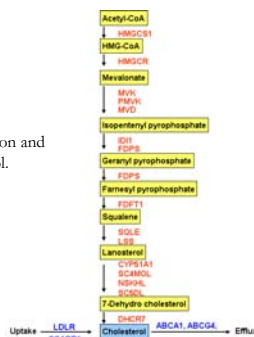


Figure 4.

Pathway for the production and metabolism of cholesterol.

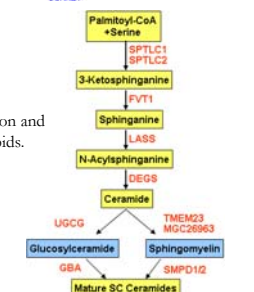


Figure 5.

Pathway for the production and metabolism of sphingolipids.

Table I. Expression of genes responsible for fatty acid formation.  
Red= up-regulation ( $p \leq 0.05$ ). Blue=down-regulation ( $p \leq 0.05$ ).

Acronym	Gene Name	Fold Change	
		Intrinsic aging (Buttock samples)	Photoaging (Forearm samples)
CS	Citrate synthase	-1.2	-1.23
ACLY	ATP citrate lyase	-1.57	-1.44
ACACA	Acetyl-Coenzyme A carboxylase alpha	-1.32	-1.52
FASN	Fatty acid synthase	-2.37	-2.26

Table II. Expression of genes involved in cholesterol production.  
Red= up-regulation ( $p \leq 0.05$ ). Blue=down-regulation ( $p \leq 0.05$ ).

Acronym	Gene Name	Fold Change	
		Intrinsic aging (Buttock samples)	Photoaging (Forearm samples)
<b>Cholesterol Biosynthetic Genes</b>			
HMGCS1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1	-1.87	-1.8
HMGCR	3-hydroxy-3-methylglutaryl-Coenzyme A reductase	-1.32	-1.32
MVK	Mevalonate kinase	-1.57	-1.53
PMVK	Phosphomevalonate kinase	-1.47	-1.69
MVD	Mevalonate decarboxylase	-1.72	-2.18
IDI	Isopentenyl-diphosphate delta isomerase 1	-1.36	-1.24
FDPS	Farnesyl diphosphate synthase	-1.41	-1.67
FDFT1	Farnesyl-diphosphate farnesyltransferase 1	-1.36	-1.37
SQLE	Squalene epoxidase	-1.39	-1.82
LSS	Lanosterol synthase		1.13
CYP51A1	Cytochrome P450, family 51, subfamily A, polypeptide 1	-1.48	
SC4MOL	Sterol-C4-methyl oxidase-like	-1.83	-1.71
SC5DL	Sterol-C5-desaturase		
NSDHL	NAD(P) dependent steroid dehydrogenase-like	-1.66	-1.71
DHCR7	7-dehydrocholesterol reductase	-1.65	-1.65
<b>Cholesterol Uptake and Efflux Genes</b>			
LDLR	Low density lipoprotein receptor	-1.54	
SCARB1	Scavenger receptor class B, member 1	-1.28	
ABCA1	ATP-binding cassette, sub-family A, member 1	1.43	1.56
ABCG4	ATP-binding cassette, sub-family G, member 4		

Table III. Expression of genes responsible for sphingolipid formation.  
Red= up-regulation ( $p \leq 0.05$ ). Blue=down-regulation ( $p \leq 0.05$ ).

Acronym	Gene Name	Fold Change	
		Intrinsic aging (Buttock samples)	Photoaging (Forearm samples)
<b>Sphingolipid Biosynthetic and Processing Genes</b>			
SPTLC1	Serine palmitoyltransferase, long chain base subunit 1	-1.23	1.41
SPTLC2	Serine palmitoyltransferase, long chain base subunit 2	-1.35	1.11
FVT1	Follicular lymphoma variant translocation 1	1.12	
LASS2	LAG1 longevity assurance homolog 2		1.37
LASS4	LAG1 longevity assurance homolog 4		1.52
LASS5	LAG1 longevity assurance homolog 5	-1.51	-1.54
LASS6	LAG1 longevity assurance homolog 6		-1.44
DEGS1	Degenerative spermatocyte homolog 1, lipid desaturase		-1.32
DEGS2	Degenerative spermatocyte homolog 2, lipid desaturase	-1.69	-1.52
UGCG	UDP-glucose ceramide glucosyltransferase	-1.23	-1.94
MGC29963	Hypothetical protein MGC29963		
TMEM23	Transmembrane protein 23		1.31
GBA	Glucosylase, beta, acid	-1.32	-1.17
SMPD1	Sphingomyelin phosphodiesterase 1		
SMPD2	Sphingomyelin phosphodiesterase 2		

## SUMMARY

Both intrinsically and photoaged skin show increased uneven texture and discoloration, both more pronounced in photoaging, suggesting common underlying pathways. In both intrinsic and photoaging there was a coordinated down-regulation of genes involved in SC lipid metabolism pathways.

As compared to younger skin, the expression of genes involved in fatty acid production was down-regulated in both intrinsic and photoaging [Table I].

Similarly, the expression of cholesterol synthetic pathway genes was down-regulated in both intrinsic and photoaging [Table II]. In addition, the major cellular cholesterol efflux pathway (ABCA1) was up-regulated in both, while influx (LDL, SCARB1) was down-regulated only in intrinsically aged skin.

Genes involved in the biosynthesis and processing of sphingolipids were also down-regulated, however this was more pronounced in intrinsically than photoaged skin [Table III].

## CONCLUSIONS

The coordinated down-regulation of SC lipid pathways at the level of gene expression in both intrinsic and photoaging is consistent with previously reported global decreases in SC lipids in aging skin, and likely contributes to the decreased capacity of aged skin to maintain and repair the epidermal barrier.

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- References
- Wertz P, Norlen L. "Confidence intervals" for the "true" lipid composition of the human skin barrier. In: Foellmeier B, Lindberg M, eds. Skin, Hair, and Nails. Structure and Function. New York: Marcel Dekker Inc, 2003:85-106.
  - Mao-Qiang M, Feingold KR, Jain M, Elias PM. Extracellular processing of phospholipids is required for permeability barrier homeostasis. J Lipid Res. 1995 Sep;36(9):1925-35.
  - Uchida Y, Han M, Nishio H, Sidransky E, Inoue S, Ohsota F, Suzuki A, Elias PM, Holleran WM, Hamanaka S. Lipidomic sphingomyelins are precursors for selected stratum corneum ceramides. J Lipid Res. 2000 Dec;41(12):1071-82.
  - Rassner U, Feingold KR, Crumrine DA, Elias PM. Coordinate assembly of lipids and enzyme proteins into epidermal lamellar bodies. Tissue Cell 1999;31:489-498.